

A narrative review comparing SARS-CoV-2, SARS-CoV-1 and MERS-CoV highlighting their characteristic features, evolution and clinical outcomes

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ABSTRACT COVID-19 pandemic caused by SARS-CoV-2 created a bio threat situation throughout the world. This article features evolution and clinical outcomes of SARS-CoV-2, SARS-CoV-1 and MERS-CoV. COVID-19 originated in Wuhan, China and resulted in severe morbidity and mortality. Features of SARS are similar to COVID-19. MERS exhibited a relatively milder disease, mainly in Middle East countries. Coronaviruses are large (100 nm) viruses exhibiting a spherical shape with a lipoprotein envelope and can cause diseases in animals and humans. All coronaviruses are sensitive to physicochemical agents. They attach to angiotensin Converting Enzyme -2 (ACE-2) and serine protease receptors of lungs. Literature review and genetic homology were conducted using data sources and bioinformatics tools for the comparison of SARS-CoV-2 with SARS-CoV-1 and MERS-CoV. Genome analysis between SARS-CoV-2 with SARS-CoV-1 and MERS-CoV revealed that SARS-CoV-2 and SARS-CoV-1 are 95% related with each other whereas SARS-CoV-2 and MERS-CoV are 65% related. SARS-CoV-2 and SARS-CoV-1 are genetically more related than MERS-CoV. Animal reservoirs for SARS-CoV-2 and SARS-CoV-1 may be bats, pangolins, etc. MERS can be transmitted from infected camels. SARS-CoV-2 might have evolved from SARS-CoV-1 or from another animal reservoir coronavirus. It can be transmitted from infected animals and humans through respiratory route. Strict public health measures such as physical distancing and maintaining good hygiene should be taken to contain their community spread. SARS-CoV-2 can undergo antigenic variation resulting in difficulty to develop drugs and vaccines. COVID-19 has caused a severe blow to the economy of both developed and developing nations.

KEYWORDS COVID-19, SARS-CoV-2, SARS-CoV-1, MERS-CoV, Coronaviruses

Coronavirus disease – 2019 (COVID-19) is caused by a coronavirus called, severe acute respiratory syndrome – coronavirus -2 (SARS-CoV-2) (Kannan et al., 2020). SARS-CoV-2 belongs to a diverse group of beta coronaviruses. COVID-19 was first reported in Wuhan, Hubei Province, China in the end of December 2019 (Li et al., 2020). It was stated that the virus outbreak occurred after contact with slaughtered or living animals in a wet market in Wuhan (Nishiura et al., 2020).

Afterwards, it resulted in rapid community spread in Wuhan and adjoining places (Ralph et al., 2020). Within two months COVID-19 has spread to several countries around the world.

The World Health Organization (WHO) declared this disease as a pandemic on March 11, 2020 (Sohrabi et al., 2020). Infection due to SARS-CoV-2 has caused severe morbidity and mortality throughout the world (Lai et al., 2020). COVID-19 resulted in millions of human infections with 6,535,354 clinical cases, 387,155 deaths and these figures are increasing rapidly (WHO, 2020).

COVID-19 has also posed as a severe blow to every country's economy. It is observed that COVID-19 has caused a loss of more than 4 trillion dollars to the global economy (McKibbin & Fernando, 2020). According to the United Nations, there is a need for more than 2.5 trillion dollars as a global COVID-19 rescue package. All developing countries especially countries in Africa are affected severely (Baldwin & Mauro, 2020).

Coronaviruses have a broad range of hosts and can cause various types of diseases in animals and humans (Cavanagh, 2005; Corman et al., 2013; Lim et al., 2016; Wang et al., 2018). It has been reported from amphibians (frogs), reptiles (snakes and lizards), birds (fowls) and mammals (bats, primates, humans, etc.).

