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COVID-19: REVIEW ON ORIGIN, TRANSMISSION, ETIOLOGY, CLINICAL DIAGNOSIS & TREATMENT STRATEGIES

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Abstract: World has suffered from rapidly spreading Coronavirus disease (COVID-19) caused by SARS-COV2 .This is disease of zoonotic origin is linked to wet animal market in Wuhan City, China. This global pandemic has challenged to human health security worldwide and put the whole world in lockdown mode putting massive load on global economy. Human to human transmission of COVID -19 lead to isolation and quarantine of patients as well as suspected cases. Extensive efforts have been taken by health care providers to protect the population from this Pandemic. In this review we have highlighted some characteristics of, its zoonotic origin, symptoms, transmission and treatment strategies followed for treatment of this fatal disease.

Index Terms - Coronavirus, COVID-19, SARSCoV-2, Wuhan, Pneumonia, Zoonotic disease.

I. INTRODUCTION

Recently in past 2 years most of the countries are landed in severe health emergencies and peoples across the globe are feared due to sudden outbreak of pneumonia like respiratory illness originated from Wuhan city of China in late of December 2019.This outbreak has its epidemiological connections to Huanan Seafood Wholesale market from Hubei province in China. This febrile respiratory illness rapidly spread to other provinces of China and also in several other countries across the world.[1,2]This lead Chinese health authorities to notify World Health Organization (WHO) on 31st December 2019 expressing the possibility that it could cause sever threat to public health.[3] By 11th February 2020 the disease was spread across China and to at least 23 countries in the world with more than 44,000 confirmed cases of COVID-19 and more than 1,100 deaths in China alone. The causative agent of this outbreak was reported to be a novel coronavirus (2019-nCoV) and, since Feb 11, 2020 and the viral pneumonia was named as COVID-19 i.e. "Corona Virus Disease (COVID19)", by World Health Organization (WHO). [4] After phylogenetic and taxonomic analysis of this novel coronavirus the international Committee on Taxonomy of Viruses (ICTV) suggested its name as "SARSCoV-2" [5]

2. CHARACTERISTICS AND PHYLOGENETIC RELATIONSHIP OF 2019 NOVEL CORONAVIRUS:

Coronaviruses belong to the family of Coronaviridae, of the order Nidovirales, and constitutes plus-stranded RNA as their genetic material.[6,7] Human coronaviruses (HCoVs) constitutes most portion of group of coronaviruses (CoVs) and these HCoVs represents one of the most rapidly evolving viruses due to its high genomic nucleotide substitution rates and recombination [8,9]

Based on comparison of sequences of entire viral genomes, the International Committee for Taxonomy of Viruses, further classified these Corona viruses into four main genera, ie. Alpha (α), Beta (β), Gamma (υ) and Delta coronaviruses (δ). These Coronaviruses has varied host range, including avians, swine and humans. Human coronaviruses belongs either the Alpha (α)- or Beta coronaviruses(β). The Alpha coronaviruses constitutes HCoV-229E and HCoV-NL63, and Beta coronaviruses constitutes HCoV-HKU1, SARS-CoV, MERS-CoV and HCoV-OC43. [10, 11] (Table I)

Table 1. Classification of human coronavirus.

Coronavirinae General	Strains	Host	Cellular Receptors	References
Alpha-coronavirus	HCoV-229E	Bats	Amino peptidase N (CD13)	6,7,12
	HCoV-NL63	Palm Civets, Bats	ACE2	12,13
Beta-coronavirus	HCoV-OC43	Cattle	9-O-Acetylated sialic acid	14,15
	HcoV-HKU1	Mice	9-O-Acetylated sialic acid	16,17
	SARS-CoV	Palm Civets, Bats	ACE2	18,19,20
	MERS-CoV	Bats, Camels	DPP4	21

