Mini Review

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): Why is it so lethal?

Abstract

COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been the most dreadful mass public health threat for more than a year. An array of clinical trials with repurposed and repositioned drugs as well as with the candidate vaccines are being conducted with the aim of mitigation of COVID-19. While a few antiviral drugs and several candidate vaccines showed satisfactory results in the clinical trials, the side effects after vaccination and the evolution of new SARS-CoV-2 variants appear as a major challenge for the scientists. Present review focused on the possible reasons behind the lethality of SARS-CoV-2.

Keywords: COVID-19 pandemic, severe acute respiratory syndrome coronavirus (SARS-CoV-2), antiviral drugs; vaccines, SARS-CoV-2 variants, lethality

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Introduction

The rise and re-emerging of new historical virulent strains of respiratory viruses from animals have put human health to a significant danger.[1,2] At a time when we edit the human genome, breed test tubes, and try to cure aging, the recent pandemic outbreak has put everything to halt. Coronaviruses (CoVs) are known to be enveloped, non-segmented, positive-sense RNA viruses which are further grouped into alpha (α), beta (β), gamma (γ), and delta (δ) genera; of which the β-CoVs comprise the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing the current COVID-19 pandemic, the SARS-CoV-1 causing the epidemic in 2002; and the Middle East respiratory syndrome coronavirus (MERS-CoV) causing the endemic in 2012.[1,2] In the last of December 2019, the latest human coronavirus, SARS-CoV-2 emerged in the Wuhan city of China, and the transmission occurred very quickly all over the world causing 2,644,461 deaths out of 119,222,995 infected cases so far.[3] While the world initially (at the beginning of 2020) ignored and underestimated the dreadfulness of the virus, it slowly schemed the death of thousands of people across the globe.

The structural features together with the genomic organization of SARS-CoV-2 has been well described in the earlier reports.[2,4,5] Briefly, this RNA virus mainly possesses the spike (S) proteins as the major virulence factor which are heavily N-linked glycosylated; the membrane (M) proteins impart the viral shape and bind to the nucleocapsid which constitutes the nucleocapsid (N) protein; the envelope (E) proteins promote the assembly and release of the newly synthesized virus particles.[2] The hemagglutinin esterase (HE) proteins bind to the sialic acid that is present on the surface glycoproteins; and they also have the acyl-esterase activity that is required during the S protein-mediated cell entry.[2,5] Upon the detailed study on the coronavirus genome in relation to its pathogenesis potential, the biggest question has arisen that what made the SARS-CoV-2 so lethal?

Indeed, the answer has been given by a lots of research groups mainly focusing on the evasive strategy of the host immune system by SARS-CoV-2 as well as the generation of mutated strains (principally the mutations in the spike protein of the virus).[2,4,6,7] Besides the use of repurposed drugs and immunomodulatory agents, the world population has already under the process of administration of COVID-19 vaccines.[5,8,9] The clinical severity of SARS-CoV-2 is mainly brought by the upregulation of interleukins IL-2, IL-7, IL-10, IL-17, elevation of the other inflammatory cytokines IL-6, IL-8, IL-1β and the anti-viral cytokines TNF-α, interferon (IFN)-β and IP-10, the chemokines CXCL10, CCL2, CCL3, and CCL5 as well as high leucocyte count, C- reactive protein level, the D-dimer level and the high expression of granulocyte colony stimulating factors (G-CSF), macrophage inflammatory protein (MCP)-1-α, and tumor necrosis factor (TNF)-α causing the cytokine storm thereby leading to the onset of acute respiratory distress (ARDS) and the major organ malfunction.[2] While a huge study on SARS-CoV-2 have been reported regarding the coronavirus life cycles, the viral pathogenesis/ dodging the host protective immunity and the related immunopathology, transmission dynamics, diagnosis, designing suitable drugs and the implementation of vaccines together with the clinical trials, the current mini-review will attempt to focus on the possible reasons of the increased virulence traits of the SARS-CoV-2.

How does the SARS-CoV-2 appear to be lethal against host protective immunity?

As the SARS-CoV-2 enters the respiratory tract, a coordinated network between the airway epithelial cells, alveolar resident macrophages and dendritic cells, naive lymphocytes, the toll-like receptors (TLRs) 3, 7, 8; and the pathogen-associated molecular patterns (PAMPs) by the pattern recognition receptors (PRRs) takes place to generate an anti-viral state.[5] According to the previously published reports, the spike protein of the SARS-CoV-2 binds to the host angiotensin-converting enzyme 2 (ACE 2) receptor which instigates the plasma membrane-associated type II transmembrane serine protease (TMPRSS2) to boost the spike protein to accelerate the membrane fusion required for the release of the viral RNA; and subsequently, the viral pathogenesis starts.[1,2,10] As reported earlier, avoidance of the host protective innate and adaptive immunity appears to be the main tactic to facilitate the viral pathogenesis.[1,4,11,12]

