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Epidemiology of Novel Corona Virus (Covid-19): A Review

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ABSTRACT

Corona virus (COVID-19) is a RNA virus infects the respiratory, hepatic, enteric and neurological systems. The past few decades have seen endemic outbreaks within the Variability of Middle East Respiratory Syndrome coronavirus (MERS-CoV) and Severe Acute Respiratory Syndrome related coronavirus (SARS-CoV). The recent outbreak initially presented as pneumonia of unknown etiology during a cluster of patients in Wuhan, China. The epicenter of infection was linked to *seafood and exotic animal* wholesale markets in that. SARS-CoV-2 is Very highly contagious and has resulted during a rapid pandemic of COVID-19. This review article leads to general overview of coronavirus and describe the clinical features, evaluation, and treatment of COVID-19 patients. It'll also provide a simplest way to extend the awareness among primary and secondary healthcare providers during this pandemic. Furthermore, our review focuses to up-to-date clinical information for the effective management, prevention, and counseling of patients worldwide. In December 2019, several patients from Wuhan, China were admitted with symptoms of pneumonia because the number of patients presenting with similar symptoms began to rise, the causative agent was eventually isolated from samples. It had been initially called the 2019 novel coronavirus (2019-nCoV) and has been recently relabeled as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); the disease it causes has been named coronavirus disease 2019 (COVID-19). There are multiple drug trials occurring with some positive results. However, since no vaccine is present, the simplest method to combat the virus is by preventive methods. In this, we offer a basic understanding of CoV infections and their potentially detrimental involvement to society.

Keyword-- COVID-19, pneumonia, respiratory syndrome, Structure, Virus

BACKGROUND

On February 11, 2020, the World Health Organization (WHO) announced the disease caused by this novel virus as coronavirus disease-2019 (COVID-19). These viruses spread a variety of human and animal host cells, and also do their infection and replication. Also, many proteins have most important role in the replication mechanism, although that role is, as yet, poorly defined. In this case, it is necessary to know the definition of these proteins in terms of this mechanism. This research explains the classification and genome organization of corona viruses so it brief the structure, replication and transcription mechanism from a more biophysical point of view by using molecular modeling methods. This information is predicted to help assist elucidation of the replication and transcription mechanism of the CoV. The repeated emergence and outbreaks of CoVs indicate a public health threat. This implies the chance of animal-to-human and human-to-human transmission of newly emerging CoVs. This change in ecology and climate make future emergence of such infections more likely.

Severe Acute Respiratory Syndrome (SARS):

Severe acute respiratory syndrome (SARS) which had begun the prior year in Asia and secondary cases elsewhere within the world, the WHO stating this coronavirus identified by a variety of laboratories was the causative agent for SARS. The virus was universally named the SARS coron avirus (SARS-CoV).

Middle East Respiratory Syndrome (MERS)

A new type of corona virus was identified, and named Novel Coronavirus in 2012, and named Middle East respiratory syndrome corona virus as (MERS-CoV). The WHO issued a worldwide alert soon after. The WHO update this on 28 September 2012 said the virus didn't seem to pass easily from person to person. But, a case of human-to-human transmission in France on 12 May 2013 was confirmed by the French Ministry of Social Affairs and Health. Additionally, cases of human-to-human transmission were reported by the Ministry of Health in Tunisia. Two confirmed cases involved those people who caught with this disease from their late father, who became ill after a visit in the country of Qatar & Saudi Arabia. Despite this, it appears the virus had trouble spreading from human to human, as most people who are infected don't transmit the virus. By 30 October 2013, there

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have been 124 cases and 52 deaths in the country Saudi Arabia. After this Dutch Erasmus Medical Centre sequenced, the ultimate name of this virus - Human Corona virus–Erasmus Medical Centre (HCoV-EMC). The final name for the virus is Middle East respiratory syndrome corona virus (MERS-CoV). The only 2 United States cases of MERS-CoV infection were recorded in May 2014, both are healthcare workers who worked in the country of Saudi Arabia so travelled to the U.S. One was treated in Florida and one in Indiana. Both were hospitalized temporarily & discharged.