Respiratory system is the first target of Coronaviruses in humans; i.e. Sever Acute Respiratory Syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV). Outbreak which occurred in 2002–2003 and in 2012, was resulted in fatal severe respiratory infections in humans [22–24].These SARS-CoV and MERS-CoV are the members of β-Coronaviruses [25]. According to WHO, these are the most infectious and potent strains of human coronaviruses with 10% mortality rate in SARS-CoV , and 36% mortality rate in MERS HCoV[26–30]. The patients infected viral pneumonia in December 2019 in Wuhan city demonstrated clinical symptoms such as high fever, cough, and myalgia or fatigue the symptoms were also seen with appearance abnormal chest CT Scans. [31-33]. Based on the phylogenetic analysis it has been found that the infectious agent of this viral pneumonia happening in Wuhan also belongs to β-Coronaviruses but are different than SARS-CoV and MERS-CoV and identified as a novel coronavirus (2019-nCOV), another new member in the family of coronaviruses that infect humans. [34] All human coronaviruses (HCoVs) positive- sense single-stranded RNA with length of about 30000 base pairs. The complete virus structure composed basically two types of proteins. Nucleocapsid (N), Matrix (M) ,Spike(S) and Envelope (E) constitutes structural proteins and RNA dependent RNA polymerase (RdRp) (nsp12) constitute nonstructural proteins & is the crucial enzyme in the life cycle of RNA viruses [35]. This 2019-nCoV shares about 70% similarity in nucleotide sequences with SARS- CoV and while that of with MERS-CoV is about 50% and cause more severe respiratory illness and comparatively higher rate of human to human transmission [35-41].

The specific amino acids that changed between SARS and nCoV were found to be ORF1ab locus, and at ORF8 locus. The structural difference in protein of two viruses is due to the mutation in ORF8 resulting in one of its two variants, ORF8-L and ORF8-S, The amino acidic region aa83-aa89 is more likely to be disordered in the ORF8-S isoform [42].The nucleotide sequence similarity between novel coronavirus and bat coronavirus suggests its zoonotic origin. About 96.2% of nucleotide sequence similarity is found in bat coronavirus (BatCoV RaTG13) isolated from the bat *Rhinolophus affinis* from Yunnan Province, China and 2019-nCoV. This finding supports that bat is natural host of nCoV. [43] Possibility of intermediate host other than bat is also expressed due to low sequence similarity in receptor binding motif (RBM) of these two genomes. Examination of several metagenomic databases for sequence similarity to receptor binding motifs closer to nCoV-2019 suggests that coronavirus with host Malayan pangolins (*Manis javanica*) shares a higher sequence identity with nCoV-2019. [44]

3. VIRUS STRUCTURE AND MORPHOLOGY:

Electron microscopic structure of novel coronavirus (SARS-CoV-2) virus reveals that this virus is roughly spherical, measuring 50–200 nanometers in diameter.[45]The four structural proteins forming virion are in the order of spike (S), envelope (E), membrane (M) and nucleocapsid (N).The Spike(S),envelope(E), and membrane(M) proteins forms viral envelope.[46] While the nucleocapsid(N) encloses viral genome of positively sense single stranded RNA of about 30000 base pairs length.[35] The M protein in virion which nothing but the matrix glycoprotein joins the viral nucleocapsid to the envelope.[47] Spike (s) protein is considered to be the most important protein in context with getting entry into the human hosts. This S protein demonstrates metastable confirmations and is trimeric Class I fusion protein. This protein interacts with host and undergoes conformational changes leading to structural rearrangements of its units in order to fuse viral membrane with host cell membrane [48 -49].The S protein exposes its receptor binding domain to receptors on host cells human angiotensin converting enzyme 2 (ACE2).[50] After binding on host cell receptors is eventually destabilized and is shaded and in turn is achieves stable confirmation as a post fusion event.[51]Thus the receptor accessible state of spike protein subunit of novel coronavirus (SARS-CoV-2) is less stable.[52-55] Hence the coronavirus (SARS-CoV-2) spike (S) glycoprotein can is the most important target for diagnostics, development of vaccines, therapeutic antibodies[56]. Other functional proteins of coded by virus are nucleoproteins RNA polymerase, 3-chymotrypsin-like protease, papain-like protease, helicase, glycoprotein, and accessory proteins [57, 58, 59]

