SARS-CoV-2, SARS-CoV, and MERS-CoV: a comparative overview

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SUMMARY

The recent outbreak of SARS-CoV-2 that started in Wuhan, China, has now spread to several other countries and is in its exponential phase of spread. Although less pathogenic than SARS-CoV, it has taken several lives and taken down the economies of many countries. Before this outbreak, the most recent coronavirus outbreaks were the SARS-CoV and the MERS-CoV outbreaks that happened in China and Saudi Arabia, respectively. Since, the SARS-CoV-2 belongs to the same family as of SARS-CoV and MERS-CoV, they share several similarities. So, this review aims at understanding the new scenario of SARS-CoV-2 outbreak and compares the epidemiology, clinical presentations, and the genetics of these coronaviruses. Studies reveal that SARS-CoV-2 is very similar in structure and pathogenicity with SARS-CoV, but the most important structural protein, *i.e.*, the spike protein (S), is slightly different in these viruses. The presence of a furin-like cleavage site in SARS-CoV-2 facilitates the S protein priming and might increase the efficiency of the spread of SARS-CoV-2 as compared to other beta coronaviruses. So, furin inhibitors can be targeted as potential drug therapies for SARS-CoV-2.

Keywords: SARS-CoV-2, COVID-19, MERS-CoV, S protein, coronavirus.

INTRODUCTION

In the past two decades, there have been two major coronavirus outbreaks, the SARS-CoV (2002) and the MERS (2012) [1, 2]. The recent coronavirus outbreak happened in the Wuhan city of China, which is known as the 2019-nCoV outbreak, recently renamed as SARS-CoV-2 outbreak or COVID-19 [3-5].

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The first case of SARS-CoV-2 infection was reported in Wuhan, China, on 31st December 2019 with the presentation of symptoms of atypical pneumonia. This case was further confirmed to be caused by the novel coronavirus, SARS-CoV-2. According to the WHO, as of 10 AM CET 17 March 2020, 179, 112 cases of COVID-19 have been reported with associated 7426 deaths worldwide [6]. There were 81,116 confirmed cases of SARS-CoV-2 infections in mainland China, including 3,231 deaths [6]. In terms of death related to COVID-19, after China, the highest troll of death due to COVID-19 has been reported in Italy (2,503) followed by Iran (853).

The most potential risk for the spread of COVID-19 worldwide is related to travel that is causing the regional and global spread of the disease [7].

The origin of coronaviruses is primarily animal. When these viruses cross the species barrier and infect humans, outbreaks happen. SARS and COVID-19 share many similarities in terms of their transmission and pathogenicity. All of them cause acute respiratory illness and follow human to human transmission. Although the coronavirus SARS-CoV-2 responsible for COVID-19 has been successfully isolated and the viral infectivity and pathogenicity has been understood, there is much room for the understanding of the viral antigenic structure, mode of action, and pathogenicity [1, 2]. In order to contain the infection and develop effective management systems to handle viral infections in an outbreak scenario, we should understand the nature of infection or pathogenicity of the novel virus and evaluate the similarities and dissimilarities of the novel virus with the viruses that have caused outbreaks in the past. The SARS-CoV-2 is less pathogenic as compared to SARS and MERS virus that belongs to the same family of viruses (*Coronaviridae*). In the premise of this background, this review was written to explore the similarities and dissimilarities of the SARS-CoV-2 with other Coronaviruses (SARS and MERS).