Corona Virus Disease 2019 (COVID-19)

A pneumonia outbreak was reported in Wuhan, China in December 2019. On 31 December 2019, the outbreak was traced to a completely unique strain of coronavirus, which was given the interim name 2019-nCoV by the WHO later renamed SARS-CoV-2 by the International Committee on Taxonomy of Viruses. Some researchers have suggested that the Huanan Seafood Wholesale Market might not be the initial source of viral transmission to humans. As of 28 March 2020, there are an approximate 28,125 confirmed deaths and more than 607,965 confirmed cases in the corona virus pneumonia pandemic. The Wuhan strain has been identified as a new strain of Beta corona virus from group 2B with approximately 71% genetic similarity to the SARS-CoV. The virus features a 96% similarity to beta corona virus, so it is widely suspected to originate from bats moreover. The pandemic has resulted in travel restrictions and nationwide lockdowns in several countries.

INTRODUCTION

Corona virus is a large family of positive-sense; single-stranded RNA viruses belong to the Nidovirales order. The order includes Arteriviridae, Roniviridae and Coronaviridae families. It is enveloped; non-segmented, positive-sense single stranded RNA virus genomes in the size ranging from 26 - 32 kb, the largest known viral RNA genome. The virion has a nucleocapsid composed of genomic RNA and phosphorylated nucleocapsid (N) protein, which is buried inside phospholipid bilayers and covered by two different types of spike proteins: the spike glycoprotein trimmer (S) that can be found in all CoVs, and the hemagglutinin esterase (HE) that exists in some CoVs. The membrane (M) protein (a type III transmembrane glycoprotein) and the envelope (E) protein are located among the S proteins in the virus envelope. CoVs were given their name based on the characteristic crown like appearance. The structure of CoV virion is shown in fig. 1.

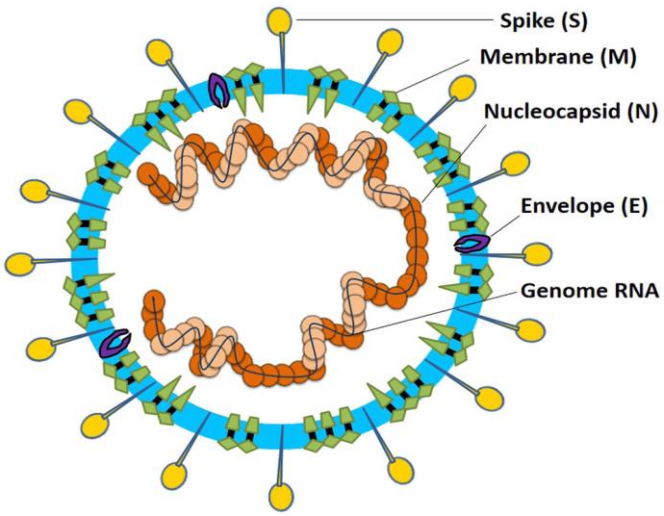

Figure 1: *Coronavirus particle.*

CLASSIFICATION OF CORONAVIRUSES

The Corona viruses has been classified as A) supported genomic organization, B) genomic sequence, C) antigenic properties of viral proteins, D) replication strategies, and E) structural characteristics of virions, cytopathogenic, pathogenic and physic-chemical properties. The Coronaviruses (CoVs) are species of virus belonging to the Nidovirales order, which has Coronaviridae, Arteriviridae, Roniviridae and Mesoniviridae families. The Coronaviridae family is that the largest one in all four families, by its genomic sizes of coronaviridae range from 26 to 32 kb. This virus family subdivided into two subfamilies: 1. coronavirinae 2. torovirinae. It's now divided into four genera, Alpha coronavirus, Beta coronavirus, Gamma coronavirus and Delta coronavirus (fig. 2).

