SEVERE ACUTE RESPIRATORY SYNDROME (SARAS COVID-2): A COMPREHENSIVE REVIEW

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Abstract. Severe infection is cause by novel strain of coronaviruses this novel strain is related to human infecting SARS coronavirus. Coronaviruses are present in animals and transfer occur from animal (mammals) to human beings. The virus spreads from Wuhan to other Chinese cities, and then to other countries e.g. Canada, Australia, Singapore, Thailand, Japan, Malaysia and Vietnam. This virus contains functional and structural proteins and single stranded positive sense RNA molecule. SARS-Cov-2 attaches to particular receptor ACE2 in human's beings, and has its own RNA polymerase. SARS-Cov-2 genome mutation occur with environmental changes and it's become more harmful in future. The Severe acute respiratory syndrome-Cov-2 is a s.sRNA (positive sense) genome having two lateral unidentified regions, has polyprotein that is coded by a single long ORF and organized in 5' replicate arrangements then constitutional protein such as (S, E, M and N). Coronavirus genome contains 5′ untranslated region with a leader sequence of 5′, ORF 1a/b encoding functional proteins for replication, constitutional proteins with envelope, membranes and nucleoproteins, necessary proteins such as SARS-Cov-2, of 3, 6, 7a, 7b 8 and 9b, and 3′ untranslated region. For treating SARS-Cov-2, FDA approved five drugs that include penciclovir, nafamostat, chloroquine, ribavirin, nitazoxanide and two well-known antiviral drugs, favipiravir (T-705) and Remdesivir (GS5734) evaluated in- vitro for the SARS-Cov-2 clinical isolate for the purpose of checking the antiviral efficiency of these drugs against the virus. To calculate the effectiveness of the drugs on the pathogenicity, infection rate and yield of SARS-Cov-2 standard assay were carried out.
Keywords: *SARS-Cov-2, ACE2, remedsivir, chloroquine, MERS-CoV*

Introduction

On 31 of December in 2019, Wuhan SARS-Cov-2 epidemic occur causing hundreds of deaths in China. Severe infection is cause by novel strain of coronaviruses this novel strain is related to human infecting SARS coronavirus. Coronaviruses are present in animals and transfer occur from animal (mammals) to human beings The virus spreads from Wuhan to other Chinese cities, and then to other countries e.g. Canada, Australia, Singapore, Thailand, Japan, Malaysia and Vietnam. This virus contains functional and structural proteins and single stranded positive sense RNA molecule. SARS-Cov-2 attaches to particular receptor ACE2 in human's beings, and has its own RNA polymerase. Nucleoside analogues can be used for treatment as they prevent virus replication by two processes. Remedsivir is application of nucleoside analogue as it has adenine analogue which incorporate into viral RNA inhibit its replication. Chloroquine drug is also effective as it has both antiviral and immune modulating activity. Worldwide 60,416 cases are reported out of this 1,370 are died and 6,295 are recovered till 13 February 2020. There is a need to provide awareness about disease symptoms, testing and treatment to people. SARS-Cov-2 cases are on the decline, there has been an upsetting increase of the disease in Wuhan and also in another region of World. This

review article reveals that our main concentration on SARS-Cov-2 epidemiology, its genotype, possible cures, immune responses and future perspectives.

Literature review

SARS-Cov-2 is non-segregated enveloped single stranded positive-sense RNA that belongs to the family Coronaviridae that are widely spreader among humans and other mammals (Masters, 2006). in spite of the fact that many human coronavirus inflammations are slight, spread of the two beta coronaviruses, severe acute respiratory coronavirus syndrome (SARS-CoV) and coronavirus respiratory syndrome (MERS-CoV) in the Middle East have resulted in more than 10 thousand collaborative instances having the mortality rate of about 10% in case of severe acute respiratory syndrome (CoV), and 37% for MERS-CoV in the last two decades (Xu et al., 2020). The already identified coronaviruses may only be the head of the black ice, with even more new and hazardous zoonotic diseases to find out (Xu et al., 2020).