Specifically, the protective innate immunity has been reported to be escaped in case of high lymphopenia the natural killer (NK) cells as well as rushing of monocytes and macrophages towards to the infected site resulting a hyperinflammatory state.[1] The antigen presenting cells like macrophages or the dendritic cells (DCs) could be ineffective

in coordination with the MHC class I and II molecules which in turn result in T cell response and hence hindering the T cell- B ell interaction required for the appropriate antibody production.[2-5] This is to be noted that the avoidance of NK-cell mediated immunity triggers the viral spread among lungs and other major organs.[2,12] The viral RNA adapts the strategy of circumventing the innate immune cells employing the cap-snatching mechanism which in turn helps them to be recognized by the host translational machineries.[2,13] Besides, the 2'-O methylation of the viral cap-structures by the non-structural protein nsp16 also helps to escape recognition by the immune sensor melanoma differentiation-associated protein 5 (MDA5).[2] This is also interesting to note that the N protein may play a role in reducing viral mRNA degradation.[2]

How about the efficiency of the antiviral drugs and immunomodulatory agents/ vaccines against SARS-CoV-2?

Among various repurposed and repositioned drugs, so far chloroquine/hydroxychloroquine (both antiviral and immunomodulatory agent), remedisivir (a prodrug of adenosine analogue hindering the viral RNA-dependent RNA polymerase), ribavirin, favipiravir (an RNA-dependent RNA polymerase inhibitor), cepharanthine, lopinavir/ritonavir **(**protease inhibitor which can play as the key enzyme in controlling the coronavirus replication**),** opinavir/ritonavir, arbidol (an indole derivative which has been approved in China and Russia as the antiviral against influenza A and B) ostalmovir (**n**euraminidase inhibitor possessing activity against influenzas viruses) and even dexamethasone (immunomodulatory agent) has been found to be effective against SARS-CoV-2 to some extent.[5,8,14] However, the clinical consequences are often not reliable especially in case of lopinavir/ritonavir, ostalmovir and arbidol; and even with ribavirin (causing hemolysis and bradycardia) while only the short-term therapy has been noticed to be useful for remdesivir and favipiravir.[14] Indeed, the majority of the antiviral drugs has been found with the adverse outcome among the COVID-19 patients as revealed from the randomized controlled trials (RCT) and lots of case reports.[14]

Besides antivirals, several vaccines are currently under the Phase III clinical trials: especially AZD1222 (ChAdOx1nCoV19, working against the viral spike protein), developed by University of Oxford & AstraZeneca; mRNA-1273 working against the viral spike protein (Moderna); CoronaVac (PiCoVacc), working against the recptor binding domain or RBD) developed by Sinopharm/Sinovac Biotechat; Sputinik V (working against the viral spike protein), developed by Gamaleya Research Institute of Epidemiology and Microbiology; and BNT162b2 working mainly against the non-structural protein nsp5 (BioNTech/Pfizer).[9,15] Currently mRNA-1273 (Moderna), BNT162b2 (BioNTech/Pfizer), ChAdOx1/AZD1222 (Oxford/AstraZeneca), JNJ-78436735/ Ad26.COV2.S (Johnson&Johnson), Sputnik/ Gam-Covid-Vac (Gamaleya), NVX-CoV2373 (Novavax), BBIBP-CorV (Sinopharm), CoronaVac (SinoVac), and BB152/ Covaxin (Bharat Biotech) vaccines are being administered worldwide.[15–18] However, along with the side effects generated by the vaccines, it is important to ponder how long the protection lasts by the vaccination as well as to what extent the viral transmission dynamics reduces.[15,17] The host immunity induced by the vaccination may be diminished along time which is really dreadful for the mass public health. Such type of lethality may also come from the occurrence of mutations generating new SARS-CoV-2 variants.[15]

SARS-CoV-2 variants

According to Santos (2021), more than 245,000 SARS-CoV-2 genomic sequences are currently available which have been collected since December 2019.[15] At the start of the COVID-19 pandemic, only L type and S type variants were identified on the basis of the differences in two single nucleotide polymorphisms within the open reading frame ORF1ab and ORF8 which was further classified as A, B and C (based on the amino acid changes) when more genomes of SARS-CoV-2 were analyzed.[15,19,20] Afterward, more new genome sequences generated newer clades named as V, G, GR, GH, T and O.[15] A major example of the mutation increasing the viral lethality may be the D614G mutation (shift from the original D614 form to the G614 variant) that is known to replace the amino acid glycine in the spike protein of the virus, resulting in the interference within the binding affinity of SARS-CoV-2 to the host cell receptor angiotensin-converting enzyme 2 (ACE2).[15,21] Such mutation may accelerate the transmissibility of the strains[21]

Conclusion

The results of the randomized clinical trials of the candidate drugs and vaccines apparently seem to be effective against SARS-CoV-2; however, in course of long-term immunity scientists need to put more emphasis on the trials as well as on the mode of action of the candidate drugs and vaccines. SARS-CoV-2 lethality may be augmented through the emerging variants due to the mutations especially of the spike proteins. Therefore, continued genomic analysis of all the variants are required.

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Conflicts of interest

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