Review Article

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Characteristic Features of SARS CoV-2

Shaista Bakhat, Yasmeen Taj

ABSTRACT

Corona-virus arose from China, spread globally and has become a great challenge for health care workers and Governments of several countries. This virus is transmitted predominately through respiratory droplets by symptomatic and asymptomatic carriers. The disease manifests itself with fever, dry cough and shortness of breath, these symptoms may be mild or have fatal outcomes. This virus attaches to the angiotensin converting enzyme (ACE) receptor, in the lung. This assessment, recapitulates the existing awareness of host features and the paths that are activated with HCOV (Human Corona virus) infection highlighting the infection derived stress response, autophagy, apoptosis and natural defense mechanism. The interaction of virulence tactics utilized by HCOV is also reviewed. This virus can be detected in the laboratory with help of reverse transcription polymerase chain reaction (RT-PCR), with up to 50%-69% false negative results. Treatment agenda is supportive therapy including supplemental oxygen, antipyretic, dexamethasone and ventilators.

Key words: Asymptomatic carrier, Corona virus, HCOV, RT-PCR

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INTRODUCTION:

Viral diseases continue to evolve with fatal outcomes. According to WHO[1] in the last twenty years many disasters like severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome corona virus (MERS CoV) have been recorded. In 2019, COVID-19 was first identified in a patient with pneumonia like symptoms from China in the city of Wuhan.[2] Later on cases like these (n=29) were labeled as "pneumonia of unknown etiology" and later known as novel Coronavirus. In month of Feb 2020, WHO declared it as COVID-19, stands for novel coronavirus infection disease-19.[3] Upto March 2020, SARS CoV-2 had amplified 13times and WHO gave it the status of a pandemic. It is named as SARS-CoV because of genetic resemblance with SARS CoV. World over, cases of SARS CoV-2 have multiplied and mortality and morbidity rate is high.[4]

METHODOLOGY:

This review article is searched through PubMed, Google, and Google Scholar engine with several key words related to Covid-19 structure, pathophysiology, prevalence, detection and therapeutic options. Articles were selected from 2001-2021. Searched is done by reviewing 200 original and review articles. Out of it, 100 were short listed.

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STRUCTURE:

Coronavirus belongs to Coronaviridae family in the order of Nidovirales. This virus is spherical single stranded, positive-sense RNA enveloped virus, covered with glycoprotein. The surface is decked with club spike like projections constituted of glucoprotein. These projections have the appearance of a solar corona, hence the name corona virus. Coronaviruses are composed of four structural proteins; Spike (S), membrane (M), envelops (E) and nucleocapsid (N). Spike protein consists of two functional subunits; S1 has a role in attachment with the receptor of the host and S2 causes the fusion of the viral envelops with the cell membrane of the host.SARS-CoV-2 has a protein furin which plays a vital function in replication and pathogenesis. There are four sub-types alpha, beta, gamma and delta with numerous serotypes.[5] The replicase genes of SARS CoV-2encodes two polyproteins, pp1a and pp1ab, these polyproteins are essential for replication and transcription.[6, 7]

REPLICATION CYCLE

Coronavirus replication cycle constitutes fusion and entry into the host cell, genome transcription and replication, translation of structural proteins, assembly, and release of new viral particle.[8] SARS CoV-2 attaches to host receptors ACE2 on epithelial lining cells of bronchial tract and pneumocytes lining the lungs with the help of viral spike (S), which is activated by type 2 trans-membrane serine proteases (TMPRSS2), within the host cell. The virus gains entry through endocytosis or membrane fusion, later it enters the nucleus where it replicates, mRNA, transcribes and new virion particles are made and released by exocytosis.

