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Review Article

Factors for COVID-19 Infection that Govern the Severity of Illness

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Abstract

Coronaviruses have been posing a serious threat to mammals and birds and a new class of SARS-CoV is creating havoc to the world after its first incidence in Wuhan City in China in December 2019. These viruses are mainly responsible for causing serious respiratory tract infections which generally appear initially as the common cold and can be lethal just like SARS-CoV. The problems seem to vary and worsen from one person to another depending on age, gender, ethnicity, blood groups, host genetics, and associated comorbidities. Complications should also arise as this virus keeps mutating and evolving. This review points out the various underlying causes behind the severity of the illness and the mechanisms associated with it. This review will help society to understand the risks and severities associated with COVID-19. Individuals with health complexities and predispositions listed in this review are the most vulnerable in terms of severity and should take every possible measure to protect themselves from getting infected. As a consequence, this will lead to a decrease in mortality rates arising from COVID-19.

Keywords: SARS-CoV-2; COVID-19; Coronavirus; Severity; Comorbidity.

1. Introduction

The newly evolved SARS-CoV-2 that had originated in the Wuhan City, Hubei Province in China in December 2019, has by now affected almost 218 countries of the globe [1]. Initially World Health Organization (WHO) named the disease 2019 novel coronavirus (2019 n-CoV) on 12th January 2020, and on 12th February 2019 they coined the term coronavirus disease 2019 (COVID-19). The name SARS-CoV-2 was finally issued by the Coronavirus Study Group (CSG) and this sudden outbreak was declared by WHO as Public Health Emergency of International concern by January 30th 2020 [2, 3]. As per the reports of WHO of March 20 2021, there are 121,969,223 confirmed cases of COVID infection, 2,694,094 deaths worldwide [4]. The patients were reported to have pneumonia like symptoms with other ancillary clinical SARS-CoV like symptoms such as dry cough, dyspnoea, fever, myalgia, and fewer having symptoms like fatigue, diarhhoea, haemoptysis, abdominal pain [5, 6]. Bilateral pneumonia was recorded in 75% of the patients [5]. In this review, we discuss the newly emerging SARS-CoV-2 virus, its origin, trying to address the

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underlying causes of severity due to gender, genetic and molecular differences, existing diseases as well as socio-demographic factors that further exacerbate the disease.

2. Structural, Genomic Composition, And Sequence Homology Of SARS-Cov-2 Virus-Relation To Pathogenesis

Coronaviruses are one of the two genera besides toroviruses of the Coronaviridae family [7, 8]. Coronaviruses and Toroviruses are regarded now as a family in the order of Nidovirales that has an envelope in which the genome is a positive-sense single-stranded RNA. Coronaviruses are considered much more powerful compared to HIV-1 as the infectivity of SARS-CoV is high and remaining viable for 1-4 days compared to MERS-CoV virions which are comparatively fragile than SARS [9]. SARS-CoV-2 is closer to SARS-CoV sharing about 79.5% maximum sequence homology, and 94.4% identity with SARS-CoV in the ORF1ab amino acid sequence carrying seven conserved sequences of replicase [10] and just 50% with MERS CoV [11].

Cats, ferrets [12], rodents [13] can be considered as intermediate host reservoirs for SARS-CoV-2, barring pangolin and Civet cats which cannot serve as direct intermediate host because the full length genomic homology of the pangolin coronavirus is 90.3% with that of SARS-CoV-2 and Spike glycoprotein (S) [SRR10168377] homology about 75% with SARS-CoV [13, 14], and lacking polybasic cleavage site required for ACE2 receptor expressed in human cells [15] On the other hand, the sequence homology of the S protein of Civet cats to that of humans SARS-CoV-2 is 75.4% [13].

The 2019 COVID SARS-CoV-2 has been found to have 14 ORFs encoding 27 proteins as was proposed by Wu *et al*. The four structural proteins for spike surface glycoprotein (S), small envelope protein (I), matrix glycoprotein (M), and nucleocapsid protein (N), along with eight accessory proteins 3a, 3b, p6, 7a, 7b, 8b, 9b and orf 14 is present in the 3’ terminus of the genome (Figure 1).

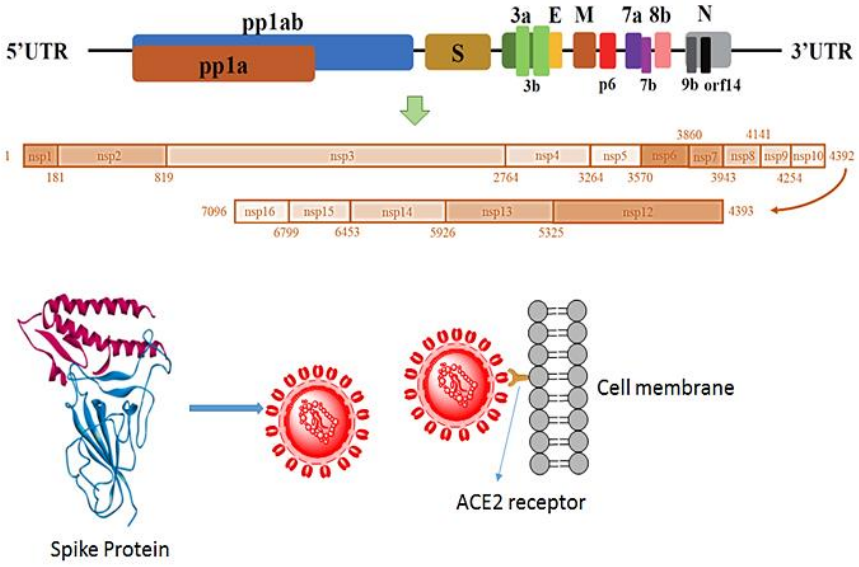

Figure 1. Spike protein development of coronavirus and its binding with ACE2

The 5’ terminus of the genome contains orf1ab and orf1b genes encoding pp1ab and pp1a protein respectively. Further phylogenetics and Molecular Evolutionary Genetics analysis (MEGA version 7.0) in their study showed the SARS- CoV-2 2019 virus can be placed in parallel to SARS Bat CoV as almost all encoded protein of pp1ab, pp1a, envelop, accessory protein 7a in the 2019 SARS-CoV-2 have similarity with SARS- CoV along with the spike gene and 3ab and 8b have closest resemblance to SARS-CoVs [16]. However, their study revealed that there are marked differences between SARS-CoV and SARS-CoV-2 (2019) virus in terms of their accessory proteins, their presence, and relative amino acid composition. The 8a protein is present in SARS-CoV and not in SARS-CoV-2, the 8b protein in SARS-CoV-2 is 121 amino acid long but is only composed of 84 amino acids in SARS-CoV. The 3b protein is 154 amino acid long in SARS-CoV while it is only 22 amino acid long in SARS-CoV-2 virus [16]. How this amino acid variation in the accessory protein composition of SARS-CoV-2 contributes to being more virulent than its counterpart SARS-CoV is still needs to be elucidated. However, as it has been seen the degree of binding patterns of the S glycoprotein of the newly evolved SARS-CoV2 with the ACE2 receptor expressed on the lung cells strikingly differ from that of SARS-CoV [17]. Earlier reports suggest spike protein of SARS-CoV contains a receptor-binding domain (RBD) that specifically binds to ACE2 [18]. Joseph Thomas *et al*. proposed via molecular docking techniques that the increased binding capability of the viral spike protein with the ACE2 is due to the several amino acid substitutions in

the RBD domain of the SARS CoV-2. They showed the two longer cappings of the RBD of the SARS-CoV-2 is providing tight binding to the receptor ACE2 [19].