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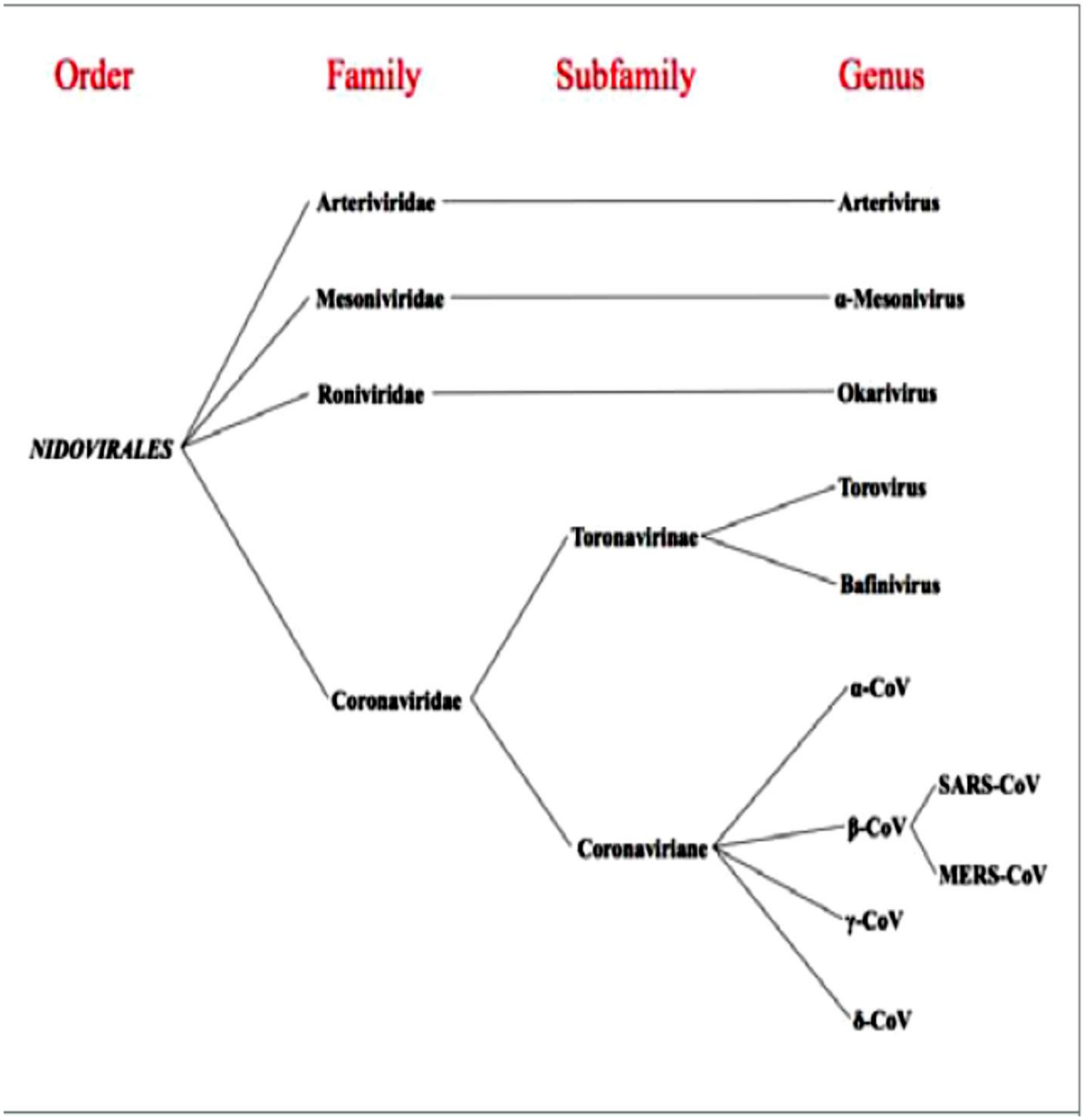

