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Pathophysiology Manifestations of SARS-CoV-2: A Comprehensive Review

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Abstract

Coronaviruses (CoVs) are wrapped up positive-sense RNA viruses, classified by Club -like spikes that stretch across the surface and follow exceptionally large RNA genomes and unique amplification mechanisms. The diseases caused by coronaviruses in animals and birds range from potentially fatal respiratory infections in humans to enteritis in pigs, cattle, and poultry with upper respiratory illnesses. Here, we provide a short overview of viruses, including their morphology, categorization, mechanisms of replication, and pathogenicity, particularly in humans, as well as the most recent approaches to COVID-19 prevention and therapy. We have presented the pandemic virus relationships with pathophysiological human conditions like blood group cases and age group mortality, the effect on men's fertility and obstetricians in pregnant women, and also address the outbreaks greatly pathogenic SARS-CoV ("Severe Acute Respiratory Syndrome Coronavirus") & MERS-CoV ("Middle East Respiratory Syndrome") recently reported. The novel coronavirus disease (COVID-19) is a pandemic cause for the whole world so its scientific data or information will be beneficial for the research and development in the recent scenario as well as for future perspective.

Keywords

Characteristic; COVID-19; Human Pathophysiological conditions; life cycle, Blood group; Age; pregnancy in women.

Introduction

More than 25 countries around the world have been infected with a novel coronavirus termed COVID-19, which had been 1st identified in the city Wuhan of China. As of 1st, March 2020, 79968 infected patients in China alone and 7169 tests outside China were positive for COVID-19 (1). Coronaviruses are enclosed, non-segmented, positive RNA viruses that are common in other animals and humans. They are members of the Coronaviridae family and the Nidovirales order. Despite the fact that the majority of human coronavirus infections are moderate, there have been two epidemics of beta coronaviruses in North East Asia. These outbreaks have been identified as SARCoV & MERS CoV (2-4). This has resulted in over 10,000 cases collectively in the last 20 years, with fatality rates of 10% for SARS-CoV & 37% for MERS-CoV (5). Wuhan, Hubei province, China, became the center of an outbreak of unknown pneumonia in December 2019, which raised significant interest not only in China but Chinese health authorities launched an urgent investigation to identify and manage the disease, including isolating people suspected of having the disease, closely tracking contacts, gathering patient epidemiological and clinical

data, and establishing diagnostic and treatment (6). On Jan 7, 2020, a novel coronavirus (CoV) had been isolated from patients in Wuhan by Chinese scientists. The genetic makeup of the 2019 novel coronavirus (2019-nCoV) enabled the quick creation of RT-PCR real-time point-of-care testing methods that are unique to the 2019-nCoV (based on entire genome sequence data on the platform of the Global Initiative on Sharing All Influenza Information. The 2019-nCoV cases are no longer limited to Wuhan. The average time for incubation is estimated to be 14 days(7) while the median time for symptoms onset to admission to the intensive care unit (ICU) is about 10 days. The WHO has revealed that the interval between the beginning of symptoms and death varied from around 2 weeks to 8 weeks (8-11).

Materials and methods

In this present review work, the clinical characteristic of the present pandemic virus-COVID-19 was elaborated with emphasis on the pathophysiological conditions of human begins main blood group, age, and mortality, effect on men's fertility and obstetricians in pregnant women. The data highlighted in this short review were included from world-reputed open sources such as the WHO COVID-19 database, Pubmed, Elsevier, and Science Direct.

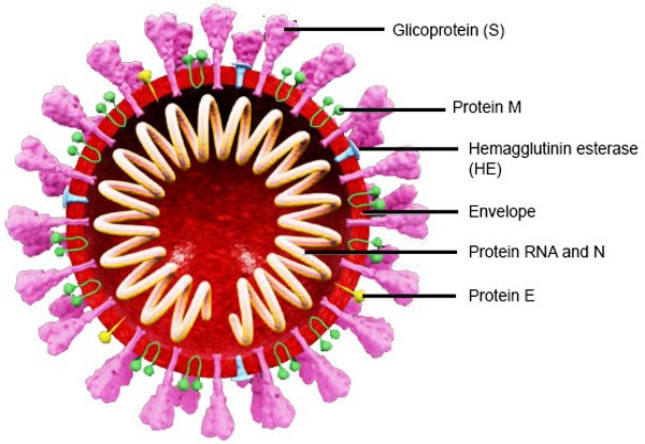

Fig-1: Morphology of Corona Virus

CATEGORIZATION:

Coronaviruses, often known as CoVs, common type of virus in the order Nidovirales, that also involves the families Arteriviridae, Roniviridae, and Coronaviridae. The Coronavirinae family can be further classified into four different forms of coronaviruses, which are referred to as delta, gamma, beta, and alpha viruses. The viruses have been first classified into these groups on the basis of their serology, however, they are now separated into their own phylogenetic clusters (12).