The coronaviruses are associated with many clinical syndromes including respiratory diseases and diarrhoea (Fehr & Perlman, 2015). There are many clans of coronavirus diseases that include severe acute respiratory syndrome caused by SARS-CoV-1, Middle East respiratory Syndrome (MERS) caused by MERS-CoV and COVID-19 caused by SARS-CoV-2.

The first pandemic of coronavirus disease caused by SARS-CoV-1 was reported in the year 2002 in Yunnan Province, China (Ge et al., 2013). Humans acquired this virus infection zoonotically through cave-dwelling horseshoe bats (*Rhinolophus*) (Luk et al., 2019). The outbreak of SARS lasted from 2002 to 2004 involving 29 countries, 8,096 cases and 774 deaths with a case fatality rate of 9.6% (Cheng et al., 2007; De Wit et al., 2016). The clinical features of SARS patients include flu like signs with high fever (above 100° F), lethargy, myalgia, cough, sore throat and running nose (Hui & Zumla, 2019). SARS may proceed to severe pneumonia, difficulty in breathing and shortness of breath. The pneumonia due to SARS-CoV-1 is due to either by direct infection of the virus or due to secondary bacterial infections like Staphylococcal, Streptococcal or Haemophilus influenzae type B. The incubation period of SARS ranges from 1 day to 2 weeks (G. Chen et al., 2020). The mechanism of spread of SARS is through respiratory droplets, nasal secretions or fomites. Along with pneumonia, SARS patients also showed symptoms of diarrhoea (Manocha et al., 2003). But it was found that feco-oral route of transmission is not a prime mode of the spread of SARS-CoV-1. There were no SARS cases reported around the world after the year 2004.

MERS-CoV causes MERS (camel flu) – a highly infectious disease prevalent in Middle East countries and is transmitted through infected camels (Subbaram et al., 2017). The infected patients show symptoms similar to SARS, with an incubation period of 2 days to 14 days (Memish et al., 2020). MERS may show high severity in patients who are active smokers, with underlying diseases and other respiratory problems (Ramadan & Shaib, 2019). Saudi Arabia and other neighboring countries frequently reported nosocomial or hospital acquired MERS infection (Cotten et al., 2013). In the year 2012, MERS was first identified in Saudi Arabia, until then it

had been reported in many countries with 1360 clinical cases, 527 deaths (fatality rate is 39%) (De Wit et al., 2016).

Viral Morphology

Coronaviruses have a spherical shape and structure with a lipoprotein envelope. They are relatively large viruses with a size of 100 nm (Kothai & Arul, 2020). On the surface of their lipoprotein envelope, the virus possesses spikes made up of glycoprotein (Figure-1).