Figure 2: *Classification of Coronaviruses.*

VIRAL LIFE CYCLE

Coronaviruses attach to specific cellular receptors via the spike protein. This triggers a conformational change in spike which then mediates fusion between the viral and cell membranes which ends up within the release of the nucleocapsid into the cell (Fig..3). Upon entry into the cell, the 5′ end of the genome RNA, ORFs 1a and 1b, are translated into pp1a and pp1ab; pp1ab is translated via a frameshift mechanism, which occurs at high frequency (25 to 30%). ORF 1a encodes one or two papain-like proteases (PLpro or PLP) and a picornavirus 3C-like protease (3CLpro), which functions to process pp1a and pp1ab into the mature replicase proteins. Also, encoded within the X domain of ORF 1a may be a (putative) ADP-ribose 1"-phosphatase activity. Encoded in ORF 1b and processed from pp1ab are an RNA-dependent RNA polymerase (RdRp) and a helicase, in addition to other enzymatic activities, including a (putative) 3′-to-5′ exonuclease (ExoN), poly (U)-specific endoribonuclease (XendoU), and (putative) S-adenosylmethionine-dependent ribose 2′-O-methyltranferase. A further putative enzymatic activity, cyclic phosphodiesterase, is encoded downstream in ORF 2a. These multiple enzymatic activities are purported to play roles in metabolism of coronavirus RNA and/or in interfering with host cell processes.

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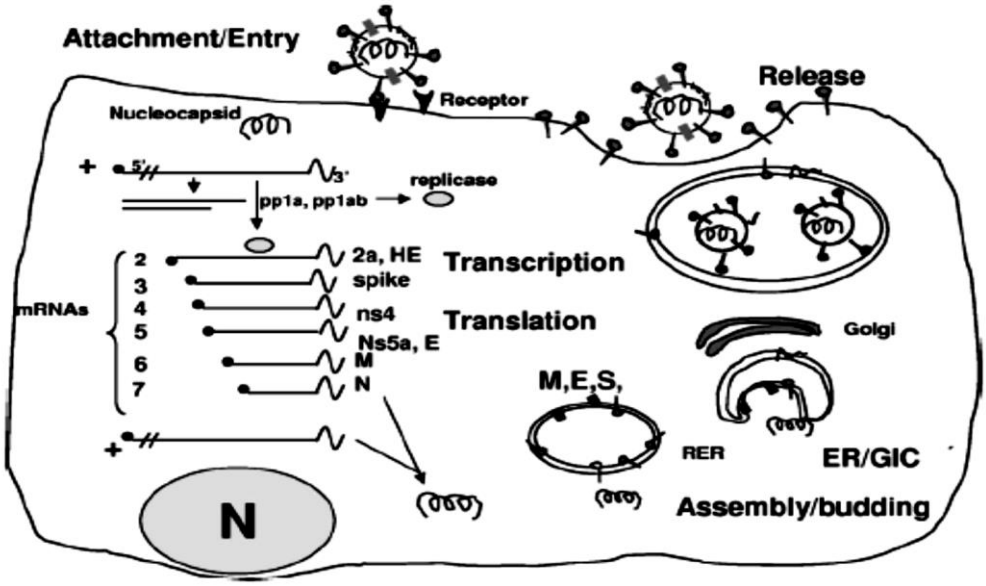