4. EPIDEMIOLOGY OF (SARS-COV-2):

4.1 ORIGIN:

The outbreak of this novel coronavirus has its origin in China. In late December 2019, around 4 cases of pneumonia of an unknown etiology were hospitalized in Wuhan. Wuhan is a large city located in central china with population of 11 million people and is known for seafood and wet-animals wholesale market across the world. [60-62] All these clinical cases were epidemiologically linked to this seafood and wet animals wholesale market in Wuhan.[63-64] This linking was identied by local hospitals as surveillance mechanism was already established in 2003 for "pneumonia of unknown etiology "in relation to SARS outbreak.[65] Pneumonia of unknown etiology is defined as an illness without a causative pathogen identified that fulfills the following criteria: fever (≥38°C), radiographic evidence of pneumonia, low or normal white-cell count or low lymphocyte count, and no symptomatic improvement after antimicrobial treatment for 3 to 5 days following standard clinical guidelines.[66] Up to 31st January 2020 the number of cases with similar symptoms fever, malaise, dry cough, shortness of breath, and respiratory distress exponentially increased and the outbreak was reported to spread in 9720 peoples with 213 deaths in China and 106 infected cases and 19 deaths in other

countries.[67] In connection with that on 30th January Public health emergency was declared by World Health Organization. Chinese researchers got success in isolating the cause of viral pneumonia and sequencing its genome .[68] Finally the virus was identified as novel coronavirus and was named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) .World Health Organization named the disease resulting from (SARS-CoV-2) as- coronavirus disease 2019 (COVID-19). By February 27, 2020, there were 78630 cases and 2747 deaths in China, and the COVID-19 was spread to 46 other countries. [69]

On 11th February 2020 the causative virus has been temporarily named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the relevant infected disease has been named as coronavirus disease 2019 (COVID-19) by the World Health Organization respectively. According to the daily report of the World Health Organization, the epidemic of SARS-CoV-2 so far registered 78630 cases and 2747 deaths in China, spread to 46 other countries that reported a total of 3664 cases by February 27, 2020.[69] The ongoing COVID-19 is the third and largest epidemic caused by coronavirus in 21st century and affected human health globally. The number of reported COVID-19 cases exceeded earlier coronavirus outbreaks of Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) .[70-71] Wuhan outbreak of COVID-19 is the best lesson of zoonotic infections and its threat to global health security. Thus in this context studies must be planned for animals' health and researches must be designed for characterization of virome of animals, it's interaction with different hosts and risk posed by these viruses to human health. [72]

4.2 SYMPTOMS:

Based on the epidemiological survey it was noticed that, earlier the symptoms developed in individuals who had the history of close contact with patient suffering from COVID-19 as well as travel history of Wuhan City or Hubei province, China. But at present the disease has developed as global pandemic causing severe threat to human health across the globe. [73] After getting entry into susceptible human host, the incubation period is required for onset of symptoms. In case of SARS-CoV-2 infection, it has been reported that the incubation period depends on age as well as immune system status of an individual. Shorter incubation periods were observed in older patients (age>70-years) compared to younger ones. The average incubation period in COVID-19 approximately 5.2 days (within 14 days). [74]Mostly the symptoms of COVID-19 are nonspecific. Afebrile patients having confirmed SARS-CoV-2 infection were also reported. [75] Since respiratory system is the first target of SARS-CoV-2, after incubation period, the symptoms begins with fever, weakness, dry cough. While in some patients sputum production, headache, haemoptysis, dyspnoea, and lymphopenia are also seen.[76-78] Like SARS and MERS, diarrhoea is often identified in cases of COVID-19 patients.[79] Most of the patients experience shortness of breath(dyspnoea) within 8 days after of SARS-CoV-2 infection.[80] If infection is not controlled disease may lead to development of acute respiratory distress syndrome (ARDS), septic shock, refractory metabolic acidosis and coagulation dysfunction in severe cases.[81] Although symptoms like fever ,dry cough, dyspnea are also associated with other beta coronaviruses infections, SARS-CoV-2 infection manifests some unique symptoms associated with lower airway as well as some upper respiratory tract illness with characteristics symptoms including rhinorrhoea, sneezing, and sore throat.[82 -83]