GENOMIC SEQUENCING:

As was said before, the genome of a coronavirus is approximately 30 kilobases in length and is composed of non-segmented, positive-sense RNA. The virus genome is made up of a structures-5' cap and a 3' poly(A) tail, both of that have the potential to perform the role of an mRNA polyprotein replicase conversion.

In contrast to the accessory and structural proteins, which each takes up the only 10 kilobytes of storage in the genome, the replicase gene, that codes for the NSPs (Non-Structural Proteins), consumes 2/3 of the viral genome. This is because NSPs do not form part of the viral structure. Both the core sequence and the untranslated region, also known as the UTR, may be found at the 5' end of the genome. The UTR is comprised of a number of stem-loop structures that are necessary for the transcription of the RNA. Also, sequences for the transcriptional regulatory, also known as TRSs, can be found in the initial stage of each gene. These sequences are required for the expression of every structural gene and accessory gene.

VIRUS MORPHOLOGY:

Recent research conducted with cryo-electron tomography and cryo-electron microscopy has shown that coronavirus virions have a circular shape and a width of about 125 nanometers. (13-14). The coronavirus is composed of four important structural proteins that compensate for various components. These sections contain the spike-like structures that are “encoded largely within the 3' end of the viral genome. They are the nucleocapsid (N), membrane proteins (M), envelope proteins (E), and spike proteins (S). The S protein, which is approximately 150 kDa in size, employs an N-terminal signal sequence in order to enter the ER.” Additionally, the N-linked highly glycosylate is required for this process. The characteristic spike shape on the surface of the virus is compensated by homotrimers of the coding S protein. A class I hybrid protein that mediates as host receiver obedience is the S trimeric glycoprotein. S is characterized through a host cell furin-like protease, S1 and S2, into 2 distinct polypeptides, although S2 is the more abundant of the two. This occurs in almost all, but not all, coronaviruses. The S-protein board receptor-binding domains are denoted by the letter S1, whereas the stalk of the spike molecules is denoted by the letter S2 (15-17).

GENOME ORGANISATION:

The genome of the SARS-CoV virus has a total of 29,727 nucleotides, with the exception of a 30-nucleotide poly (A) tail, of that 265 and 342 nucleotides, correspondingly, are situated in the 50 & 30-nucleotide untranslated regions. It is anticipated that the human genome would include a total of 14 open reading frames (ORF). The replicase gene is created by two big ORFs that are located at the 50-terminal position, 1a and 1b. These ORFs encode the proteins which are necessary for the synthesis of viral RNA (and probably having another function). The remaining of the 12 ORFs are responsible for encoding the 4 structural proteins known as E, N, M, and S, as well as 8 accessory proteins. These accessory proteins are not thought to be necessary for the growth of tissue, but they may offer a survival benefit to the infected host. Based on unrooted phylogenetic trees, it has been first believed that SARS-CoV would give rise to a new group in the coronavirus genus that would be classified as group 4 (18-19).

LIFE CYCLE:

CELL ATTACHMENT AND PENETRATION:

Connections among the S protein and the carrier that it employs are what allow for the initial attachment for the virion to the host cell. This is how the viruses enters the cell. There is a possibility of variation in the RBD ("Receptor Binding Domain") positions that are found inside the S1 area of a CoV, S protein depends on the virus. Other coronaviruses, such as SARS-CoV, have an S1 C-terminus RBD site, but most of coronaviruses, known as MHV, have an S1 N-terminus RBD location (20-21). The coronavirus's capability to infecting the host cell is mostly determined by the way in which the S-protein of the virus interacts with the receptors of the host cell. This interaction also decides which tissues are prone to infection by the virus. Peptidase is the cellular receptor for a variety of coronaviruses, all of which are distinct from one another. SARS-CoV and HCoV-NL63 utilizing the angiotensin-converting enzyme 2 (ACE 2) as the receptors, MHV enters via CEACAM1, and MERS-CoV combined to DPP 4 (Dipeptidyl-Peptidase 4) have recently been revealed their entry into the cell. Many α-CoV uses APN (Aminopeptidases N) as the receptors. Regardless of whether the receptor is bound, the virus still needs to enter the cytoplasm of the host cell. In general, it is achieved through the "acid-dependent proteolytic cleavage of the S protein through the cathepsin, TMPRR2, or another protease, which is preceded by the fusing of the viral membrane and the cellular membrane. Cleavage" of the S protein happens in 2various places in the S2 region of the protein, having the very 1st cleavage being the one that is required to differentiate between the RBD and the S -protein fusion domains (22).