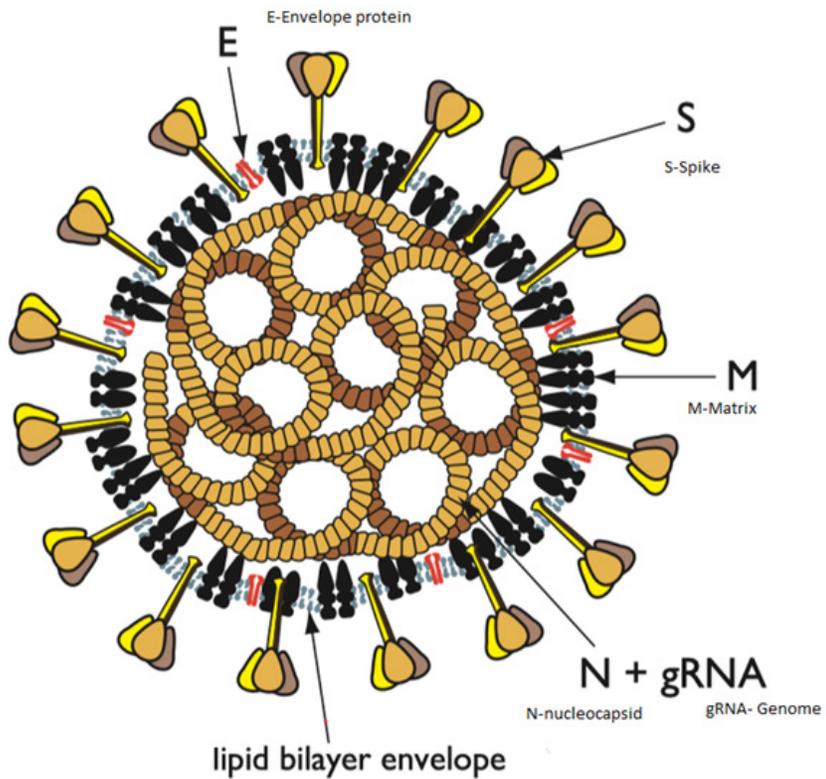


Figure-1 - Structure of SARS-CoV-2

Figure 1. Structure of SARS-CoV-2

Courtesy: Field's Virology, 6th edition – Dr. Ian.M.MacKay, PhD. Blog

Within the circular lipoprotein studded envelope, the virion has RNA with a capsid protein in helical symmetry. The glycoprotein spikes are responsible for attachment to host cell receptors. The viral envelope is not coded by a viral gene; rather it is acquired from host cell cytoplasmic membrane through a process called budding at the time of release from infected cells (Chung et al., 2020).

Even though the morphology of SARS-CoV-2, SARS-CoV-1 and MERS-CoV resembles one another, there are structural and antigenic differences that exist among them. There are two membrane proteins (hemagglutinin and acetyl esterase) present in SARS-CoV-1 and MERS-CoV but they are absent in SARS-CoV-2.

Genome Properties

Coronaviruses possess RNA with polarity of positive sense RNA (+RNA) (Lu et al., 2020). This positive RNA enables the virus for rapid multiplication because unlike other RNA viruses, Coronaviruses with +RNA can directly act as messenger RNA (mRNA) thus facilitating swift transcription and translation of viral proteins (Ashour et al., 2020).

The coronavirus genome possess heredity information for making viral proteins like glycoproteins, RNA, capsids and enzymes needed for viral replication (Woo et al., 2005). The increased pathogenesis of SARS-CoV-2 is due to its genome (RNA) properties. Viral RNA during transcription may undergo transcriptional errors (Zhang & Holmes, 2020). This may result in the emergence of new types of antigens in the glycoproteins and capsids. Thus suggesting that the antibodies formed earlier may not offer protective immunity against reinfection. The same mechanism may also result in formation of new virion with enhanced virulence and pathogenicity.

Basic genomic properties of SARS-CoV-2, SARS-CoV-1 and MERS-CoV are similar to each other. But all the three viruses differ in their genetic sequences and expression of messenger RNA (mRNA), internal and external antigenic proteins and viral enzymes.

Physicochemical properties

SARS-CoV-2 like other coronaviruses are very fragile and delicate viruses (Sajadi et al., 2020). This virus can be easily inactivated by antiseptics, disinfectants, soaps, detergents and high temperature (Kratzel et al., 2020). These agents can easily destroy the virus envelope. So, these properties are attributed to the virus lipoprotein envelope. The virus envelope containing spikes are very important for attachment to host cells. Once the virus envelope is destroyed the virus is unable to initiate infection and is inactivated.

SARS-CoV-1 and MERS-CoV also exhibit similar susceptibility patterns to different physicochemical agents. This is due to the fact that all these viruses possess lipoprotein envelope that can be disintegrated easily.

Epidemiology

SARS-CoV-2 spread from infected person to another by virus containing aerosol, respiratory droplets, nasal secretions and through fomites (Epidemiology of

COVID-19, 2020; Rothan & Byrareddy, 2020; Sun et al., 2020; Team, 2020). Research showed that 0.01 PFU/ml (Pock Forming Unit) is sufficient for causing the infection in a new host.