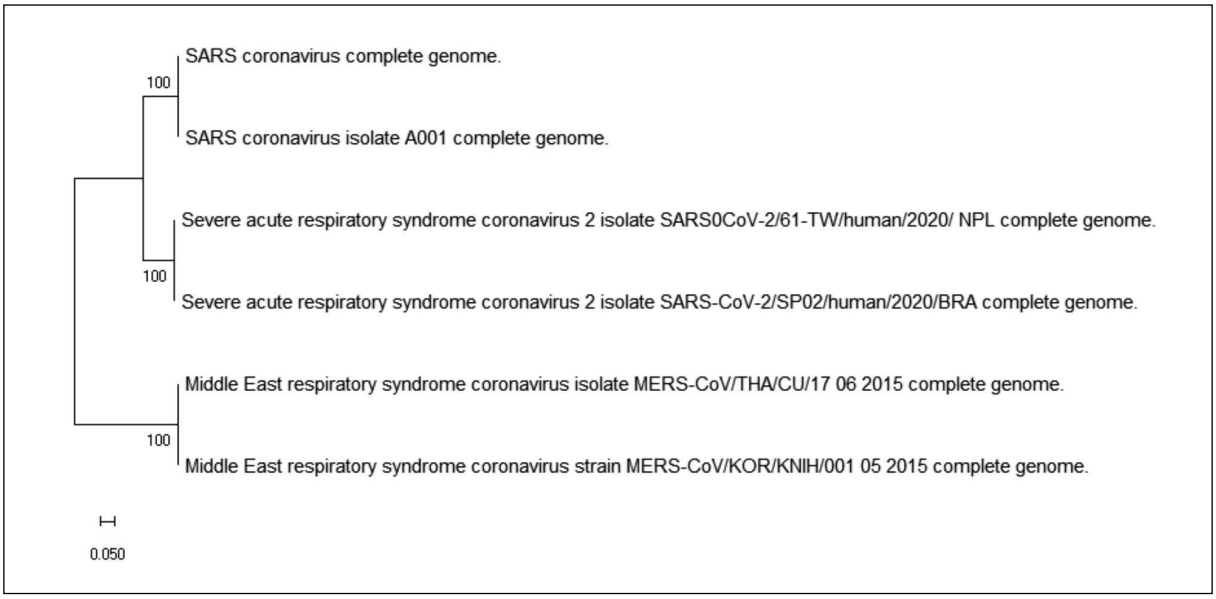

Figure 1 - Evolutionary analysis of SARS-CoV, MERS-CoV-2 and SARS-CoV-2 by Maximum Likelihood method. SARS-CoV genomes used belong to China, MERS-CoV to Thailand and South Korea, and SARS-CoV-2 to Nepal and Brazil. All available at the GenBank. Sequences alignment and phylogenetic tree were run at MEGA® v.10.05.

The evolutionary history was inferred by using the Maximum Likelihood method and Kimura 2-parameter model [91]. The tree with the highest log likelihood (-94634.25) is shown. The percentage of trees in which the associated taxa clustered together is shown next to the branches. Initial tree(s) for the heuristic search were obtained automatically by applying Neighbor-Join and BioNJ algorithms to a matrix of pairwise distances estimated using the Maximum Composite Likelihood (MCL) approach, and then selecting the topology with superior log likelihood value. The tree is drawn to scale, with branch lengths measured in the number of substitutions per site. This analysis involved 6 nucleotide sequences. Codon positions included were 1st+2nd+3rd+Noncoding. All positions containing gaps and missing data were eliminated (complete deletion option). There was a total of 28729 positions in the final dataset. Evolutionary analyses were conducted in MEGA X [92]. 1.

AN OVERVIEW OF VIROLOGY: SARS, MERS-CoV, AND SARS-CoV-2

Coronaviruses belong to a family that comes under the order "*Nidovirales*". Nidovirales order includes the viruses that use a nested set of mRNAs for their replication. Further, the coronavirus sub-family has four genera (alpha, beta, gamma, and delta coronaviruses). The coronaviruses infecting humans (HCoVs) belong to two of these genera (alpha coronaviruses and beta coronaviruses). The alpha coronaviruses infecting humans are HCoV-229E and HCoV-NL63, and the beta coronaviruses infecting humans are HCoV-HKU1, HCoV-OC43, Middle East respiratory syndrome coronavirus (MERS-CoV), the severe acute respiratory syndrome coronavirus (SARS-CoV), and SARS-CoV-2 (Figure 1) [8, 9].

VIRAL COMPOSITION

Coronaviruses appear crown-like structures under electron microscope hence named as coronavirus. They have positive-stranded RNA as their genomic material and have an outer envelope [10,11]. Coronaviruses have the largest RNA genomes (27 to 32 kb) among the RNA viruses. The viral envelope is derived from the host cell and has glycoprotein spikes. The viral genome is protected within the nucleocapsid. The nucleocapsid is helical in shape when relaxed and spherical when inside the virus. The viral RNA replicates uniquely. The coronavirus RNA replicates in the cytoplasm of the host cell. The RNA polymerase attached itself to the leader sequence of the viral genomic RNA, and in the event of repeated attachment and detachment, a nested set of mRNAs are generated with common 3′ ends.