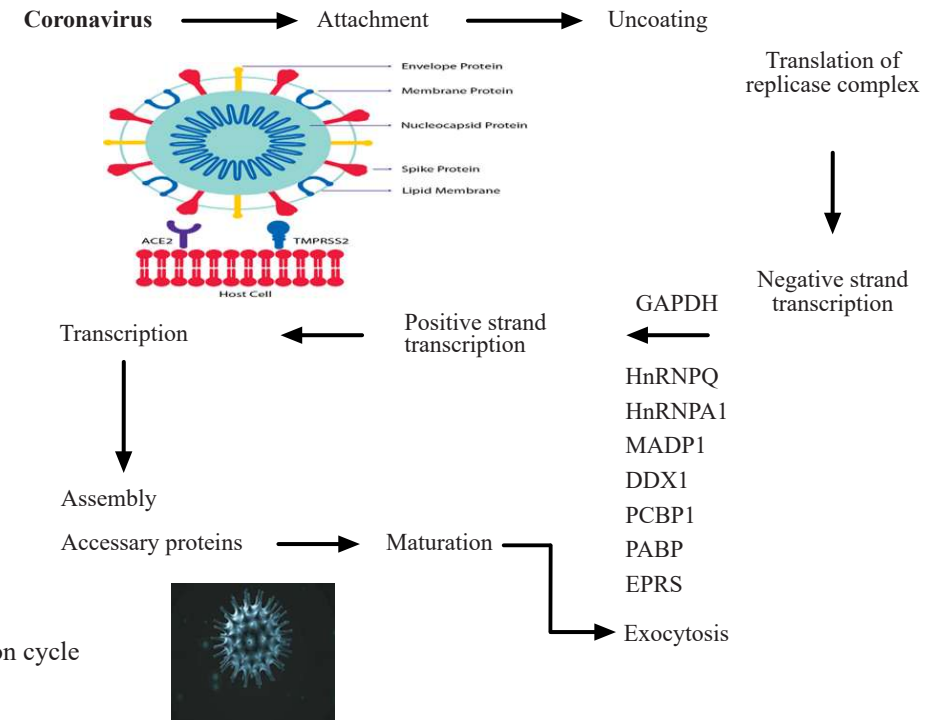

Fig 1: Replication cycle

PATHOPHYSIOLOGY:

According to gene ontology (GO) enrichment analysis, presence of ACE2 receptors on the epithelial cell lining the alveolar cells indicates increased activation of viral multiplication linked genes. These are the regulatory genes for viral life cycle. SARS CoV2 down regulates ACE2 signaling and responsible for inflammation, vasoconstriction and fibrosis. In later stages of infection, this virus can provoke excessive immune reaction, which is known as cytokine storm. The damage to the lung is linked with an inflammatory response and thrombosis in the micro vessels in the lungs. Autopsy studies have demonstrated that alveolar walls are diffusely thickened with mononuclear cells and macrophages infiltration. As a result interstitial mononuclear inflammatory infiltrates and edema occurred. Pulmonary edema along with hyaline membrane formation leads to acute respiratory distress syndrome. In critical cases, fulminant activation of intravascular coagulation takes place, resulting thrombosis in deep veins, embolism in the lungs, and systemic thrombotic response syndrome.[9]

In the universal GenBank researches from all over the world have deposited, analyzed and known to the public several gene sequences of SARS CoV-2.This gene recording is of primary significance in tracing the origin and phylogenetic tree of virus andmost importantly identification of different mutated strains. According to the latest research a mutation in the spike protein occurred in late Nov 2019 prompting it to jump to humans. One study related the pathogenic SARS CoV-2 gene sequence with that of the non-pathogenic SARS CoV. They studied the trans-membrane helical protein in envelop protein and found that location 723has a serine residue instead of glycine residue while the 1010 location has a proline instead of isoleucine. Viral mutate ion is the fundamental key for making it virulent allowing it to cause severe disease relapses.[10]

VARIANTS OF CORONA VIRUS

Scientists have classified coronavirus into 4 sub-groupings, known as alpha, beta, gamma and delta.

a. Alpha—229E, NL63
b. Beta—OC43, HKU1, MERS-CoV, SARS CoV
c. Gamma
d. Delta

Coronavirus variants found in United Kingdom (B.1.1.7), Brazil (P.1) and South Africa (B.1.35 share some mutations with B.1.1.7).[11]