The COVID-19 pandemic occurred through human to human transmission via community spread. According to WHO (Situation report -137, dated 5/6/2020), globally there are 6,535,354 cases and 387,155 deaths due to COVID-19.

Table 1
COVID-19 Global Disease Burden With Major Affected Countries

S.No	Countries	Confirmed cases	No. of deaths
1.	USA	1,857,872	107,911
2.	Brazil	614,941	34,021
3.	Russian Federation	449,834	5,725
4.	UK	281,665	39,904
5.	Spain	240,660	27,133
6.	India	236,657	6,642
7.	Italy	234,013	33,689
8.	Germany	183,271	8,613
9.	Peru	183,198	5,162
10.	Turkey	167,410	4,648

Source: WHO – COVID-19 – Dashboard, dated 6/6/2020

SARS-CoV-2 is highly infectious virus than SARS-CoV-1 and MERS-CoV. From the epicentre of COVID-19, Wuhan the transmission occurred rapidly involving community spread. This is followed by spread of the disease to neighbouring areas of Hubei Province. Later the virus swiftly spread to other countries leading to a pandemic within a brief period of time.

Pathogenesis

For the infection of SARS-CoV-2 two host receptors are very important (Thomson, 2020). These receptors are abundantly located in the pneumocytes of lungs (Patten et al., 2016). Angiotensin converting enzyme – 2 (ACE-2) receptors and serine protease (TMPRSS2) receptors are very important for virus attachment and entry (Liu et al., 2020). ACE-2 receptors are binding hold for the viral spikes and serine protease TMPRSS2 acts as priming and activating site for spike (S) viral protein (Hoffmann et al., 2020). With the aid of ACE-2, and TMPRSS2 virus attachment occurs then virus envelope fuses with the host cell membrane followed by penetration, uncoating, biosynthesis and release (Y. Chen & Li, 2020).

It is to be noted that apart from lungs, ACE-2 receptors are distributed in heart, kidney, intestine and arteries (Agarwal et al., 2020; YIN & ZHANG, 2020). This may suggest why many case reports due to COVID-19 have experienced myocardial infarction, renal failure, stroke apart from pneumonia which is the prominent symptom (Casella et al., 2020; Jiang et al., 2020; Yasri & Wiwanitkit,

2020).

SARS-CoV-1 and MERS-CoV also require ACE-2 receptors for attachment and replication. In SARS-CoV-1 and MERS-CoV the role of serine protease receptor is not clearly understood.

Clinical Features

Several research on COVID-19 established that the incubation period for SARS-CoV-2 is variable from 2 days to 12 days (Lauer et al., 2020). In many cases patients were found to be healthy, asymptomatic yet infectious (Gao & Li, 2020).

Symptomatic patients showed flu like signs like nasal discharge, fever, cough, later may lead to atypical pneumonia or other severe respiratory complications (Guan et al., 2020). This disease is highly pronounced in patients with other underlying health conditions like asthma, wheezing or atopy. Patients who are heavy smokers has a high chance of acquiring the disease (Qian et al., 2020).

The incubation period for SARS is approximately 12 days and for MERS is 14 days. The clinical features of SARS is similar to COVID-19 but more pronounced. In case of MERS the symptoms are relatively milder than COVID-19.

Evolution

Previous researches have shown that more than 97% relatedness exist among SARS-CoV-1 and SARS-CoV-2 (Andersen et al., 2020; Prompetchara et al., 2020). This indicates that due to mutation SARS-CoV-1 might have evolved to SARS-CoV-2. Another possibility is that Coronavirus present in wild animals, after mutation, might have evolved into a novel coronavirus (SARS-CoV-2).