3. Role of ACE2 Receptor in Virus Adherence, Its Presence – A Boon or Bane? Immune Cells Playing a Peekaboo?

ACE2 is a type I glycoprotein [20] which acts as a key component in RAS signalling. In the RAS signalling pathway, Angiotensin I (Ang I) is metabolised by ACE, a dipeptide carboxypeptidase which leads to Angiotensin II (Ang II) which is then metabolised by ACE2 that forms Angiotensin 1-7 [21]. The ACE2 receptor thus regulates the balance of angiotensin II (Ang II) that induces pulmonary vasoconstriction. ACE2 is expressed almost in all types of cells but the presence of it is more in type II alveolar epithelial cells of the lungs, and thus it efficiently facilitates the adhesion, translocation, and replication of the SARS-CoV and the new SARS-CoV-2 responsible for the outbreak in 2019-2020. Therefore, it can be said that heightened ACE2 expression is associated with an enhanced risk in COVID-19 cases [22]. Increased levels of Ang II cause vascular permeability which causes pulmonary oedema [23]. The etiology of the SARS-CoV-2 2019 has been seen to be largely associated with differential ACE2 expression. Jiawei Chen *et al*. performed a study of the ACE2 expression in 30 different tissues among thousand individuals by Gene Tissue Expression (GTEx) and found that high levels at about 100 % of ACE2 expression are seen in East Asian, and >30% in other ethnic groups. Their study further pointed out two important findings: a) higher ACE2 expression is seen in Asian females than in Asian males. It has been related to the secretion of estrogen levels in female, which decline with age and thus decreasing the levels of ACE2 expression and thus making them more prone to infection; b) The study pointed out that transgender males who sought estrogen therapy and androgen therapy for a year show high levels of ACE2 expression and the Sertoli cells of their body showed a large number of ACE2 expressing cells [24]. Zhao *et al*. pointed out via single-cell RNA sequencing that the expression of ACE2 expression in the lung cells is more in the Asian race compared to those belonging to African-American ethnicity [25].

However, Vinciguerra *et al*. put forward a hypothesis that lack of ACE2 expression may be a protective factor against SARS-CoV-2 as the virus enters by binding to the ACE2 receptor and thus they proposed that black people has an advantage over other ethnic groups but also it was concluded that once contracted with the virus it may pose detrimental effects to the host. As it was seen that in the black people, 20 out of 31 individuals by April 2020 was hit hard by the infection due to reduced ACE2 expression and subsequent rise in Ang II levels and thereby contributing to the ancillary risk of comorbidity [22]. However, there emerge contrary explanations that say though the SARS-CoV-2 virus employs the ACE2 as a podium to demonstrate its dramatic effects, the worsening effects are largely contributed due to differences in ACE/ACE2 races among individuals irrespective of gender, and have comorbidities. The ACE/ACE2 expression is downregulated in pathological conditions and also with associated comorbidities like hypertension, diabetes, cardiovascular diseases [26, 27] Alzheimer's disease [28, 29] and is upregulated in cigarette smokers [30]. The three different macrophage population that predominates in the lung cells has got a huge role to play because of its differential activation, and its subsequent response via inflammation varies largely following decreased ACE2 expression once the virus enters the cells further aggravating the predicament [31]. Older age is related to "inflammaging" which is a surge of the proinflammatory cytokines like IL-1 [32], IL-6, and TNF-α [33] COVID-19 patients have been diagnosed with higher number of immune cells like macrophages and also monocytes. Also, the neutrophil-monocyte ratio gets substantially elevated in the course of infection with increased proinflammatory cytokines [33]. A point to be considered here is that the dubious role of ACE2 is directly linked to monocytes and macrophages as they both express ACE2 on their cell surface and both SARS-CoV-1 and SARS-CoV-2 causes downregulation of ACE2 and its reduction with age further flares up the susceptibility of infection [34]. It has been seen that aged monocytes contribute to a proinflammatory phenotypic appearance brought about by reduced mitochondrial functioning [2, 34]. Further aging has been seen to directly impair with the phagocytosis of alveolar macrophage cells and thereby promoting the death of mice when infected with influenza virus by downregulation CD204 responsible for the internalization of apoptotic cells [35]. This has been accompanied by cellular changes in the endoplasmic reticulum which are associated with an increased amount of misfolded or unfolded proteins. Reduced activity of these misfolded protein degradations by unfolded protein response capacity (UPR) and reduced autophagic potential can lead to increase in production of these vicious cytokines, TNF and C-reactive protein [36].

4. Vitamin D can Influence COVID-19 Infection and Severity

Another important aspect that needs to be pointed out in this regard is the disparity of Vitamin D deficiency among different races. Ronald Evans *et al.* pointed out that the deficiency of Vitamin D may fail to activate the Vitamin D Receptor (VDR) that has a role to negatively regulate TGFß signaling by interfering with Smad 3 transcriptional silencing in the hepatic stellate cells (HSC) [37]. Vitamin D plays a key role in suppressing pathologic responses to the virus [38]. Vitamin D has been seen to play effective action in reducing the proinflammatory cytokines by the inhibiting factors of the NFBκB pathway and in turn suppressing immune-mediated injury in the body [39-41]. High levels of TGFß has been seen in COVID-19 patients [42] and thereby initiating several inflammatory cytokine release

(IL-Iß1, IL-6, TNF) which causes alveolar damage [43]. There had been evidence that African people have low circulating 25 (OH) D compared to that of the Caucasians and are at high risk of Vitamin D deficiency [44]. This has led to the connection that SARS-CoV-2 is associated with Acute Respiratory Distress Syndrome (ARDS) individuals with low (27.6nmol/L) to very low (13.7nmol/L) 25(OH) D concentration in their blood levels [45, 46]. In a retrospective cohort study conducted by Eboni G *et al.* it was revealed in Lousiana between March 1 and April 11 2020, 59% of COVID-19 mortality rates was related to the black non-Hispanics though they comprise only 33% of the population besides white non-Hispanics and about 80% received mechanical ventilation [47]. Variations in the genes encoding Vitamin D binding protein, VDBP (GC), vitamin D 25-hydroxylase (CYP2R1), genes encoding enzyme 7-dehydrocholesterol reductase and 1,25-hydroxyvitamin-D3-2 4-hydroxylase (the region around DHCR7 and CYP24A1 respectively) and variance in either of these four genes may result in a total variance of 1.5% in these genes. This may appear insignificant but may largely affect 25 (OH) D levels. A variant of the rs4588A allele has been seen to contribute to low 25 (OH) D in the European population which however is not seen in individuals of African ethnicity. So, to conclude it is clear that COVID-19 incidence has a clear connection to vitamin D deficiency, with a majority of COVID-19 patients are found to be deficient in this particular vitamin [48, 49].