TRANSMISSION

The coronavirus infections most commonly spread via droplets throughout face to face exposure while a person is talking, coughing and sneezing. Contact to a person who has infection within a distance of six feet and a time limit of 15 minutes is also associated with risk of high transmission. Short contact with asymptomatic carriers is less of a risk. Contact touching is also a role.[12] Vertical transmission for maternal SARS CoV-2 is associated with low risk and no maternal deaths or unfavorable neonatal outcomes.[13] The clinical importance of SARS CoV-2 infectivity from nonliving objects depends on the viral load which appears to be high on porous surfaces like stainless steel and plastics.[14]Virus has been isolated from hospital surfaces for up to 3-4days,

Table 1: Events in pandemic of Coronavirus[17, 18]

Dec 2019	Jan 2020	Feb 2020	Mar 2020	April 2020	May 2020	June 2020	July 2020	Aug2020
Dec 31: China informs WHO about cluster cases of pneumonia with unknown etiology	Jan 7:WHO officially announce a new coronavirus named 2019-nCoV	Feb 2: first death of Chinese outside in Philippines	Mar 11: WHO declares it as pandemic	April 1: cases of COVID-19 goes beyond 1 million	May 9: global cases surpasses 4 million	June 29: global cases go above 10 million	July 31: 17106007 reported cases and 668910 deaths globally	Aug 31: 25 million cases and 800000 deaths globally
	Jan 13: in Thailand first confirmed case outside the China	Feb 11: WHO declared it as COVID-19	Mar 16: cases outside china are increased	April 9: cases in Italy more than 132000	May 22: in Brazil 330000 cases			
	Jan 30: WHO proclaims coronavirus a global emergency as coronavirus cases detected in Australia, US, Nepal, Japan, France, Singapore, Malaysia, Taiwan, South Korea and Vietnam.	Feb 14: first case reported in Egypt and f death of first case was reported in France	Mar 18: WHO publicizes the International Solidarity Trial	April 28: cases in US exceeds 1 million with 58000 deaths				

Sep 2020	Oct 2020	Nov 2020	Dec 2020	Jan 2021
Sep 7: 27million reported cases and 900000 deaths globally	Oct 5: 34.8 million morbidity and over 1 million mortality rate globally	Nov 3: 46 million reported cases and 1.2 million mortality rate globally	Dec 1st week: 61.8 million reported cases and 1.4 million deaths globally	Jan 5: 83 million reported cases and over 1.8 million mortality rate globally
Sep 28: 32.7 million reported cases and 991000 deaths globally	Oct 20:over 40 million reported cases and 1.1 million mortality rate globally	Nov 10: 49.7 million reported cases and 0ver 1.2 million mortality rate globally	Dec 22: 75 million reported cases and 1.6 million mortality rate globally	Jan 12: 88 million reported cases and over 1.9 million mortality rate globally
		Nov 17: 53.7 million reported cases and 1.3 million mortality rate globally	Dec 29: 79 million reported cases and over 1.7 million mortality rate globally	

although it can disintegrate within 48-72hours.This emphasizes the need for adequate environmental and hand sanitization strategy.[15] viral particles in the oral and nasal passages attain the significant levels at the time of beginning of symptoms and viral discharge occurs 2-3 days before the onset of symptoms. Although PCR test shows a presence of detectable nucleic acids in throat swabs, six weeks after the commencement of symptoms, reports show that viral cultures do not show any growth a week after onset of symptom. Therefore it can be recommended that infected individuals can be unconfined from quarantine on the improvement of clinical symptoms. CDC (the center for disease control) recommends isolation for at least 10days after onset of symptoms and 3days after improvement of symptoms.[16]

Patients with clinical evidence of SARS CoV-2 may be tested by RT-PCR which is a quantitative test for detection of viral nucleic acid. The samples are obtained from nasopharyngeal swab, sputum and lower respiratory tract aspirates or wash.[20]This is the gold standard method for isolation of viral infections, as it is simple, quick and reliable method. Major disadvantage with the real-time RT-PCR test is the hazard of acquiring false-positive and false-