Figure 3: *Model of Coronavirus Replication.*

During infection with coronaviruses, like all other RNA viruses, replication of genome and transcription of mRNAs must occur. Replication of the genome involves the synthesis of a full-length negative-strand RNA that's present at very less concentration and is template for full-length genomic RNA. Multiple (6 in the case of MHV) overlapping 3'coterminal subgenomic RNAs function mRNAs, as does full length genomic RNA. Each mRNA features a common (75- to 78-nucleotide) leader sequence at its 5' end; this leader comes from the 5' end of genome RNA. Additionally, negative-strand RNAs corresponding long to every of the mRNAs because the full genomic length are present at low concentrations. The mechanism by which the group of positive- and negative-strand RNAs is synthesized involves a novel discontinuous transcription mechanism that's not completely understood. However, subgenomic mRNA synthesis is believed to be regulated by transcription-regulating sequences, present within the genome RNA, at the transcriptional start sites for every mRNA. This model is that discontinuous transcription occurs during the synthesis of subgenomic negative- strand RNAs, with the antileader sequences being added onto the 3' ends of negative-strand RNAs which then function templates for synthesis of mRNAs. Viral proteins are translated from individual mRNAs, generally from the 5' ORF only (Fig. 3). The replicase, for instance, is translated from the 5' end of the genomic RNA. In some cases there could be two ORFs carried on and translated from one mRNA. An example of that can be the E protein of MHV, which is translated from a downstream ORF (ORF 5b) on mRNA 5; it's believed that the translation of ORF 5b is mediated by an interior ribosome internal entry site. After translation, the M and E membrane proteins are localized to the Golgi intracellular membranes near, but just beyond, the endoplasmic reticulum Golgi intermediate compartment, which is believed to be the particular site of budding. Thus, additionally to M, other viral and/or cellular factors are probably required to work out the positioning of budding. M and E proteins, expressed within the absence of other viral proteins and viral RNA, is sufficient to supply virus like particles. The spike protein is distributed on intracellular membranes in addition because of the plasma membrane. This protein interacts with the Trans membrane region of the M protein during assembly. In a few viruses, spike mediated cell-to-cell fusion occurs, thus promoting syncytium formation and this viral spread. Nucleocapsid protein formed a complexes with genome RNA, forming a helical structures. The N protein interacts with the M protein and budding into vesicles occurs. Virus is then transported to the cell surface, where it leaves the cell. Interestingly, TGEV and MHV looked as if it would exit epithelial cells from opposite sides. When the 2 viruses are occustomed experimentally infect the identical cells, porcine epithelial cells (expressing MHV receptor), TGEV is released preferentially at the apical membrane, while MHV is released preferentially at the basolateral surface, suggesting that vesicles containing the 2 coronaviruses are targeted differently. This means that the 2 viruses are sorted at the Golgi into different transport vesicles carrying information directing them to different surfaces. The main difference in virus spread found between TGEV and MHV is the site of release. This TGEV causes a localized enteric infection, while MHV spreads to multiple organs.

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Epidemiology

As of March 3, 2020, the WHO has confirmed 87,317 cases worldwide. Of these confirmed cases, 2,977 (3.42%) patients have succumbed to the virus. The majority of cases and deaths have been reported in China. Of the total number of cases, 79,968 (92%) patients have been identified in China. Likewise, the majority of fatalities (2,873 [96.5%]) have also been reported in China. It is important to note that confirmed cases are clinically diagnosed and laboratory-confirmed. Outside China, a total of 7,169 cases have emerged in 59 countries. Due to the ongoing nature of the pandemic, the number of cases and involved countries are expected to vary. Table 1 provides a comparison of the epidemiological characteristics of SARS-CoV, MERS-CoV, and SARS-CoV-2.

Table 1: *Comparison of epidemiological characteristics between SARS-CoV, SARS-CoV-2, and MERS-CoV.*

Features	SARS-CoV-2	SARS-CoV	MERS-CoV
Estimated R0	2.68	2-5	>1
Host of virus	Bats are natural hosts, pangolins are Intermediate hosts, and humans are terminal hosts	Chinese horseshoe bats are natural hosts, masked palm civets are intermediate hosts, and humans are terminal hosts	Bats are natural hosts, dromedary camels are intermediate hosts, and humans are terminal hosts
Transmission mode	Human-to-human through fomites, physical contact, aerosol droplets, nosocomial transmission, zoonotic transmission	Human-to-human through aerosol droplets, opportunistic airborne transmission, nosocomial transmission, fecal-oral transmission, zoonotic transmission	Respiratory transmission, zoonotic transmission, nosocomial transmission, limited human-to-human transmission, aerosol transmission
Incubation period	6.4 days (range: 0-24 days)	4.6 days	5.2 days