5. Impact of Ethnicity, Gender and Age

There is a differential gender-related epidemiology in the SARS-CoV-2 infection and men can be seen as more affected than females. During earlier times, in case of viral infections like Ebola and Zika, women have been seen to have least affected than males though serving roles as frontline caregivers during 2014-16 Ebola virus outbreak in West Africa [50]. A study carried out with COVID-19 confirmed 1,190 adult patients in Wuhan Infectious Disease Hospital and it was found that 635 (53.4%) patients were male and 555 (46.6%) were females although there had been more female health workers than male. There had been marked differences in not only laboratory reports but also in immunological biomarkers. Male patients had higher leucocyte and neutrophil counts, lower lymphocyte, and platelets count and comparatively lower CD4/CD8 ratio, and high levels of inflammatory cytokines than females [51]. There had been previous reports of "cytokine storm" generated due to high plasma levels containing an array of inflammatory interleukins-IL-1ß, IL-6, IL-7, IL-8, IL-18, Granulocyte Colony Stimulating Factor (GSF), and Tumor Necrosis Factor (TNF-α) which results from macrophage activation ultimately leading to mortality (Figure 2) [52].

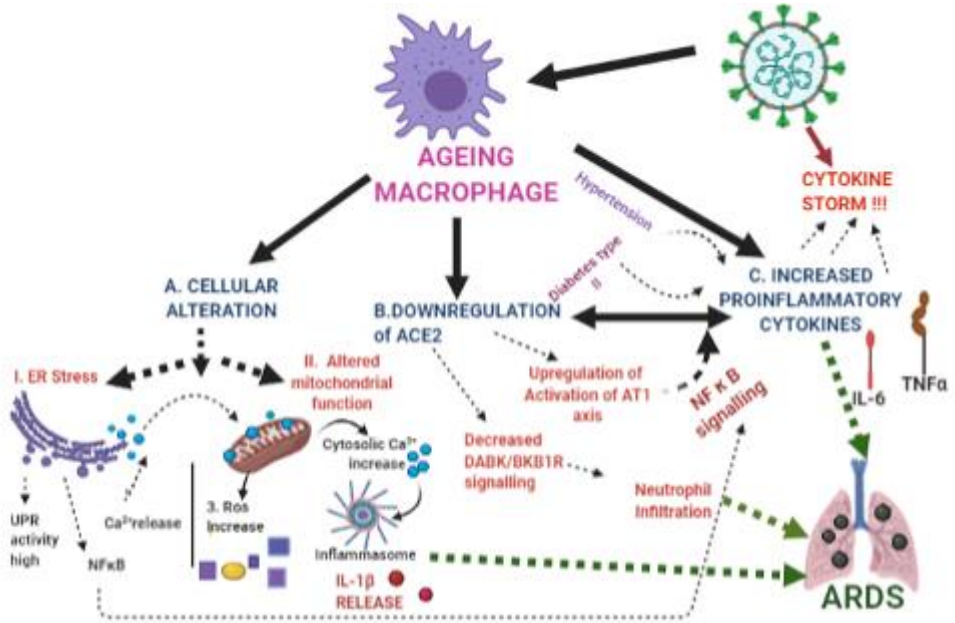

Figure 2. ACE2 downregulation in Aged macrophages: a putative pathway that leads to increased inflammation due to SARS-CoV-2 infection. Cellular pathway alteration leading to defective ER and Mitochondrial dysregulations are important markers in the pathway. The ER releases Ca^{2+} which is taken by mitochondria leading to cytosolic Ca^{2+} pool and ultimate inflammasome formation. Downregulation of ACE2 leads to neutrophil infiltration. Further increased levels in proinflammatory cytokines are consequences of severity of lung distress.

An additional 15 cytokines namely M-CSF, 1L-10, IFN-α2, IL-17,1L-4, IP-10, IL-7, IL-1ra, GSF, IL-2, IFN-γ, IL-1α, IL-2, HGF and PDGF- BB have been identified as biomarkers who increased level causes lung severity when 48 cytokine levels in blood were checked in a case study with 12 COVID-19 patients [53]. In a study conducted by Satis *et al.* with 58 individuals, it was found that the concentrations of Il-8 along with other inflammatory biomarkers had shown to worsen up the situations in SARS- CoV-2. The concentrations of IL-8 along with IL-6 was found to be higher in males than in females [54].

Expression of differential *TMPRSS2*, an androgen-responsive gene, which affects fusion of the viral membrane with the ACE2 receptor has given rise to sexual dimorphisms. It has been seen that TMPRSS2, a transmembrane serine protease 2 cleaves viral S-glycoprotein, and its expression is higher in males than in females. Single nucleotide polymorphisms in the *TMPRSS2* gene play a pivotal role in general population (rs2070788, rs7364083, rs99745890) and gender-related perspective (rs8134378) [55]. This has got a direct relation to the secretion of sex hormones, as estrogen (E2) has been seen to be affected by TMPRSS2 expression, and estrogen in turn, regulates ACE2 expression. E2 treated NHBE cells has been seen to lower ACE2 expression [56, 57]. However, this discrepancy in the infectivity can be attributed to the X-chromosome in humans. The genes for *ACE2* (locus Xp 22.2) and Ang-II receptor Type 2 (*AGTR2*, alias *AT2*, locus Xq23) happens to be located on the X-chromosome. Females have two X chromosomes and are heterozygous than males who have only one chromosome and are hemizygous [58]. One of the X chromosomes in females is inactivated by a process called Lyonization or X-inactivation by which the RNA transcribed from the Xist gene spreads to coat the whole chromosome [59]. The inactivation is however skipped in the Xp22.2 where the *ACE2* gene is located on the X chromosome [60]. The sixteen residue binding of SARS-CoV-2 RBM with 20 residues of ACE2 is somewhat different due to this difference in the X-chromosome inactivation. Out of the two X chromosomes in females, only one X chromosome has the *ACE2* which recognizes the SARS-CoV-2 receptor, the chance for the second X chromosome for binding is low and thus the chance for pulmonary oedema in COVID-19 is lowered. This can be seen as a boon for the females in contrast to males having a single X chromosome [61].