4.3 TRANSMISSION:

Based on the studies conducted on SARS-CoV-2 isolated from cases in City of Wuhan, China and its higher (96.2%) nucleotide sequence similarity with bat coronavirus, it has been confirmed that the COVID-19 has zoonotic origin.[43]. The studies conducted strongly supported the possibility of human to human transmission of COVID-19 infection.[84-85] The most common route of transmission associated with COVID -19 includes contact transmission (i.e. contact with oral, nasal fluids , mucous membranes of eyes of infected person),droplet inhalation infection(through cough, sneeze)of infected person.[86] Additionally studies conducted have been also reported that Saliva of infected person can also transmit COVID-19 infection directly or indirectly.[87] In studies conducted on women who were infected with coronavirus in third trimester of pregnancy , no evidence of mother to fetus transmission has been reported. However, since all women under study underwent cesarean section, so it remains ambiguous whether mother to fetus transmission occurs during vaginal delivery or not. [88] Although eyes are not the target of COVID-19, but still it has also been reported that eye exposure to infected droplets could also be the effective portal for entry of virus. [89] Contact with asymptomatic person is the potent route of transmission of COVID-19 infection. [90] In medical practices which produces aerosols (like dental practices) airborne spread is the main route of transmission of SARS-CoV-2. Several research articles have reported that many dental processes which produce aerosols and droplets contaminated with virus can transmit same. [91] rRT-PCR testing of 7th day stool samples of infected patients revealed the presence of SARS-CoV-2 in stools. [92] Therefore studies must be carried out to test faecal oral and urinary transmission of virus through patients as well as healthcare workers in order to reduce the risk of transmission to control COVID-19.[93-94]

4.5 DIAGNOSIS:

Information on contact history, development of symptoms associated with COVID-19 and radiographic changes observed makes the diagnosis. Since some of similar symptoms developed other respiratory illness, the COVID-19 infection is confirmed by laboratory diagnosis. The World health Organization (WHO) and CDC have issued guidelines on clinical and epidemiological findings associated with COVID-19 infection. [95] The RT-PCR test is considered as the important test for primary laboratory diagnosis of COVID-19 from nasopharyngeal swab specimens of suspected patients.[96-99] The success and accuracy of test is important in order to evaluate viral kinetics and in COVID-19 patients. If patient is confirmed for COVID-19 then it is transported to designated, isolated from community and treated strategically on the basis of treatment guidelines issued by WHO based on the severity of symptoms. Other than RT-PCR several other diagnostic tests assay RdRP, N, and E genes of the SARS-CoV-2 genome are also developed for rapid detection of SARS-CoV2 associated RNA in respiratory exudates of clinical cases. [100] In addition to above methods several other clinical laboratory diagnostic tests are also recommended in suspected patients. Higher level of

CRP(C-reactive proteins), elevated ESR (erythrocyte sedimentation rate), prolonged prothrombine time, lactate dehydrogenase, serum creatinine, are the key indicators in diagnosis. [101]