The coronavirus genome encodes for four to five structural proteins: spike (S), membrane (M), envelope (E), nucleocapsid (N), and hemagglutinin-esterase (HE) proteins. SARS-CoV-2, SARS CoV, HCoV-229E, and HCoV-NL63 genome has four genes that express S, M, N, and E structural proteins. The HCoV-OC43 and HCoV-HKU1 coronavirus have an extra gene that expresses the HE protein [12].

The S protein is a 150 kDa protein that is highly N-glycosylated and helps in assessing the ER. Trimers of the S protein make the peculiar spike structure on the virus surface [13, 14]. This trimeric S protein is a class I fusion protein that facilitates the receptor attachment [15]. Frequently the S protein is cleaved by a host protease (furin-like protease) into two functional domains, S1 and S2 [16, 17]. S1 mainly helps in receptor binding, while S2 gives structural support in the form of the stalk of S protein [18].

The M protein is a 25-30 kDa protein found in abundance in the virion. It has three transmembrane domains [19]. The M protein has an N-terminal ectodomain and a C-terminal endodomain. It gives the virion its shape [20]. M protein is found in the virion as a dimer and helps in maintaining the membrane curvature and binding to the nucleocapsid [21].

The E protein is an 8-12 kDa protein found scarcely in the virion [22]. Studies suggest that the E protein is a transmembrane protein with an N-terminal ectodomain and a C-terminal endodomain. It also has an ion channel activity. The E protein plays a vital role in the virus assembly and release. Besides this, the E proteins have other functions too, such as the ion channel activity, required for the pathogenesis of SARS-CoV and probably SARS-CoV-2 [23].

The N protein is a part of the nucleocapsid. It has an N-terminal domain and a C-terminal domain. Each domain of the N protein can bind to RNA [24, 25]. The N-protein is highly phosphorylated that increases the affinity of the N protein for the viral RNA [26]. The N protein binds to the viral RNA and gives beads on a string structure. The genomic packaging signal and the TRSs are the two RNA substrates for the N protein. The C-terminal domain of the N protein binds to the genomic packaging signal [27-29]. The N protein helps ultimately in the packaging of the encapsidated viral genome into the viral particles by interacting with the M protein and nsp3 which is a component of replicase complex facilitating the binding to the replicase-transcriptase complex (RTC) [25, 30, 31].

The hemagglutinin-esterase (HE) protein is only found in some β-coronaviruses. HE binds to sialic acids present on the glycoproteins on the surface of the virion. Together, the binding to sialic acid and the esterase activity facilitate the viral entry into the host cell-mediated by the S protein [32]. The HE proteins also help in the viral spread through the mucosa [33].

SPIKE PROTEIN ON THE SARS-CoV-2 IS DIFFERENT: REASON FOR THE RAPID SPREAD OF COVID-19

Although there is a strikingly high similarity between SARS-CoV and the novel SARS-CoV-2, the SARS-CoV-2 is spreading rapidly as compared to the SARS-CoV. This may be explained by the structural differences in the S proteins among the coronaviruses. To understand this, we have first to understand the mechanism of viral entry into the host cell utilizing the S protein in different coronaviruses.

The attachment of the virion to the host cell surface is facilitated by the S protein and its receptor. The receptor-binding domain (RBD) within the S1 domain of the S protein lies either in the N-terminus of S1 (MHV) or in the C-terminus of the S1 (SARS-CoV) [34, 35]. This interaction between the S protein and its receptor is responsible for the species specificity and tissue tropism of the virus. Many coronaviruses utilize peptidases as their cellular receptor. The α-coronaviruses use aminopeptidase N (APN) as the cellular receptor while SARS-CoV and HCoV-NL63 utilize angiotensin-converting enzyme 2 (ACE2) as their receptor. The surface of the RBD of S1 utilizes 14 amino acid residues to bind to the ACE2 [36]. Out of these 14 residues, 8 are strictly conserved in SARS-CoV-2. This observation indicates that SARS-CoV-2 also utilizes the ACE2 receptor for binding to the host cell surfaces [37].