REPLICATION AND TRANSCRIPTION MECHANISM:

Translation and the assembly of complexes of viral replicas are both involved in viral RNA replication. During the process of viral RNA generation, genomic and subgenomic RNAs are also generated. The functional and accessory genes that are present downstream of replicas of polyproteins are regulated by subgenomic RNAs, which act as mRNAs for those genes. Both of the positive-sense subgenomic RNAs are located 3'-co terminal with the entire viral genome. Both genomic and subgenomic RNAs are formed via intermediates of the negative strand. Because of this, they come together to form a collection of nested RNAs, which is a distinctive characteristic of the process. These negative-strand intermediates are only around one percent as common as their counterparts and consist of both the polyuridylates and anti-leaders. The frequency of these negative-strand intermediates is approximately one percent (23). There are cis-acting variations that playsa significant role in the viral RNS replication. Within the 5' untranslated region of the chromosome, there have been seven stem-loop formations that have the potential to extend into the replicase 1a gene. The 3' UTR has several structural features, including a bulged stem-loop, a pseudoknot, as well as an area of hypervariability. Interestingly, at the 3' end the stem-loop as well as the pseudoknot overlaps, and thus cannot form at the same time. In addition, it has been hypothesized that these arouse structures are responsible for the regulation of alternate stages of RNA creation; however, it is not yet understood precisely which stages are controlled or their particular mode of operation (24-29). It's possible that the most interesting thing about the way coronaviruses replicate is the way in which the member and body TRS segments join throughout the process of subgenomic RNA growth. At first, it was thought that it occurred during the favorable synthesis; however, it is now generally accepted that it takes place during most of the negative-RNA discontinuous extension. In order to follow this pause, the RdRp either needs to continue to lengthen to the next TRS or switches to amplify the leader sequence at the 5' end of the genome-guided by the TRS-