6. Role of Blood Groups in COVID-19 Infection

There had been a correlation with Landsteiner's ABO Blood grouping system with SARS-CoV-2 infection. The ABO blood grouping system is based upon the difference in the carbohydrate residues on the RBC cell surface which is inherited following Mendelian inheritance [62]. A close view of the common ABO blood groupings out of the 29 blood group systems reveal that ABO antigens are oligosaccharides formed of conjugates of carbohydrates and proteins. ABO antigens are biosynthesized when fucose gets attached to the terminal end of galactose via α1→2 linkage, which results in the H antigen that determines the O phenotype. A and B antigens are formed via enzymatic modification of the H epitope when the D isotope of the N-acetylglucosamine or galactose gets attached to the galactosyl residues [63, 64].

The difference in carbohydrate residues can be accounted to the difference in infections caused due to different pathogenic organisms. The RBC cell surface of different carbohydrate residues serve as receptors for toxins produced from the body of the microorganisms, it can be a rich habitat where they can colonize and multiply; pathogens like bacteria stimulate antibodies against RBC antigens [65]. ABO Blood Groupings are based on the surface antigens on the RBC which are either sugars as in the case of the RBC surface markers or proteins as seen in Rh blood group (encoded by the Rh D gene) [66, 67] Some studies indicate there is a high incidence of infection among non-O blood group types [68]. The risk of intubation was highest in B and AB types, and less for individuals with A blood groups, and least for type O individuals [68]. The risk of death was most for AB and less for A and B type individuals [68].

6.1. Role of Adhesion Molecules and Blood Groups

The explanation of the discrepancy of blood groups with COVID infection, however can be attributed to the participation of the adhesion molecules, their binding with the leucocytes, subsequent inflammation [69]. Reduced blood flow results as hemodynamic changes occur due to inflammatory or pathogenic response in the capillaries. This may drive leucocyte adhesion upon activation via chemokines like IL-8, released from the cells of the endothelium which activates neutrophils, MCP-1 and MIP-α that activates Monocytes, leading to their adhesion, subsequent extravasation and diapedesis. Effective receptor- ligand interaction is however mediated by an array of cellular adhesion molecules expressed on the surface of the endothelium cells [70, 71]. Intercellular Adhesion Molecule (ICAM-1) is a transmembrane glycoprotein and member of the immunoglobulin superfamily [72], facilitates immune cell adhesion to the surface of endothelium. ICAM-1 undergoes proteolytic cleavage to form soluble sICAM-1 which inhibits leucocyte-lymphocyte adherence to capillary endothelial wall [73]. ß2 -integrins are expressed largely on the leucocytes and they bind to ICAM-1 in the endothelial cells. ICAM-1 binds to ß integrins like LFA-1 and Mac T expressed on leucocytes that enable them to roll , and the adhesion process is further augmented by a set of selectin molecules like, L-Selectin (expressed on the leucocytes), E-Selectin and P-Selectin (expressed on the endothelial cells) [74, 75]. A1 allele of Blood group A has been seen to have low sICAM-1 and P-selectin levels which is an important biomarker that indicates increased adhesion of leucocytes promoting vascular inflammation [73, 76]. Further glycosylation of sICAM and cellular ICAM-1 is required for P Selectin binding with P-Selectin receptor ligand 1. The glycosylation activity of the A1 allele of Blood group A is seen to be more producing more glycosyltransferases that transfer sugar moieties to H-antigen. This glycosylation process mediates adhesion molecule clearance and the low sICAM1 and P-Selectin concentration in A blood group is strongly indicative of the clearance ability of the A1 allele unlike the O blood group which being devoid of the A and B antigens does not have transferase activity. Low sICAM1 concentration leads to less cellular adhesion of the leucocytes, promote vascular diseases and inflammation [69].

6.2. Difference in the Distribution of Blood Groups in the World

Blood group O considered as "universal donors" are known as the most common type of blood group and the frequencies of their incidence are extremely high among Central & South America, and Australian aborigines. Blood group A is widely distributed in Central Europe and in America. The Asian population is inhabited with Blood group B and Blood group AB which are "universal recipients", is least found in a population and are found in Japan, Korea, and in some regions of China [66, 67].

6.3. Probable Role of Sialic Acids in the Difference in SARS-CoV-2 infection among the Blood Groups

Sialic acids (Sia), are hydrophobic, negatively charged acidic sugars having 9 carbon backbone formed by the acetylation of N-acetyl glucosamine. They are almost ubiquitous in all cells on all cell surfaces and secreted proteins and serve as binding sites for pathogens and toxins. Cell and host-specific interaction by viruses is accomplished by binding with selective sialic acid subtypes [77]. Sialic acids determine half-life of glycoprotein in circulation and its absence causes the glycoprotein to clear away. Besides, Sia regulates cell-cell interactions and immune responses. They are recognized by toxins and pathogens by their specific linkages with the sugar chains thus posing detrimental effects to the host cells. Beta CoVs OC43 CoV, HKU1 CoV use 9-O acetylated sialic acid (9-O-Ac-sialic acid) as the substrate for the haemagglutinin esterases (HFs) which are glycoprotein in the viral envelope that act as receptor destroying enzymes (RDEs) and arise from influenza C like HE fusion protein (HEFs). The O-acetyl residues are detached and that is how viruses are released from host cells and virus aggregation is prevented [78, 79].

The spike protein of coronaviruses responsible for the typical "crown" structure emerges from the viral envelope. Bibliographical review suggests this spike protein yields two subunits S1 and S2 when cleaved by host protease from three equal monomers that compose the spike protein. The subunits are essential for the attachment of the virus with that of the host cell membrane. Prior virus-host interactions indicate that the amino acid bridging the two subunits are cleaved by TMPRSS2 in coronavirus species. However, SARS-CoV-2 virus has an additional furin priming in its spike protein which is a serine endoprotease that can cleave R-X-(R/K/X)-R↓(S)(V/A/L) multi basic protein which is not seen in other coronavirus species like bat coronavirus strain (Bat-RaTG13, Bat -ZXC21 or Bat-ZC45) and SARS-CoV which are not cleaved due to absence of furin [80]. The N- terminal of the S1 monomer has 4ß rich domain A, B, C, D. A or B domain acts as a receptor-binding domain. Coronaviruses use sialic acid residues for binding. Cryo-M studies have revealed a conserved siaglycan binding site in a groove in the A domain that attaches 9-O-acetyl-sialic acid (9-O-Ac-Sia) which is attached to the glycoprotein and gangliosides in the host cell membranes [81].