Table 2: Prevalence of SARS CoV-2 in Pakistan[19]

Feb 2020	March 2020	April 2020	May 2020	Jan 2021
Feb 26: 1st case of Coronavirus detected in student at University of Karachi 2nd case from Federal Territory Both returned from Iran	March 2: 5th case reported from Federal area	April 1: 2291 cases were reported	May 29: 900 children under age of 10 had tested positive	Confirmed cases-519,291 Deaths-10.951 Recovered-473,639
	March 8: 7th case reported in Karachi	April 2: 2450 cases		
	March 10: 1st case in Quetta	April 3: 2708 cases		
	March 11-19: 30-80 in Punjab 23-81 in Baluchistan	April 5: 3000 cases		
	March 20: 1st death was reported in Sindh	April 7: 4005 cases		
	March 22: 3rd death in Khyber Pakhtunkhwa	April 11: 5000 cases		
	March 29: 1526 cases were reported	April 22: 10,000 cases		
	March 30: 1865 cases were reported			

Table 3: Comparison of RT-PCR Test and Ag-RDT[23]

Features	RT-PCR Test	Ag-RDT
Target	Viral RNA	Viral antigens
Specimen type	Nasopharyngeal and oral swabs	Nasopharyngeal swab
Sensitivity	High	Moderate More false negative
Specificity	High	High
Test complexity	Complex	Easy to use
Lab settings	Highly sophisticated lab settings	May be outside conventional lab settings
Cost effectiveness	Expensive	Low cost

negative results. Therefore a result which is negative does not mean that SARS CoV-2is not present and should not be used as the only guide for management and treatment presenting the symptoms. The diagnostic test like real-time RT-PCR and clinical presentations are the guidelines for management of this pandemic.[21]

SARS-CoV-2 can also be assessed by serological testing. These tests can evaluate previous encounter with the virus but are not helpful in making any diagnosis of current infection. Drawback of serology is cross reactivity with other Corona virus. This test is enzyme-linked immunosorbent assay (ELISA)-based and useful in detecting IgM and IgG antibodies in serum, plasma and whole blood. This test was developed by CDC to find out how many people in the US have already been exposed to this virus. This test utilizes SARS-CoV-2 S protein as antigen rather than live virus. This test was designed by the center for vaccine development for research at the institute of National Health. This test has specificity more than 99% and a sensitivity of 96%. CDC utilizes this test for surveillance purpose.[22]

Another serological test used as Rapid antigen testing (Ag-RDT) in which antigen is nucleocapsid protein (N) within the core of SARS-CoV-2.This protein is irregularly expressed in infected cells. The test has specificity of 98.5% and sensitivity of 84.1%. This test does not have disadvantage of cross reactivity and can generate result within 10-30

minutes at low cost.

Ultrasonography also plays an important role in guiding the treatment of patients. LUS (lung ultrasound) helps to evaluate cardiorespiratory failure.[24]

Chest CT scanning in SARS CoV-2 associated pneumonia shows ground-glass opacification and consolidation. Some studies have showed that abnormalities on chest CT scans are usually bilateral with Pleural effusion, pleural thickening, and lymphadenopathy.[25]

Support tests are CBC (complete blood count), C reactive protein, D dimer which is increased in patients with acute venous thromboembolism).[26]

THERAPEUTIC OPTIONS

There are no specific therapeutic options for SARS CoV-2. Physicians deal it with supportive and oxygen therapy.

In acute respiratory distress syndrome, when SpO2 (oxygen saturation) =93-94%, respiratory rate more than 28-30/min, or dyspnea then 40% oxygen should be provided. Patient should be reassessed first within 5-10 minutes then after 6 hours, if there is no improvement; the physician has to go for non-invasive treatment.