SARS-CoV-2: Severe acute respiratory syndrome corona virus 2
SARS-CoV: severe acute respiratory syndrome corona virus
MERS-CoV: Middle East respiratory syndrome corona virus
R0: reproduction number

Immunology

The coronavirus subfamily is genotypically and serologically divided into 4 genera, ie alfa, Beta β, gamma ɣ, and Delta δ corona viruses. The β-corona virus are often further classified into 4 viral lineages, namely A-D. There are nearly 30 recognized CoVs that infect mammals, fowl, humans, and other animals. Human corona virus infections are mainly caused by α- and β-CoVs. CoVs are common human pathogens, and 30% - 60% of the Chinese population is +ve for anti-CoV antibodies. The viral infections are generally associated with upper respiratory tract infections, of which the signs and symptoms commonly include fever, headache, and cough; some patients may have lower respiratory tract infections. In contrast, SARS-CoV and MERS-CoV infections may remain asymptomatic in the early stage until severe pneumonia, dyspnea, renal insufficiency, and even death. Histopathological observations of pulmonary lesions in SARS cases not only show nonspecific inflammatory responses such as edema and inflammatory cell infiltration but also exhibit severe exfoliation of alveolar epithelial cells, damage to alveolar septa alveolar septal widening, and alveolar space infiltration in a distinctly organized manner. Pathologically, inflammation includes degeneration, infiltration, and hyperplasia. This SARS-CoV infection can cause pathological changes, degeneration, infiltration, and hyperplasia. Inflamation response causes due to the damage of the pulmonary interstitial arteriolar walls that plays an important role throughout the course of disease in spites of the pathogenic effect of CoVs.

Although the pathologies of SARS and MERS are not yet fully understood, viral and host factors play a key role in SARS-CoV and MERS CoV infections. During virus infection, host factors trigger an immune response against the virus. However, it should be noted that immunopathogenesis is associated with an immune response out of control, which may result in pulmonary tissue damage, functional impairment, and reduced lung capacity. Chemotactic factors are essential to the immune responses against the virus infections, given their regulatory effect on dilations and positions of leukocytes in the host lungs. Therefore, spectral changes in chemotactic factors may lead to severely maladjusted immune responses. Immune insufficiency or misdirection may increase viral replication and cause tissue damages. In contrast, overactive immune responses may induce immune-pathological conditions.

Transmission

The initial cases were presumably linked to direct exposure to infected animals (animal-to-human transmission) at a seafood market in Wuhan, China. However, clinical cases with diversity in exposure history have emerged. This

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helps further elaborate that human-to-human transmission of the virus is also possible. Therefore, human-to-human transmission is now considered the main form of transmission. Individuals who remain asymptomatic could also transmit the virus. However, the most common source of infection is symptomatic people. Transmission occurs from the spread of respiratory droplets through coughing or sneezing. Data also suggest that close contact between individuals can also result in transmission. This also indicates possible transmission in closed spaces due to elevated aerosol concentrations.

SARS-CoV-2 has a basic reproduction number of 2.2. This suggests that a patient can transmit the infection to two other individuals. Current data suggest that the virus has an incubation period of three to seven days. These findings are based on initial cases. Therefore studies are needed to address transmission dynamics and incubation times.

Definition of contact

A contact could be a one that experienced any body of the subsequent exposures during the two days before and therefore the 14 days after the onset of symptoms of a probable or confirmed case:

1. Face-to-face contact with a probable or confirmed case within 1 meter and for over 15 minutes;
2. Direct Physical contact with a probable or confirmed case.
3. Direct look after a patient with probable or confirmed COVID-19 disease without using proper personal protective equipment1; OR
4. Other situations indicated by their local risk assessments.