Expression of 7,9- O- Ac, 9-O-Ac, and Neu5Gc sialic acid are seen in mouse tissues. Sialic acids are predominant in body secretions and it is seen that with age the concentration of sialic acids increases. In the case of diabetes patients the sialic acid concentration has been seen to be more in the retina, iris, and vitreous humour compared to that of normal patients. Case studies have even revealed that tears and ocular fluids contain viral load of SARS-CoV-2 [82-85].

A hypothesis was put forward by José Caetano Silva Filho *et al.* that sialic acid distributions in RBC can be determined by A, B, AB, O antigens, whereby A and B antigens through cis- carbohydrate-carbohydrate interaction can trigger sialoside cluster formation in cells which in turn may promote the SARS-CoV-2 interaction with the ACE2 and CD147 via their RBD and NTD domains [63].

7. Comorbidity

Along with the virus, the associated array of symptoms, and illness, several existing diseases may flare up the severity of COVID-19 requiring absolute hospitalization and intensive care admission. It has been seen though mortality rates resulting from comorbidities are associated with old age and gender, but also significantly younger populations and neonates having pre-existing diseases are highly susceptible to infection. Countries with less economical advantage have received the maximum blow from the pandemic along with healthy realms like USA [86]. According to the recent global epidemiological reports by WHO, as of 22nd November 2020, the African region had an increase of 15% in new cases and about 30% increase in deaths. In India, cumulative deaths as of 22nd Nov 2020 count to almost 1,33,227 according to WHO. Centres for Disease Control and Prevention has enlisted comorbid diseases according to high increased risk and probable chance list of infectivity by COVID-19. In India, however, it has been seen that about 10-20% of patients receive intensive care unit (ICU) admission and 3-10% require intubation and mechanical ventilation [87].

In a retrospective study conducted in the early months in India around April 2020, it was seen that in 206 deaths, diabetes and hypertension tops among other comorbidities, contributing to about 27.8% and 22.1% deaths respectively. Diabetes prevalence is comparatively seen to be highest in India than in any other country [86, 88]. Not only for aged patients, but in fact, children from neonates to up to 16 years of age has been seen to be in the risk zone for COVID-19 complexities who have pre-existing comorbidities. Those include cerebral palsy, Wilson's disease,

dilated cardiomyopathy. Intensive care support and invasive mechanical ventilation have been given to children affected with COVID-19 who had been previously suffering from hydronephrosis, leukemia, and intussusception [89, 90].

Other autoimmune diseases like AITD (Chronic autoimmune thyroid disease) lead to altered immune function as human lymphocytes express nuclear receptors for thyroid hormones. B cell development has been seen to be impaired in the bone marrow of C.RF hyt/hyt mouse where TSHR was defective and TSH production was impaired and mouse was hypothyroidic and subsequent treatment of T4 leads to increase in pro B cells in the S-G2/M phase of the cell cycle [91, 92]. Thyroid gland has been seen to have the highest expression of ACE2 along with other vital organs like the kidney, heart, and small intestine [93]. In a retrospective cohort study conducted on 251 COVID-19 patients who had hypothyroidism as comorbidity, it was seen that 68.1% received hospitalization but not in an increased risk of mechanical ventilation. However, their study indicated that hypothyroidism if well managed will not lead to deleterious extremities like death but the chance of infection remains high for poorly controlled hypothyroidism [94]. Other than this, obese Polycystic ovary syndrome (PCOS) women are also susceptible to higher risk for COVID-19 infection accounted for hypercoagulable state induced due to elevated BMI and insulin resistance.

7.1. Chronic Obstructive Pulmonary Disease (COPD) and COVID-19

A case related study showed that COPD patients who received prescribed inhaled corticosteroids (ICS) were at high risks of COVID-19 infection [95]. In China, patients experienced pneumonia-like symptoms at the onset of December 2019 which was basically the symptoms of the rising COVID-19. It was seen about 7% of patients in China and about 13.7% of patients in Italy who contracted COVID-19, had COPD as pre-existing disease [96]. The expression of ACE2 receptors had been found to increase which contributes a major factor in contracting the disease leading to hyper mucous formation [97]. Tobacco smoking has been correlated with the severity of SARS-CoV-2 when contracted. COPD patients have been recognized by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) as the worst affected individuals who contract COVID-19. Not only current smokers but individuals having a previous history of smoking are equally susceptible to infection. There is differential ACE2 expression like the whole Cigarette smoking largely culminates in upregulation of ACE2 expression while a research group showed that nicotine present in cigarette causes disruption in RAS pathway and both ACE2 and AT1R (Angiotension type 1 receptor) gets downregulated [30, 98, 99]. Second-hand smoking (SHS), use of snuff and air pollution both indoor pollutants like cooking in kerosene and other biomass fuels in village areas, smoke of mosquito coils and exposure to outdoor pollutants like automobile emissions can be other important ancillary causes of COPD [100, 101].

7.2. Cardiovascular Disease, Hypertension and COVID-19

Worldwide about 1.4 million people are affected by hypertension [102]. The 3rd report of Joint National Committee on Detection Evaluation, and Treatment of High Blood Pressure in 1984 (JNC III) proposed that normal bp counts to systolic blood pressure (SBP)<140 mm Hg and diastolic blood pressure (DBP)<90 mm Hg [103]. High cardiovascular risk is seen in patients who have elevated SBP and a low DBP [104]. As per the WHO, in September 2019, it was reported that the African population has the highest incidence of hypertension about 27% while the prevalence is low in America which is about 18%. (World Health Organization, Hypertension (13th September 2019)). It is prognosticated that by 2025 the number of hypertensive patients will increase to 1.56 billion worldwide [105]. Women are seen less to suffer from hypertension compared to males (12% vs 27% respectively). Menopausal women and men are at high risk of cardiovascular diseases can be due to various biological factors like sex hormones, chromosomal differences, behavioural and lifestyle factors like high body mass index (BMI), smoking habits, limited physical activity. Intra-abdominal adiposity has a relationship with high BP and the levels are higher in males compared to females and this relates to increased sympathetic activity in males consequently leading to cardiac arrhythmias, cardiovascular hypertrophy [106-109]. High androgen levels as of testosterone, is associated with noradrenaline synthesis and subsequent vasoconstriction [110]. Low levels of serum androgen promote hypertension and cardiovascular anomalies in males while the reverse is true in females where hypertension and CVD arise from elevated androgen levels. A study conducted on 5α-dihydrosterone (DHT) treated male rats showed intrarenal expression of CYP4A and 20HETE (Hydroxyecosatetraenoic acids) and elevated BP level via NFκB activation and increased production of reactive oxygen species (ROS) and decreased nitric oxide (NO) production paving the way to renal vasoconstriction [111, 112]. Another important factor involves salt levels in the diet, an increased salt consumption leads to an increase in water retention thereby increasing BP levels [113].