On 31 of December in 2019, multiple issues of a non-identified cause of COVID-19 occurred in Wuhan, China, with laboratory exposure closely relating viral pneumonia). Careful sequence studies of the samples from the lower respiratory tract suggested narrative forms of coronavirus called SARS-Cov-2. The inner neighbors are coronaviruses similar to SARS or SARS, including those that infect humans (Woo et al., 2006). Some inner joint neighbors and out-groups have been found as natural hosts in various species, such as bat coronaviruses and HKU3-1 in Rousettus bats & bat coronavirus HKU5-1 (Poon et al., 2005). Therefore, bats being acting as the host of the SARS-Cov-2 would be the authentic and reasonful, perhaps it lefts possible that there were intermediate hosts from bats to humans in the transmission cycle (Poon et al., 2005). The SARS-Cov-2 is quite similar to the groups of SARS coronaviruses in the phylogenetic tree, having bats (coronavirus HKU9-1) as the immediate outgroup (Poon et al., 2005). (Such coronaviruses can share a common ancestor, such as the HKU9-1 bat coronavirus. Nevertheless, repeated recombination events can blur their evolutionary path, as evidenced by patches of high homologous sequences between their genomes.

Materials and Methods

Overall, there is a significant genetic divergence between SARS-Cov-2 and the human-influencing SARS-CoV, even larger distance from MERS-CoV. That discovery opened an paricular case as to regardless SARS-Cov-2 contained the similar procedures as SARS-CoV or MERS-CoV used for humans spreads, or regardless it followed a new, separate transmission route greater than 800 cases of SARS-Cov-2. This infection are counted in Wuhan, including health employers and several cases in many other provinces of china city, and in Thailand, united states, south Korea, and japan (Woo et al., 2006). Coronavirus have been found in large number of animals and can transfer from animal to human via process known as spillover, this may occur due to enlarged contact between animal and human or due to mutation in virus Worldwide 7700 cases are reported over SARS-Cov-2, transmission occurring in people who have not visited china. Till 13 February 2020 China’s National Health Commission has confirmed 1,367 deaths in country caused by SARS-Cov-2.

Results and Discussion

Classification of Coronavirus

Coronavirus are present all over the world, human coronavirus infects human and causes severe respiratory infection and also present in severe species of animal, corona virus spread from animal to human. Three classes of human corona virus are SARS coronavirus, MERS coronavirus and SARS-Cov-2 (Schoeman and Fielding, 2019). In 2012, (MERS) caused severe respiratory and kidney inflammations nearly 90 cases were reported worldwide, it is a beta coronavirus consisting of single stranded positive sense RNA (Xu et al., 2020). In 2003, the outbreak of (SARS CoV) severe acute respiratory syndrome affects 8096 reported cases around the worldwide with 774 deaths (Chu et al., 2020). At Wuhan on 31 of December in 2019 outspread of this narrative type of coronavirus, zoonotic origin and homologous to SARS coronavirus, this strain influences severe respiratory infections and now transferred to other countries of the globe (Corman et al., 2018).

Coronavirus sources

Coronavirus is transmitted from mammals to human beings and then from person to other person transmission, the origin of SARS coronavirus is thought to occur from civet cats to humans and cat has inherited this virus from bats. MERS coronavirus which causes severe respiratory infection research work showed that human got this virus from camels while MERS virus was present in almost camels in Africa, Middle East, and Asia (Chu et al., 2020).

Viral structural and genomic organization

SARS-Cov-2 is a positive sense single stranded RNA enveloped virus with genome of 32kb, spike protein of this virus binds less tightly to human cells receptor ACE2 (Dong et al., 2020). The envelope E protein has application in arrangement and escape of virus and also important for viral disorders (Chen et al., 2020; DeDiego et al., 2007). The proteinacious membrane of SARS-Cov-2 has 3 transmembrane domains, 1st give shape to virion 2nd enhances membrane curvature and 3rd domain bind to nucleocapsid (Chen et al., 2020; Neuman et al., 2011). The N protein of coronavirus has 2 domains both domains binds to viral RNA genome, N protein can also bind to nsp3 protein (Chen et al., 2020). And non-structural proteins nsp1 to nsp16 have described about SARS-Cov-2 and the roles of all proteins are not understood (Chen et al., 2020).