Moderate Disease

These patients present with respiratory symptoms of cough, shortness of breath, and tachypnea. However, no signs and symptoms of severe disease are present.

Severe Disease

Patients with severe disease present with severe pneumonia. acute respiratory distress syndrome (ARDS), sepsis, or septic shock. Diagnosis is clinical, and complications can be excluded with the help of radiographic studies. This review include the presence of severe dyspnea, tachypnea (respiratory rate > 30/minute), respiratory distress, $SpO2 \leq 93\%$, $PaO2/FiO2 < 300$, and/or greater than 50% lung infiltrates within one to 2 days. Even in severe disease, fever can be absent or moderate.

In addition, 5% of patients can develop a critical disease with features of respiratory failure, RNAaemia, cardiac injury, septic shock, or multiple organ dysfunction. Data from the Chinese Centers for Disease Control and Prevention (CDC) suggest that the case fatality rate for critical patients is 49%. Patients with preexisting comorbidities have a higher case fatality rate. These comorbidities include diabetes (7.3%), respiratory disease (6.5%), cardiovascular disease (10.5%), hypertension (6%), and oncological complications (5.6%). Patients without comorbidities have a lower case fatality rate (0.9%).

Acute Respiratory Distress Syndrome

The development of ARDS indicates new-onset or worsening respiratory failure. It occurs as a complication within one week of known clinical insult. The values of PaO2/FiO2 are used to distinguish ARDS based on varying degrees of hypoxia. $PaO2/FiO2 \leq 100$ mm Hg is indicative of severe ARDS. PaO2/FiO2 values between 100 mm Hg and 200 mm Hg are diagnostic for moderate ARDS. PaO2/FiO2 values between 200 mmHg and 300 mmHg support the diagnosis of mild ARDS. Levels of AST (aspartate transaminase) and ALT (alanine transaminase) at the time of admission correlate with clinical deterioration to ARDS. Therefore, higher levels at admission result in rapid clinical deterioration to ARDS.

In addition to the above criteria, chest imaging modalities such as chest X-ray, computed tomography (CT) scan, and lung ultrasound can be used to diagnosis. The most frequent finding on CT scan includes ground-glass opacity (86%), consolidation (29%), crazy paving (19%), bilateral disease distribution (76%), and peripheral disease distribution (33%). It is important to note that a chest X-ray has a lower sensitivity (59%) to detect subtle opacities. A CT scan can further detect mediastinal lymphadenopathy, nodules, cystic changes, and pleural effusion. The aforementioned abnormalities might be detectable before the onset of symptoms.

Sepsis and Septic Shock

Patients with COVID-19 and sepsis are deemed the most critical of them all. The accompanying multiorgan dysfunction results as a consequence of dysregulated host response to infection. Signs of organ dysfunction include severe dyspnea, low oxygen saturation, reduced urine output, tachycardia, hypotension, cold extremities, skin mottling, and altered mentation.

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Laboratory evidence of other homeostatic dysregulation includes acidosis, high lactate, hyperbilirubinemia, thrombocytopenia, and evidence of coagulopathy. Patients with septic shock are persistently hypotensive despite volume resuscitation. This may accompany serum lactate level greater than 2 mmol/L.

Diagnosis

The U.S. CDC has developed criteria for persons under investigation (PUI). If a person is deemed a PUI, immediate prevention and infection control measures are undertaken. Epidemiological factors are used to assess the requirement of testing. These include close contact with a laboratory-confirmed patient within 14 days of symptoms or travel history to an infected area within 14 days of symptom onset.

The WHO recommends collecting samples from both the upper and lower respiratory tracts. This can be achieved through expectorated sputum, bronchoalveolar lavage, or endotracheal aspirate. These samples are then assessed for viral RNA using polymerase chain reaction (PCR). If a positive test result is achieved, it is recommended to repeat the test for re-verification purposes. A negative test with a strong clinical suspicion also warrants repeat testing.