HNFO (high nasal flow oxygen) has a great risk of aerosolization, so it should be given within a negative pressure room. In this procedure oxygen is provided 30-40L/min, FiO2 (fraction of inspired oxygen) 50-60%. At this level, if symptoms are still not improved then therapy is switched to NIV (noninvasive ventilation). It is done with positive pressure. It has a vital role in treating SARS CoV-2 associated respiratory failure.[27]It is recommended to put antimicrobial filter at expiratory valve. Ventilation with pressure support begin with positive end expiratory pressure (PEEP) at a pressure of 5 cmH2O examining the easiness, if the patient is comfortable and bring the pressure to 8-10 cmH2O, FiO2 (fraction of expired oxygen) 60%.[28]If there is still marked deterioration, intubation is required. If the patient presents with marked negative intrathoracic pressure to sustain minute ventilation, we use a bag method with a PEEP valve to make a patients ready for ventilation immediately after the intubation process. If this method is to be employed a HEPA (high efficiency particulate air) filter must be positioned between the endotracheal tube and the bag.[29]

Therapeutic guidelines includes the use of systemic corticosteroids for management of acute respiratory distress syndrome (ARDS) due to other etiological reason are not suggested but in severe CARDS (SARS CoV-2 associated acute respiratory distress syndrome) these medications are commonly utilized(e.g., methylprednisolone 1 mg/Kg/day). A current large-scale trial RCT (the RECOVERY trial) confirmed the use of steroid dexamethasone decreases deaths by one-third.[30]

Though antiviral therapy has not been effective against SARS CoV-2, many proposals have been tried like such as the use of antiviral drug lopinavir/ritonavir (400/100 mg which is given by mouth twice a day). But later on, randomized controlled studies also showed no beneficial effects.[31] The remdesivir drug is an inhibitor of RNA polymerase against RNA viruses and effective as recommended preclinical studies.[32]

Chloroquine (500 mg twice a day), and hydroxychloroquine (200 mg twice a day) were also suggested for treating the SARS CoV-2 infection and non-randomized study showed that it has adjuvant activity with macrolide and azithromycin. These drugs can inhibit the entry, uncoating and even entire replication cycle.[33]

An experimental trial in clinics has been commenced in June 11, 2020 for exploring a cocktail of antibody for the management of COVID-19 patients. In this process antibodies were received from recovered person and injected to diseased person.[34]

Patient with SARS CoV-2 also face complications like coagulopathy majorly responsible for pulmonary microvasculature thrombosis and systemic thromboembolism. In this scenario anticoagulopathy as (e.g., enoxaparin 1 mg/kg after every twelve hours) is recommended in non-hemophilic patients.So there is requirement of tailoring the clinical status of each patient.[35]

VACCINATION

a. Pfizer-BioNTech (UK)[36]
b. Johnson and Johnson/Janssen (America)[37]
c. Sinovac[38] (China)
d. Sputnik[39] (Russia)
e. Moderna[40] (America)
f. Covaxin (India)
g. Paksino (Pakistan)

CONCLUSION

As of March 2021, there have been reported 121 million people who have suffered and more than 2.67 million people have died. From a pragmatic point of view studies on HCOV interactivity and linkage is imperative in the possibility of future potential pandemics from occurring and the resurfacing of previously nonpathogenic infections as highly virulent diseases. A better appreciation of HCOV host interactivity will further allow us to pin point essential crucial factors that mastermind the mechanism of infection and institute treatment strategies. Chemotherapeutic options have shown to be less expected to select for drug resistance HCOV types. These along with boosting immunity by a vast scale vaccination campaign may be beneficial in this war. Ultimately such studies on the host and viral factors may be beneficial in extrapolating to other zoonotic diseases making us more aware on policies to prevent the discrimination of these pathogens. DNA mRNA vaccines offer huge advantage over the traditional type of vaccines since they only use genetic code from a pathogen. The hope

that gene based vaccines will one day provide a vaccine for malaria, HIV, cancers or ready to stop next pandemic or no longer fetched.

Authors Contribution:
Shaista Bakhat: Original idea, Literature search, Manuscript write up, data collection, final lay out
Yasmeen Taj: Literature search, critical review, proof reading

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