SARS-CoV-2 affected patients already having pre-existing cardiovascular diseases are prone to heart attack or myocarditis characterized by high leukocyte count with concomitant IL-6, ferritin levels due to elevated troponin concentration resulting in cytokine storm and in its worst death [114, 115]. Alongside hypertensive patients, contracted with SARS-CoV-2 has been seen to have high sensitivity to CRP compounded with procalcitonin and IL-6 suggesting heightened inflammation [116].

Coronary heart disease is also a major disease of concern in the wake of the COVID-19 pandemic. An imbalance between the ACE2 vasoprotective axis (ACE2-Ang (1-7)- Mas axis) and ACE- Ang II -AngII type 1 Receptor (AT1R axis) leads to pulmonary hypertension-related CHD (CHD-PAH). Though the concentration of ACE2 has been associated with increased inflammatory cytokine levels, however, a new explanation suggests that higher ACE2 expression at baseline can be seen from a vantage point of view as the viral molecules engage in a competition binding with angiotensin II and that maintains angiotensin 1-7 levels which inhibit the proinflammatory action of ACE2. This can be a plausible reason for the disparity of infection and severity across children and young generation with that of adults [117]. In a study conducted with 104 CHD patients (35 men and 69 women) with an age greater than 14 years, it was seen that ACE2 concentration was higher in patients with non-pulmonary hypertension while in patients with pulmonary hypertension ACE2 concentration decreases [118]. But, whether children and new-born with congenital heart disease are least susceptible to COVID-19 remains to be a debatable issue and needs to be further elucidated.

8. Mutations in Virus

Virus mutations are common and the influence of such mutations in the changing facets of SARS-CoV-2 viruses is not a surprise [119-120]. Although, there are more questions than answers at this moment for the mutation(s) that are observed currently, and how it impacts the spreading of the virus. However, there is no denial that already researchers across the world have recorded as many as 12,000 mutations to date (Figure 3).

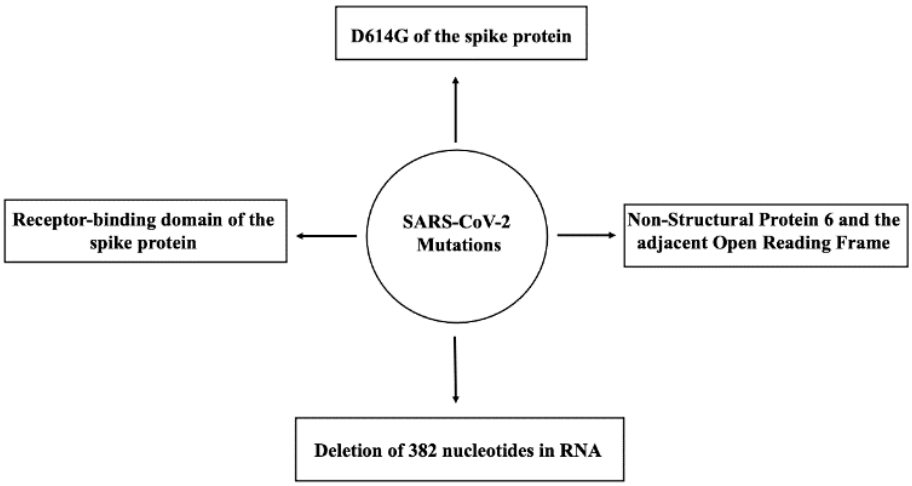

Figure 3. Range of SARS-CoV-2 mutations

It seems that there are no direct correlations between the recorded mutations and faster spreading hitherto [120]. However, the emergence of 12,000 mutations shows how the virus has evolved in the last year (three major variant types – A, B, and C) [121]. On the contrary, it also must be highlighted that this virus is evolving at a slower rate than other RNA viruses due to the presence of a proofreading enzyme which corrects any error(s) during the replication [122]. It is also believed that the virus might have already optimally evolved from the very beginning as it was able to infect such a huge number of people around the world and further mutations may not be so necessary until it faces any resistance from the host.

The most popular mutation that has been recorded for SARS-CoV-2 is the D614G (aspartic acid to glycine) that had incidence from Germany and China [123]. The D614G is reported to change the architecture of the spike protein to a more relaxed structure that might facilitate the chance of infection [124, 125]. Other reports suggest mutations in a receptor-binding domain of the spike protein [126, 127]. Moreover, deletion of 382 nucleotides in RNA has also been studied which potentially reduces the severity of COVID-19 infection [128]. In a separate study, two mutations were detected in the Non-Structural Protein 6 and the adjacent Open Reading Frame, of which one of the mutations might be contributing to the altered intracellular survivability of the virus, but that needs further investigation [129]. So, there must strict vigilance on this and further mutations which might lead to evolution and any alterations in the phenotype. That would ensure successful designing and modifications in upcoming therapeutic strategies.

9. Host Genetics

SARS-CoV-2 infections can exhibit a wide range of consequences in different individuals. Normally, it has more severe outcomes in old individuals with underlying health issues [130]. However, young adults are also prone to varying impacts of disease severity. Patients show grave symptoms like renal and cardiac injury, loss of smell and taste, persistent fever, gastrointestinal malfunctioning, and even hepatitis, among others [131-134]. Others may be

asymptomatic altogether [135]. For many infectious diseases, it is understood that allelic polymorphisms and genetic loci variations have contributed to such differences in disease susceptibility among individuals.

As already discussed in this review, ACE2 is the primary attachment and entry point of SARS-CoV-2. The scientific community thus started to investigate whether any ACE2 polymorphisms impacted viral binding and entry. There were several variants of *ACE2* (S19P, I21V, E23K, K26R, T27A, K31R, N33I, H34R, E35K, E37K, D38V, Y50F, N51S, M62V, N64K, K68E, W69C, F72V, Y83H, T92I, Q102P, G326E, L351V, G352V, D355N, H378R, Q388L, P389H, I468V, D509Y, N720D) that could change the ACE2 conformation thus altering (positively or negatively) interaction with SARS-CoV-2 [136-138]. Again, patients with hypertension, diabetes, and chronic obstructive pulmonary disease (COPD) show a much higher ACE2 expression than healthy counterparts explaining how comorbidity can influence disease severity [139].

TMPRSS2, a serine protease, has a role in viral membrane fusion. There are reports that single nucleotide polymorphism (SNP) results in higher expression of TMPRSS2, which further increases the susceptibility of an individual towards SARS-CoV-2 infection [140].