The Severe acute respiratory syndrome -Cov-2 is a s.s RNA (positive sense) genome having two lateral unidentified regions, has polyprotein that is coded by a single long ORF and organized in 5 ' replicate arrangements then constitutional protein such as (S, E, M and N). Coronavirus genome contains 5′ untranslated region with a leader sequence of 5′, ORF 1a/b encoding functional proteins for replication, constitutional proteins with envelope, membranes and nucleoproteins, necessary proteins such as SARS-Cov-2, of 3, 6, 7a, 7b 8 and 9b, and 3′ untranslated region (Neuman et al., 2011). The constitutional proteins, additional proteins and have 2 flanking open reading frames, ORF1a & ORF1b, that are translated into 2 greater poly-proteins, (pp1a and pp1ab), that polyproteins are cleaved into 15 or 16 nsp by multiple viral proteinase activities that are already exist in the viral sequence, nsp proteins form the (RTCs), having an important application in the formation of viral RNA (Cong et al., 2020;

Perlman and Netland, 2009). RTCs, along with conscripted host factors, either uninterruptedly the genome is copied in to a genome-length template or sporadically in to the several templates of sub genome-length (transcription). Such models are used to synthesize new gRNA and sub genomic mRNA molecules, the sgmRNA code for both structural and accessory CoV proteins (Cong et al., 2020).

Viral replication cycle

SARS-Cov-2 binds through its spikes protein to human cell receptor ACE2 and gains entry into cells and binds with human cell ribosome and uses the host machinery to produce two polyproteins, two enzymes one is coronavirus main proteinase and second is papain like protease are used for cleavage of polyprotein into smaller component which are used to express viral genome and it also encode polymerase which are dependent on RNA for replication of viral genome and then S,E,and M protein combine with nucleocapsid form mature virion which are release out of cell by exocytosis.

Epidemiology

Wuhan China

In 2019 on 31 of December, WHO in China was reported about pneumonia in Wuhan city due to some unknown cause and 44 case of pneumonia were reported between 31 of December (2019) to 3rd of January in 2020, on 7 January of 2020 Chinese remote this coronavirus causing pneumonia (Chu et al., 2020). On 13 February 2020, in China total 59,828 cases of SARS-Cov-2 reported from which 1,367 patients died and 6,295 recovered out of these total reported cases 59,828 cases have reported in Wuhan, Hubei 771 patients are in critical stage and 490 deaths have been reported in Wuhan. Other province of china is also affected by SARS- Cov-2 including Guangdong Province 14 cases are reported with no death, Beijing 5 cases are reported all have travel history to Wuhan and in Shanghai one female is affected who traveled to Wuhan on 20 January 2020 (Chu et al., 2020).

United States

On 13 February 2020, CDC reported 427 tested patients for pneumonia among this 15 are observed positive for SARS-Cov-2 and finalited in 7 states of US, 1 case in Washington, 2 in Illinois state,8 in California state, 1 in Arizona, 1 in Massachusetts, 1 in Texas, and 1 in Wisconsin state.

Thailand

CDC tested 116 flights from Wuhan to different cities for Thailand from 3 to 20 January in 2020, 18,383 passengers are screened for respiratory symptoms among these 2 passengers were tested positive for SARS-Cov-2 (Chu et al., 2020). On 13 February 2020, Thailand reported that 33 hardened cases of SARS-Cov-2 cases from this 9 people are recovered and 16 are getting treatment.

Japan

On 13 February 2020, WHO reported 251 confirmed case of SARS-Cov-2 case in Japan but from 20 January 2020 to 5 February 2020, total 45 cases are reported for SARS-Cov-2 in Japan with no death (Cong et al., 2020).

South Korea

In South Korea 23 cases of SARS-Cov-2 are reported and on 5 February 2020 to 13 February 2020, 5 new cases are reported with no death report and among 28 cases 1 is recovered (Khafaie and Rahim, 2020).