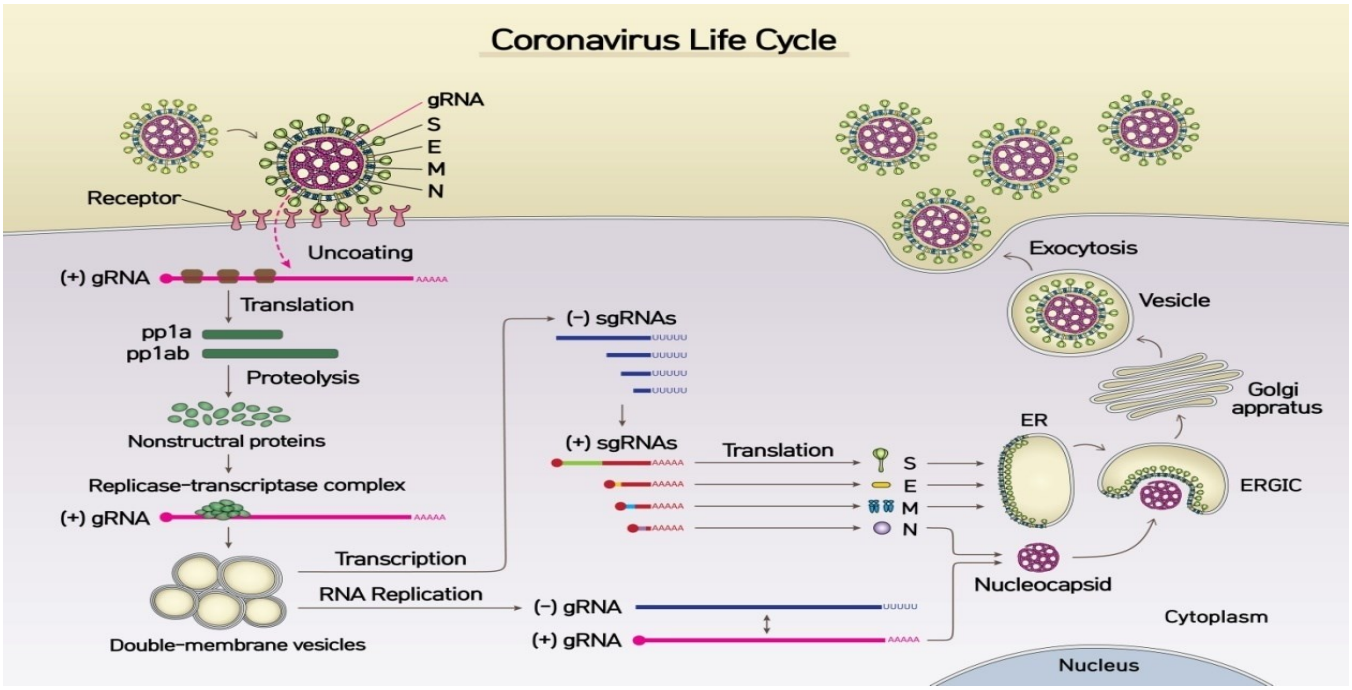

Fig-2: Life cycle of SARS-CoV-2 in the host cell

complementarity to the TRS (TRS-) leader. The current structure illustrates that perhaps the RdRp pauses at any of the TRS sequences of the body (TRS-). This idea is supported by a variety of pieces of data at the moment, one of which is the existence of an anti-leader sequence at the 3' end of subgenomic RNAs in the negative-strand form (30).

ARRANGEMENT AND RELEASE:

After the viral replication process has been finished and the viral subgenomic RNA has been synthesized, the viral structural proteins E, M, and S are translated, and then they are placed into the ER ("Endoplasmic Reticulum"). Through the secretary pathway, these proteins are delivered to the ERGIC ("Endoplasmic Reticulum-Golgi Intermediate Compartment"). During the maturation phase, the viral genomes are enveloped in ERGIC membranes, which also include the viral structural proteins. This maintains the genomes safe from damage. This leads to the creation of fully developed virions (31-33). The M protein is the one that oversees coordinating the great majority of the protein-protein interactions that are required for the assembly of the coronavirus. The production of M protein on its own, however, cannot result in the formation of virus-like particles (VLPs), hence M protein by itself is insufficient for the creation of virions. However, the expression of VLPs only occurs when the M protein is formed in combination with a protein E. This suggests that these given 2 proteins which works altogether to create the envelopes of coronaviruses (34).

The production of VLP is made easier by N-protein, which suggests that the fusion of the encapsulated genomes into the ERGIC improves the virus envelope. At this point, the S protein is already present in the virions; however, it is no longer required for the assembly process. It is essential for the S protein's localization in viral particles that it be able to travel to ERGIC and bind with the M protein (35). Although the protein M is present in the virion in very high quantities, the protein E is only found there in minor amounts. Therefore, it is expected that interactions between M-proteins will serve as the catalyst for the maturation of the envelope. It is not apparent how the E protein helps the M protein in the assembly of the virion; nevertheless, a number of different theories have been presented. It has been demonstrated by some studies that the E protein is responsible for inducing the membrane to bend, while other studies have claimed that the E protein prevents M proteins from aggregating. The E protein can also play a separate role in the promotion of a viral release by changing the pathway of secretory (36-40).

RELATIONSHIP WITH CLINICAL CONDITIONS AND COMPLICATIONS:

BLOOD GROUPS: Blood group A has been related to a greater incidence of COVID-19 than non-A blood groups, while blood group O has been correlated with the significantly infection's lower risk which is relatively to non -O blood groups. The first suggested the report on this occurrence of a connection among blood type ABO and COVID-19 (41).

AGE-WISE MORTALITY:

A recent case analysis, covering 44 cases, recorded 15 (34%) deaths among adults of the age of 85 years, and 20 (46%) among adults of age. The case-fatality rates increased with an individual's age, with no deaths has been recorded in between the people whose age is 19 to the highest percentage of adults aged 85 (42).

EFFECTIVE IN MEN FERTILITY:

Viral orchitis may be caused by viruses such as hepatitis B and C, mumps, HIV, Epstein-Barr, and papilloma, which can also result in testicular tumors and male infertility (43). The pathological investigation reveals leukocyte infiltration, thicker basement membrane, few or no spermatozoa in the seminiferous epithelium, and spermatogenic cell death in all six species. The experiments may be impaired by SARS-CoV-2.Recent research on the infection with SARS-CoV-2 offers insights into impaired male gonadal activity. This study showed that 81 COVID-19 patients experienced a dramatic reduction in the proportion of testosterone to luteinizing hormone (T to LH) compared with 100 healthy counterparts matched by age (COVID-19 patients: 0.74. Serum T to LH proportion is used as a predator of male gonadal path physiology and can be a potential marker of reproductive health impairment associated with SARS-CoV -2 (44). However, in a recent study, COVID-19 time of confirmation, 6 patients (19 percent) showed scrotal discomfort suggestive of viral orchitis. SARS–CoV–2 after a 31-day median (interquartile period, 29-36 days) diagnosis of COVID-19 was not observed in semen. Single-cell transcriptome analysis shows a sparse expression of ACE2 and TMPRSS2, having almost no expression of a gene that overlaps(45). Infection with SARS-CoV-2 is unlikely to have long-term effects on the reproductive system in both men and women (46).