Management

As we know isolation of a person is only one of the most effective measures for containment of COVID-19. There are no specific anti-viral medications or vaccines are currently available. Therefore, the treatment of COVID-19 includes symptomatic care and oxygen therapy. Patients with mild infections require early supportive management. This can be achieved with the use of acetaminophen, external cooling, oxygen therapy, nutritional supplements, and anti-bacterial therapy. Critically ill patients require high flow oxygen, extracorporeal membrane oxygenation (ECMO), glucocorticoid therapy, and convalescent plasma. The administration of systemic corticosteroids is not recommended to treat ARDS. Moreover, unnecessary administration of antibiotics should also be avoided. ECMO should be considered in patients with refractory hypoxemia despite undergoing protective ventilation. Patients with respiratory failure may require intubation, mechanical ventilation, high-flow nasal oxygen, or non-invasive ventilation. Treatment of septic shock requires hemodynamic support with the administration of vasopressors. Organ function support is necessary for patients with multiple organ dysfunctions.

Therapeutically, aerosol administration of chloroquine phosphate, alpha-interferon, and lopinavir/ritonavir has been suggested. Other suggested anti-virals include ribavirin and abidor. In Singapore, confirmed cases that were hospitalized were also given the combined antiviral therapy of lopinavir and ritonavir. The use of three or more anti-viral drugs simultaneously is not recommended. Ongoing clinical studies suggest that remdesivir (GS5734) can be used for prophylaxis and therapy. Furthermore, a fusion inhibitor targeting the HR1 domain of spike protein is reported to have the potential to treat COVID-19.

Prevention

Preventive measures must focus on optimizing infection control protocols, self-isolation, and patient isolation during the provision of clinical care. The WHO has advised against close contact with patients, farm animals, and wild animals. Patients and the general public must cover coughs and sneezes to help prevent aerosol transmission. Frequent handwashing with soap and water is also required. As an alternative measure, hand sanitizers can also be used. Immunocompromised individuals are advised to avoid public gatherings. Emergency medicine departments must apply strict hygiene measures for the control of these infections. Healthcare personnel must use personal protective equipment such as gowns, eye protection, N95 masks, FFP3 masks and gloves.

CONCLUSIONS

Human Coronaviruses vary significantly in risk factor. Some can kill quite 30% of those infected (such as MERS-CoV), and a few are relatively harmless, like the respiratory disease. Coronaviruses cause colds with major symptoms, like fever, and sore throat from swollen adenoids, occurring primarily within the winter and early spring seasons. Coronaviruses can cause pneumonia (either direct virus infection or a secondary bacterial pneumonia) and bronchitis (either direct viral bronchitis or a secondary bacterial bronchitis). The much publicized human coronavirus discovered in 2003, SARS-CoV, which causes severe acute respiratory syndrome (SARS), features a unique pathogenesis because it causes both upper and lower tract infections.

Corona viruses are a various family of viruses that interact at multiple levels with components of host cells taking this advantage of a number of the cellular machineries for replication and proliferation. Various are known about the biology of CoVs but more information is required to be told. As an example, many of the nonstructural and accessory proteins encoded by

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these viruses remain uncharacterized with no known function, and it'll be important to spot mechanisms of action for these proteins also defining their role in viral replication and pathogenesis. The COVID-19 pandemic is spreading across the globe at an alarming rate. It has caused more infections and deaths as compared with SARS or MERS. Based on R0 values, it is deemed that SARS-CoV-2 is more infectious than SARS or MERS. Elderly and immune-compromised patients are at the greatest risk of fatality. The rapid spread of disease warrants intense surveillance and isolation protocols to prevent further transmission. No confirmed medication or vaccine has been developed. Current treatment strategies are aimed at symptomatic care and oxygen therapy. Prophylactic vaccination is required for the future prevention of COV-related epidemic or pandemic.

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