Methods

Data Sources and search Strategies

In this study, only English publications were used to conduct a detailed literature review. Information available in PubMed / Medline, Scopus, Thompson-Reuters Journals / Web of Science and Science Direct was extracted. A thorough search was conducted on all aspects of Coronaviruses, with Medical Sub Headings (MeSH) like 'COVID-19', 'SARS-CoV-2', 'SARS-CoV-1', 'MERS-CoV'. A total of 75 articles published within January 2002 to May 2020 were obtained using the key words and MeSH, and out of them 57 are used in this article.

Bioinformatics tools employed for complete genome analysis

In this research we have used bioinformatics tools, software applications, nucleotide sequence available in European Nucleotide Archives (ENA) for comparison of complete genome of SARS-CoV-2 with SARS-CoV-1, MERS-CoV and other beta coronaviruses. Phyltree.fr tool was used to bring out the phylogenetic analysis among these mentioned viruses. FASTA / BLAST tools are also used in this study.

The BLAST procedure involves five steps. Step-1 consists of selecting the BLAST program. Step-2 comprises of entering the query sequence. Step-

have less genetic homology. Branching patterns of the phylogenetic tree (figure -3) clearly shows that SARS-CoV-2 and SARS-CoV-1 rise from single genetic lineage whereas MERS-CoV has a different lineage. (Figure -3)



Figure 1: Phylogenetic tree

Figure 3. Phylogenetic Comparative Analysis Between SARS-CoV-2 With Other Coronaviruses

These findings support our opinion that SARS-CoV-2 evolved from SARS-CoV-1. Another possibility is that genetically related animal coronavirus may also be an originating point for SARS-Cov-2 evolution.

Genetic homology between SARS-CoV-2 and SARS-CoV-1 may be attributed to the geographical place or their origin (Andersen et al., 2020; Kannan et al., 2020). These two Coronaviruses originated in China, whereas MERS-CoV evolved from Middle Eastern countries (Subbaram et al., 2017). Temperature, animal reservoir, and other hosts in the particular geographical area may play a vital role in the evolution of these viruses. For SARS-CoV-2 and SARS-CoV-1 the animal reservoirs may be bats, pangolins, snakes, lizards etc. In case of MERS-CoV, the reservoir animal identified is camels.

The enhanced virulence of SARS-CoV-2 is attributed to its genome, RNA (Sardar et al., 2020). SARS-CoV-2 genome can undergo transcriptional errors leading to expression of new viral proteins. This is a major problem faced by physicians treating the COVID-19 patients. This property of the virus is associated with reinfection after recovery in the same host. Mutation of SARS-CoV-2 and associated antigenic change is also a major issue for developing vaccine and manufacturing antiviral drugs. researchers have also observed that SARS-CoV-2 can be transmitted from human to pet animals like cats and dogs (Chen, 2020; Whitworth, 2020). This is another issue in the containment of COVID-19. These pet animals may become reservoir animals for SARS-CoV-2 and pose a bio threat situation.

Conclusions

SARS-CoV-2 is genetically more related to SARS-CoV-1 than MERS-CoV. Genetic homology among SARS-CoV-2 and SARS-CoV-1 may be attributed to the geographical region from where the virus originated and the reservoir animals present in that area. For both SARS-CoV-2 and SARS-CoV-1 the animal reservoirs may be bats, pangolins, snakes, lizards etc. MERS may be transmitted from infected camels through zoonotic mode.

SARS-CoV-2 might have evolved from SARS-CoV-1 or from related animal coronaviruses like bat coronavirus. Coronaviruses are thermo-labile and cannot be active outside the body for a long time appropriate public health measures should be taken to reduce or prevent community spread. Enhanced virulence of SARS-CoV-2 could be due to the ability of the virus to undergo antigenic variation. This poses a big challenge for physicians and researchers to develop drugs and vaccine against the virus.

The COVID-19 pandemic has shaken the world economy more than anyone anticipated. Even affluent countries like USA, China, UK, Germany and France are badly affected. The impact on less affluent countries are understandably bigger. The total economic burden caused remains to be seen. But estimates of economic loss have already reached trillions of dollars.

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