OBSTETRICIANS IN PREGNANT WOMEN:

The risk of spontaneous abortion & preterm delivery during pregnancy is not raised by the presence of coronavirus causes SARS. There is no proof that the coronavirus causing severe acute respiratory syndrome may be transmitted vertically while the infection happens during the 3rd trimester of pregnancy. WHO states that it is exceedingly unusual for delayed umbilical cord clamping to increase the risk of passing infections from the mother to the baby, unless there is a maternal illness. Since osa vernix consists of antimicrobial peptides, we advise keeping it in place for 24 hours after delivery (47-48).

DIAGNOSIS, TREATMENT AND PREVENTION:

By using public health measures, the discovery of cases will guide epidemic expansion and management. In addition, it is essential to diagnose cases of severe veterinary CoV-induced infections including IBV as well as PEDV in order to control these types of viruses & protect the supplies of food . Multiplex RT-PCR assays have emerged as the approach of choice for detecting human COVs. This is due to the fact that these tests can be performed in real-time, are sensitive enough for detecting all 4 respiratory HCoVs, furtherly modified to detect

additional HCoVs. There are actually no anti-viral drugs explicitly aimed at human coronaviruses, so medications are just supportive (49-50). Interferons (IFNs) against coronaviruses are only marginally successful in vitro. It is possible that the combination of IFNs and ribavirin has enhanced the in vitro activity against various CoV when compared to the activity of IFNs alone; nevertheless, the efficiency of this combination in vivo requires more research. IFNs in combination with ribavirin that might have been enhanced the efficacy of in-vitro comparisons with IFNs alone against certain CoV; nevertheless, the efficacy of this in-vivo combination needs better examination (51-52).

There have been many potential SARS CoV vaccines developed (53), but none have received official use approval. These vaccines can take the form of attenuated recombinant viruses, live virus vectors, or particular viral proteins generated by DNA plasmids, among other possible formulations. Antibodies that are therapeutic and neutralize SARS-CoV have been created, and in the event that there is another outbreak of SARS-CoV, these antibodies might be retrieved and utilized again. Such anticorps will be of greatest benefit to protect healthcare workers. In general, live attenuated vaccines are thought to be the most effective to combat coronaviruses. It has been shown in the situation of TGEV where in the 1980s an attenuated version, PRCV, appeared in Europe (54-56). Finally, FIPV has shown that vaccination with S protein contributes to increased illness. As a result of this, numerous vaccine engineering strategies are being implemented in an effort to reduce the chances of recombination occurring. These strategies include the introduction of major deletions in nsp1 or E proteins, the rearrangement of the 3' end of the genome, the modification of the TRS sequences, and the use of mutant viruses that have abnormally high levels of mutation that significantly improve the vaccine's efficacy (57-60).

Conclusion

Future coronavirus studies will continue to look at a variety of elements of viral pathogenesis and replication. In order to predict where and when potential epidemics might occur, it is important to understand these viruses' tendency to switch among organisms, infect a new host, and identify critical coronavirus reservoirs. It would be intriguing to see how bats manage to avoid developing a clinically evident sickness given that they serve as a substantial reservoir for these viruses. Secondly, several of the un-structural and accessory proteins produced by any of these types of viruses remain uncharacterized while having little established features, and it'll be essential to understand reaction pathways for such proteins and to identify their function in viral replication and pathophysiology regarding the blood group and related mortality occurrence in our societies. Recent studies showed the significance of the virus has significantly decreased men's fertility capability and many complications in pregnant women in pre- and post-delivery conditions. Such research will significantly enhance the number of therapeutic targets that are effective in treating illness. Several of the particular coronavirus-produced enzymes, including ADP-ribose-1"-phosphatase, are also found in greater eukaryotes, making it crucial to understand these enzymes in order to comprehend broader concepts in molecular biology and biochemistry.

DECLARATIONS:

Consent for publication:

The cover letter is enclosed for your kind reference.

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Author's contributions

SB, is responsible for the Selection of the topic and guidance for the manuscript writing till the end. S.B. & PLB were involved in the information gathering, design, formatting, and referencing of this review paper as well as communication with the right publication with a solid scientific reputation. S.B. is crucial to how the material is formatted overall.

Compliance with ethical standards

Conflict of interest: Authors do not have any conflict of interests to declare.

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