Singapore

From 31 December 2019 to 20 January 2020, total 30 cases are reported for SARS-Cov-2 with one death report and on 6 February 2020 two new cases are reported. According to survey, total 58 cases are reported for SARS-Cov-2 in Singapore till 13 February (Rabi et al., 2020).

Australia

According to WHO report 13 confirmed cases are reported till 5 February 2020, out of 13 one patient have travel history to china and there is no death report in Australia due to SARS-Cov-2 (Quilty et al., 2020). According to survey, total 15 cases are reported for SARS-Cov-2 in Australia till 13 February with no deaths.

Philippines

First death due SARS-Cov-2 outside china took place in Philippines, WHO reported total 3 cases with two have travel history to China and with 1 death case (Edrada et al., 2020).

Malaysia

According to WHO report on 13 February 2020, there are 19 confirmed cases of severe acute respiratory syndrome (SARS-Cov-2) with 7 patients having travel history to china and 2 are those who have transmission outside of China (Kwok et al., 2020).

Vietnam

Total 16 cases of SARS-Cov-2 are reported and 3 are recovered on 13 February two new cases are reported (Hoang et al., 2020).

Immune response

Twenty first century is facing a continuous threat from third zoonotic human beta coronavirus as there are no approved drugs for its treatment. This is because the actual mechanism of infection is not known. Infection of coronavirus guides to the initiation and differentiation of T- cells. This ultimately results in the massive production of cytokines for amplified immune response. Scientists have found that S- protein is responsible for coronavirus infection (Xu et al., 2020) as the C terminal RBD domain of S1 unit facilitates the binding of pathogen to the host receptor ACE2 (Xu et al., 2020). Several sequences of RBD domain at positions 442, 472, 479, 487 and 491 responsible for cross specie transmission in SARS CoV-Tor2 and HP03-GZ01 have high homology with Wuhan CoV (SARS- Cov-2**)** (Li et al., 2005). Out of these five only Tyr491 is preserved in Wuhan CoV (SARS-Cov-2**)** (Xu et al., 2020). Upon infection certain cytokines and chemokine's (IL-1, IL-6, IL-8, IL-21, TNF-β, and MCP-1) are released to

combat the inflammation by the production of leukocytes and lymphocytes (Bunte and Beikler, 2019; Dutzan and Abusleme, 2019). The most effective are produced by CD8 T cells (Ng et al., 2016). Entrance of dsRNA of corona is recognized by TLR-3 and TLR-4 which activate the production of proinflammatory cytokines via MyD88- dependent signaling pathway and type I IFNs (Li et al., 2020), essential signaling proteins for the regulation of immune system through a cascaded of (IRFs and NF-KB activation) (Akira et al., 2006). Signaling of TLR-3 can be blocked by some accessory proteins of corona virus which facilitates pathogen entry and replication in host (Li et al., 2020). During replication these proteins bind with the double stranded RNA of CoV to inhibit TLR-3 initiation and help virus escape the immune response.

Treatment of SARS-Cov-2

Yet no particular treatment of this virus is available to cure SARS-Cov-2 diseased persons. Therefore, to combat the disease by identifying the effective antiviral agents is immediate need. So, to find drug against the disease it is better to test the already available drugs to check either these drugs show antiviral property against the SARS-Cov-2 or not (Wang et al., 2020). The SARS-CoV and (MERS-CoV) are also present because SARS-Cov-2 belongs to the Beta coronavirus. Although, some drugs efficiency is controversial number of drugs have been used in individuals with MERS and SARS including corticosteroids, interferon, ribavirin and lopinavir-ritonavir (Zumla et al., 2016).