HLA-typing can be another important factor that determines SARS-Cov-2 infection and disease progression. Research groups have deciphered that HLA-B*46:01 binds to fewest number of peptides of SARS-CoV-2, which suggests that individuals who have this allele can generate a feeble immune response and thus more prone to severe manifestations [141]. On the contrary, individuals with HLA-B*15:03 are more protected from the severity as they have a high capacity to present well-conserved peptides of SARS-CoV-2 and other pathogenic coronaviruses to the immune cells [141].

"Cytokine storm" mediated by increased release of cytokines such as IL-6, TNFα, IL-1β is another complication associated with SARS-CoV-2 infection [138]. Patients with severe clinical symptoms have been associated with hyper-secretion of these cytokines, along with increased levels of C-reactive protein, D-Dimer, ferritin, etc. [138]. The consequence of such a rise in the levels has been related to excessive alveolar damage which ultimately leads to acute respiratory distress syndrome [142]. These events are absent in asymptomatic or patients with milder symptoms. Studies also state that certain immune responsive genes like *AHSG*, *CCL5*, *CCL2*, *IL4* variants have a role in disease severity [143].

10. Natural compounds: Alternatives to Mitigate the Overlooked Side Effects of Common Antivirals in COVID-19

The ever-increasing rates of SARS-CoV-2 pandemic has necessitated the search for effective therapies as no proven appropriate remedy or proper prophylaxis in the form of vaccination is available so far. Nevertheless, to combat the worsening situation, several drugs and antivirals were proposed and administered for treatment. But these drugs have been seen to pose considerable side effects to the body and it calls for urgent need for alternative medical treatment. We discuss certain available chemical drugs used in spite of their known side effects to combat the increasing predicament of the disease.

Antimalarial Drugs: Chloroquine and Hydroxychloroquine – Its mode of action and possible side effects

At the very start of the SARS-CoV-2 pandemic crisis, antimalarial remedial drugs like chloroquine and hydroxychloroquine were used and still in vogue for treatment. Both being 4-aminoquinoline derivatives, chloroquine itself is effective against a spectrum of RNA viruses like Ebola, Zika, polio, influenza A and B viruses, HIV as well as an array of DNA viruses [144]. Chloroquine and its analogue hydroxychloroquine are used as a medicine for lupus erythematous, arthritis, etc. autoimmune diseases and functions by interfering with a) glycosylation of the ACE 2, the receptor for SARS-CoV-2 thereby altering the binding of the virus with the same [145], b) it raises the endosomal pH that blocks viral infection [146], c) a hypothesis suggests possibly the interaction of SARS-CoV-2 with the host cell is interfered with chloroquine treatment that brings about the inhibition of MAPK like kinases and reduces prion inflammatory cytokines [144]. However, via molecular docking studies, it has come to light the enhanced effectivity of hydroxychloroquine. It binds more efficiently to the 32 amino acids present in the four helices of the N-terminal domain (NTD) of the nucleocapsid N protein with a binding energy (-7.28 kcal/mol) much higher than the binding energy of chloroquine (-6.30 kcal/mol) [147]. Hydroxychloroquine causes S protein breakage due to the formation of autophagosomes brought about by the rise in pH of lysosomes and endosomes [145]. Hydroxychloroquine has also been seen to intervene with the antigen processing and presentation brought about by MHC Class II leading to a fall in T-cell production and thereby preventing cytokine storm [148]. Hydroxychloroquine has been reported to block toll-like receptor (TLR9) signalling by binding with nucleic acids and reducing cytokine production [149].

Side effects: Though potentially capable of inhibiting the virus, hydroxychlorine has been reported of inducing fulminant hepatic failure and ventricular arrhythmias [150] and causes more renal toxicity than chloroquine does

[151]. Both these drugs have been associated with delayed action potential in the nerves and prolonged QT interval in myocytes [152].

Antiviral Drugs: Remdesvir, Lopinavir, Ritonavir – A re-evaluation of its effectiveness and toxicity

Chloroquine and hydroxychloroquine are advised not to be used with Remdesvir as the activity of the latter may decrease with the concomitant use of these antimalarial drugs [153]. Remdesvir, an antiviral nucleotide analogue has long been used for a myriad of RNA viruses like MERS-CoV, SARS-CoV, Ebola, Nipah viruses, and other zoonotic viruses [154-157]. Remdesvir is formed by intracellular conversion and its mode of action is competitive binding by mimicking the structure of nucleotides [158]. Also, Remdesvir can halt the inhibition of viral RNA dependant RNA polymerase replication [159]. Remdesvir interestingly has been found to be effective in inhibiting SARS-CoV-2 in human liver cancer Huh 7 cells [160]. Other drugs of choice being a protease inhibitor of SARS-CoV-2 is a combinational therapy of lopinavir-ritonavir that was previously used in the treatment of SARS-CoV and MERS [154, 161]. This therapy targets 3Clpro, a 3chymotrypsin like protease that aid in the processing of viral RNA [162, 163].

Side effects: These antiviral drugs are being complained of serious side effects. Remdesvir is associated with cutaneous side effects [164], hepatocellular injury with increased levels of AST/ALT upon remdesvir [165], cardiac side effects causing hypertension, arterial fibrillation and sinus bradycardia [166]. Lopinavir-ritonavir on the other hand is not refrained from causing adverse effects. Ritonavir induces porphyria, haemophilia and is to be used with much caution for individuals with cardiac ailments [167] and are seen to cause gastrointestinal troubles with ancillary nausea, vomiting and diarrhoea [168, 169].

Natural Compounds: Its beneficiary action – Natural Compounds targeted against 3CLpro, PLpro, Spike protein, ACE2 receptor

With side effects of these practicing remedial soaring high, search necessitates for alternative treatment and natural compounds can be a judicious choice to minimize the exacerbation of the severity brought about by the same as well as providing an economical advantage for the developing countries.