4.5 CLINICAL FINDINGS OF THE PATIENTS INFECTED WITH COVID-19:

Although symptoms like fever, dry cough, dyspnea, diarrhoea are also associated SARS-CoV-2 other clinical finds are observed in COVID-19 infected individuals. Lymphopenia, thrombocytopenia was observed is reported in some patients. It has been also reported infected individuals manifests elevated levels of C-reactive proteins. Higher leukocyte numbers, abnormal respiratory findings, and elevated levels of plasma pro-inflammatory cytokines were also observed in clinical cases. [102] Severe pneumonia, acute cardiac injury, and RNAaemia were the significant clinical findings. Significantly high blood levels of cytokines and chemokines were also observed in some sever cases of COVID-19. Elevated levels of alanine aminotransferase, aspartate aminotransferase, creatine kinase and D-dimer were seldom reported in some clinical cases. Elevated levels plasma IL1B, IL1RA, IL7, IL8, IL9, IL10, basic FGF, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1A, MIP1B, PDGF, TNFα, and VEGF were also reported in both ICU patients and non-ICU patients. [103] Radiological findings using CT scan images of lungs of infected individuals demonstrate typical findings. Rapid evolution from focal unilateral to diffuse altered ground glass opacities were reported in cases of COVID-19 viral pneumonia. [104]

4.6 PATHOGENESIS:

As a viral pathogen it is necessary perquisite for any viral pathogen to get entry into host body. Attachment of viral components with some host cell receptor is the key mechanism involved. SARS-CoV-2 infection is initiated by recognition of host cell receptors via spike (S) proteins on viral envelope. Receptors on host cells are considered as the major determinants in host range of virus as well as tissue tropism and pathogenicity. A metallopeptidase - angiotensin-converting enzyme 2 (ACE2) is the main host cell receptors utilized by SARS-CoV during pathogenesis.[105] The spike (S) glycoprotein is recognizes host cell receptors angiotensin-converting enzyme 2 (ACE2) resulting in changes in its confirmation. The changes in confirmation of viral spike glycoprotein induce the fusion of viral and cellular membranes. Thus SARS-CoV-2 requires ACE2-expressing cells for attachment and entry in host and has no affinity for cells lacking ACE2 or cells with other coronavirus receptors, such as amino peptidase N and di peptidyl peptidase [106-107].

5. TREATMENT STRATEGIES FOR COVID-19:

Till date no exact antiviral drug has been found out or vaccine is developed against SARS-CoV-2 infection or potential therapy against COVID-19 in humans is developed. Considering the threat of human to human transmission COVID-19 patients are isolated and treated depending upon severity of infection, age and history of any other disease if present. However WHO and CDC have issued guidelines for treatment and prevention of spread of COVID-19 infection. [108]As a first line of treatment antipyretics and expectorants are prescribed to the patients with symptoms of fever and non-productive cough. [109] Immediate oxygen therapy is administered to patients with respiratory distress, hypoxemia, and shock or severs acute respiratory infection. The recommended level is 5 L/min to reach SpO2 targets of ≥90% in non-pregnant adults and children, and ≥92–95% in pregnant.[110-112]Use of broad spectrum antiviral drugs like nucleoside analogues and viral protease inhibitors are the best option in current situation.[113] It has been reported that antiviral drugs ribavirin, ganciclovir, lopinavir, ritonavir and oseltamivir has been administered to the symptomatic patients of COVID-19 for 3-14 days to prevent appearance of severe respiratory symptoms.[114-115] Some reports also showed that remdesivir and chlroquine are promising drugs for treatment of SARS-CoV-2 infection in vitro.These agents can be used to treat COVID-19 with controlled clinical trials in some patients.[116] From lower mortality rates in clinical cases of Sever Acute Respiratory Syndrome(SARS) use of IFN-α along with lopinavir or ritonavir has been recommended by the National Health Commission of the People's republic of China.[117] A study of Docking experiment performed using the optimized COVID-19 and SARS (PDB ID: 6NUR, chain A) RdRps concluded that, Sofosbuvir, Ribavirin, and Remdisivir can be used against COVID-19 with promising results. The study also recommended that GTP derivatives show promising results as specific inhibitors against COVID-19. [118] However it the need of the hour to identify novel chemotherapeutic agents for effective treatment of COVID-19. Researchers across the world are trying to develop vaccine against this life threatening pandemic. However for prevention of spread of SARS-CoV-2, public awareness measures are taken as most important. Frequent hand washing, use of masks, social distancing, and use of PPE masks are recommended for prevention of spread of virus.

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