For treating SARS-Cov-2, FDA approved five drugs that include penciclovir, nafamostat, chloroquine, ribavirin, nitazoxanide and two well-known antiviral drugs, favipiravir (T-705) and Remdesivir (GS5734) evaluated in- vitro for the SARS-Cov-2 clinical isolate. for the purpose of checking the antiviral efficiency of these drugs against the virus. To calculate the effectiveness of the drugs on the pathogenicity, infection rate and yield of SARS-Cov-2 standard assay were carried out. As the result showed that, high concentration of tree nucleoside analogs (ribavirin, penciclovir and favipravir) among the seven tested drugs were required to minimize the viral infection (Wang et al., 2020). In addition, Nafamostat also act as inhibitive against the SARS-Cov-2 and MERS- CoV because this drug prevents membrane attachments.

The hindrance of viral infection at low-micro molar concentration revealed more efficiently by two well-known antiviral drugs such as chloroquine and remdesivir. Recently, Remdesivir has been identified as an encouraging antiviral drug for the treatment of a wide range of RNA viruses (including SARS/MERS-CoV5) in cultivated cell, mice and non-human primate (NHP) models. Currently, it is in under laboratory trials to treat the infection of Ebola virus (Mulangu et al., 2019). Remdesivir is an equivalent adenosine that interferes into emerging chains of viral RNA, results into premature stop (Warren et al., 2016). Remdesivir shows functions at the post virus entry stage. As warren et al. also reported its 100% protection against the infection Ebola virus after the intravenous administration in NHP model (Warren et al., 2016). Remdesivir also showed inhibition of virus infection effectively in human cell line that is vulnerable to SARS-Cov-2 (Wang et al., 2020; Zumla et al., 2016).

A huge-spectrum antiviral drug has been extensively undertaken as auto-immune and anti-malarial drug, which also known as chloroquine (Yan et al., 2013; Savarino et al., 2006). Chloroquine act as antiviral drug and this drug enhanced the endosomal pH that is necessary for cell attachment and block the viral infection. In addition to block the virus infection this drug also interferes with the cellular receptors of SARS- CoV in the

process of glycosylation (Vincent et al., 2005). Like remdesivir, chloroquine also functioned at entry stage as well as post entry stages of SARS-Cov-2 inflammation. In addition to the antiviral capability, this drug also helps in the regulation of immune system activity that may boost its effect in-vivo. After oral administration chloroquine rapidly distribute in the entire body. For last 70 years, chloroquine has been used as drug due to its safe and cheap property. That's why it can potentially use against SARS-Cov-2. According to the reported data chloroquine and remdesivir showed more effective result in vitro against SARS-Cov-2 infection (Wang et al., 2020).

Conclusion

Coronaviruses are present all around and major cause of common cold. First coronavirus was isolated in 1963 caused disease in human, animals like pigs, bats, rats and mice. SARS-Cov-2 outbreak in Wuhan causes hundreds of deaths and also detected in other countries around globe. SARS-Cov-2 cases are on the decline, there has been an upsetting increase of the disease in Wuhan. According to WHO, the mortality rate for SARS-Cov-2 are 2%. Worldwide 60,416 cases are reported out of this 1,370 are died and 6,295 are recovered. There is a no vaccine still to prevent its infection but CDC has recommended that sidestep contact with sick people, use face facemask, should not rub your facial parts sach as nose and mouth when your hands are dirty, try to shelter your cough with tissue paper and use regular household cleaning spray.

After Wuhan outbreak an outstanding progress has been made towards virus discovery, genome, and structure and to discover effective drug against SARS-Cov-2 but still its mechanism of injection is unclear. Yet no specific drug has been discovered. Researcher and doctors are treating this virus by previous drug present for cold and respiratory infections to check if these drugs are effective against this strain of coronavirus. Remedsivir drug was effective against SARS and MERS coronavirus, this drug is effective against wide variety of RNA viruses. Chloroquine and Remedsivir drugs are effective against entry stage of SARS-Cov-2 and showed their efficiency in-Vitro in order to treatment of SARS-Cov-2 but still, clinical therapy remains largely sedative. Researchers are also working to discover something new about its life cycle. Researcher would have to design medicines that control viral entry into host cell and those that inhibit the activity of RNA polymerase of SARS-Cov-2. This is a biggest need to design coronavirus vaccines so that it can be completely eradicated from globe.

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Conflict of interest

There are no conflict of intrest involve any parties in this research study.

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