A number of phytochemicals and natural compounds can be used in lieu of these antivirals. Where Lopinavir-Retonavir are targeted against the 3Clpro, molecular docking studies have revealed high receptor binding (docking score S= -16.35) of a phytochemical extracted from *Psorothamnus arborescens* having an isoflavone moiety [5,7,3', 4'- tetrahydroxy-2'-(3,3- dimethylallyl) isoflavone] with that of Cys-145-His-41 catalytic dyad of the 3Clpro much higher than a potent non-competitive inhibitor ML188 (having docking score S= 8.31) when used as a reference. Besides, legume like kidney beans *Phaseolus vulgaris* having 3,5,7,3',4',5'-hexahydroxy flavonone -3-O- beta -D glucopyranoside and Indian gooseberry, *Phallanthus embellica* having (2,S)- Eriodictyol 7-O-(6"-O-gallolyl)-beta D-glucopyranoside, myricitin group from *Myrica cerifera* has been seen to show similar reactivity against the 3Clpro residues of the virus [162]. A variety of potential inhibitors for SARS-CoV-2 are found in the rhizomes of *Zingiber officinale* and galangal (*Alpinia officinarum*) [170]. From earlier reports based on coronavirus inhibition, apart from the chymotrypsin enzyme 3Clpro, there are a number of natural compounds found to be effective against another papain protease, PL^{pro}, that functions by hampering post-transcriptional modifications of host proteins, cleaving ubiquitin and attenuating interferon that aids largely on innate response of the body and thus the enzyme facilitates in the viral replication by assembling replicase complex for viral replication [171]. A number of natural compounds are seen to have inhibitory action against this Plpro protein. Examples can be cited for Curcumin obtained from *Curcumin longa* which is an easily available medicinal herb and spice, along with tanshinone derivatives obtained from an array of *Salvia sp.*, [172] baicalin from *Scutellaria baicalensis*, and Theaflavin 3,3′-di-O-gallate from *Camellia sinensis* [173]. There are several phytochemicals like Phyllaembillin A, Punigluconin, Punicafolin and Emblicanin A from Indian Gooseberry, *Phyllanthus embilica*, Rutin from Neem, *Azadirichta indica*, Lithospermic acid from *Salvia multiorrhiza*, and Kuwanon X from Mulberry plant , *Morus alba* is considered efficient for simultaneously inhibiting all the three drug targets, that is, PL^{pro}, $3CL^{pro}$ and IS -spike, a mutational variety of the spike protein of SARS-CoV-2 seen in India [having surface glycoprotein A930V, (24351C>T) [174].

Some common food items, spices, and condiments are seen to be functionally ACE2 inhibitors. A number of flavonoids scutellarin, nicotanamine can be seen as ACE2 inhibitors over conventional ACE2 blockers like telmisartan, losartan[174] as these ACE2 blockers causes upregulation of Angiotensin Type II receptor (AT1R) in diabetic and hypertensive patients thus ramifying further the severity and fatality of infection [175]. Peptide nicotinamine from *Glycine max*, anthraquinone extracted from *Rheum officinale*, apigenin from *Apium graveolus*, Delphinidin and Cyanidin from *Hibiscus sabdariffa* are found effective in ACE2 inhibition [174]. Theaflavin extracted from *Camellia sinensis* of Assamica variety has been seen to inhibit both protein ACE2 and TMPRSS2 expression at 50μg/ml concentration [176].

Besides, essential oils like limonene composed of volatile terpene compounds extracted from lemon and geranium can reduce epithelial ACE2 expression [177]. *In silico* study showed that isothymol, an essential oil extracted from an

annual herb of Western Algeria, *Ammoides verticillate* of the *Apiaceae* family has high binding energy and thus may block ACE2 interfering with the entry of SARS-CoV-2 [178]. Several compounds in the form of essential oils isolated from medicinal plants like basil, cinnamon, thyme, clove contain monoterpenes, terpenoid phenols which can be targeted against Spike S glycoprotein of SARS-CoV-2. Cinnamaldehyde, cinnamyl acetate, these two phenyl terpenoids have been found to show high chemical reactivity with a molecular dipole moment of 4.53 Debye and lower electronegativity of -4.34 that signifies its capability of inhibition [179]. Resveratol found in grape skin along with piceatannol found in berries, grapes are stilbenoids which are a class of phenolic compounds found in grape skin formed a stable complex with the amino acid residues of the S protein ACE2 Receptor complex via hydrophobic, hydrogen and ionic interactions [180, 181]. Taraxerol, Friedlin, Stigmasterol isolated from a perennial herb *Clerodendrum spp.* have high binding capacity with the amino acid residues of the SARS-CoV-2 spike protein. Friedlin interacts with Lys 444, Tyr 449 and Asn 450 while Stigmasterol with Tyr 449 and Phe 490. These compounds can be employed to target the spike protein and inhibit its further interaction with the ACE2 receptor [182]. An unbiased molecular docking study finds potential heparin-binding profiles on coronavirus spike glycoproteins, suggesting the possibility of SARS-CoV-2 interventions through the use of heparins.

Microbial metabolites and compounds from Marine microorganisms targeted against SARS-CoV-2

Recent *in silico* molecular interaction studies have revealed cyanobacterial metabolites like deoxycylindrospermin isolated from *Cylindrospermopsis* interacted with the residues of the main protease 3Clpro/Mpro through hydrophobic and hydrogen bond interactions. Cylindrospermopsin, and eucapsitrione from *Eucapsis sp*. reacts with the Plpro protein [183]. Sulphated polysaccharides from marine microorganisms like sea cucumber *Stichopus japonicus* and Fucoidan from brown algae can have an excellent inhibitory effect on SARS-CoV-2 [184]. Recent reports revealed a T3 terpenoid isolated from marine sponge *Cacospongia mycofinensis* inhibits the action of Mpro via hydrogen bond interactions [185].

Microbial dysbiosis is a common predicament in patients contracted COVID-19 with declining gut bacteria like *Lactobacilli* and *Bifedobacterium* as SARS-CoV-2 disrupts largely the gastrointestinal system where the ACE2 receptor is expressed. Thus treating patients with *Lactobacilli casei* and *Bifedobacterium* can be a suitable way as they are seen to enhance inflammatory signals and promote heightened phagocytosis and increase levels of interferons and immunoglobulins like IgA [186]. A molecular dynamics simulation study predicts an interaction between the secondary fungal metabolite Pyranonigrin A and Mpro, thus proposing this metabolite to have an effective potentiality against the SARS-CoV-2 virus [187].

11. Conclusion

This review entails the factors that lead to severity associated with COVID-19. Coronaviruses can cause a range of manifestations in different individuals – from being asymptomatic, to milder versions, and even resulting in catastrophic symptoms that ultimately leads to the death of an individual. This review explains these fine margins, thus explaining each factor's mechanisms, and how each factor contributes to the severity. Also, this helps to understand which individuals are more prone to infection. Every individual carrying a certain level of these predispositions should be more cautious and should take every step to protect themselves from being exposed to this disease.

12. Declarations

12.1. Author Contributions

Conceptualization, B.G. and S.S.; writing—original draft preparation, B.G. and S.S.; writing—review and editing, N.S., K.D., S.D. and S.G.D. All authors have read and agreed to the published version of the manuscript.

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12.4. Ethical Approval

This review contains no experiments on humans and animals, so ethical approval not required.

12.5. Data Availability Statement

Data sharing is not applicable to this article.

12.6. Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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