SARS-CoV and SARS-CoV-2 utilize the host cell ACE2 receptor while the MHV binds to CEACAM1 and MERS-CoV binds to dipeptidyl-peptidase 4 (DPP4) to enter into human cells [38]. After successful attachment to the host cell surface, the virus enters into the cytosol of the host cells by utilizing proteases such as cathepsin and TMPRRS2. These acid-dependent proteases carry out the cleavage of S protein which is then followed by the fusion of the viral and host cell membranes. The cleavage of the S protein happens at two different positions in the S2 domain of the protein. The first cleavage helps in the separation of the RBD and fusion domains, and the second cleavage happens to expose the fusion peptide (cleavage at S2′) [39]. The fusion event mostly occurs in the endosomes. However, in the MHV, the fusion takes place at the cell membranes. The exposed internal fusion peptide at the S2′ cleavage site inserts into the plasma membrane. Then the two heptad repeats in S2 join together to form a six-helix bundle structure. The formation of this helical bundle allows for the membrane fusion, and the viral genome is released into the host cytosol [40]. It is documented that the internal fusion peptide of the SARS-CoV-2 and SARS-CoV are identically highlighting that both the coronaviruses share common mechanisms of virus fusion and entry into the host cell. The SARS-CoV-2 and SARS-CoV have identical furin-like S2′ cleavage site at KR↓SF with P1 and P2 basic residues and a P2′ hydrophobic Phe downstream to the internal fusion protein [41]. The S1/S2 site in the MERS-CoV and HCoV-OC43 has RXXR↓SA, with P1 and P4 basic residues, and an Ala at P2′, making the furin mediated cleavage less favourable. It is observed that the S2′ cleavage site in other less pathogenic human coronaviruses have a monobasic R↓S sequence and the P2 and P4 do not have any basic residues which are required for furin mediated fusion. This highlights the fact that the cognate proteases expressed by the host cells decide the efficiency of the virus entry into the host cell and ultimately, their pathogenicity [42].

It is reported that the cleavage of the S protein of the MERS-CoV with RSVR↓SV is mediated by furin during viral egress [43]. However, due to the lack of furin-like cleavage site (SLLR-ST), the S-protein of SARS-CoV is not entirely cleaved. In MERS-CoV, the S protein cleavage occurs at a conserved sequence AYT↓M by the proteases (elastase, cathepsin L or TMPRS) expressed by the target cells [44-46].

The S protein of the SARS-CoV-2 has 12 extra nucleotides upstream to the single Arg↓ cleavage site 1 forming PRRAR↓SV sequence, which is similar to a canonical furin-like cleavage site [47,48,41]. The presence of this furin-like cleavage site in SARS-CoV-2 facilitates the S protein priming and might increase the efficiency of the spread of SARS-CoV-2 as compared to other beta coronaviruses [42, 43].

PATHOGENESIS AND EPIDEMIOLOGY

Human Coronaviruses

Coronaviruses (α-coronaviruses: HCoV-229E and HCoV-NL63; β-coronaviruses; HCoV-OC43 and HCoV-HKU1) were believed to cause only mild respiratory infections in the humans, and these

infections were self-limiting in nature until the SARS-CoV outbreak occurred. HCoV-229E and HCoV-OC43 coronaviruses were isolated about half a century ago, whereas HCoV-NL63 and HCoV-HKU1 were isolated after the SARS-CoV outbreak [49-53]. These viral infections contribute nearly 15-30% to the total respiratory tract infections in humans each year. These viruses target mainly the individuals with weak immunity such as the neonates, the older adults, and the ones with other chronic co-morbidities.

SARS-CoV was the causative agent for the Severe Acute Respiratory Syndrome (SARS) outbreak in the Guangdong Province of China in 2002-2003. It is considered as the most severe disease caused by any coronavirus. The SARS-CoV outbreak had a mortality rate of 9%. During this outbreak, about 8098 cases of SARS were reported, and out of these infected cases, 774 died of the infection. The mortality rate was higher (50%) in the elderly population (over 60 years). Not only higher mortality, but this outbreak also resulted in a strikingly high economic downfall with nearly 40 billion dollars loss worldwide, especially in Southeast Asia, and Toronto, Canada [38].

The SARS outbreak originally began in the hotel of Hong Kong. The spillover occurred in a live animal market in Guangdong, China. Gradually this spread to more than 24 countries. Since the Chinese horseshoe bats were found to have sequences of SARS-related CoVs and pieces of evidence were found claiming that these bats were infected with a related virus before the outbreak, it is believed that SARS-CoVs originated in the Chinese horseshoe bats [54, 55]. Further, two novel bat SARS-related CoVs were identified that showed the highest similarity with SARS-CoV than any other virus identified till date [56]. They also utilized the same receptor (ACE2) as the human SARS-CoV reinforcing the fact that SARS-CoV originated in bats. The outbreak was mostly contained because of the relative inefficient SARS-CoV transmission. It transmitted only through direct contact with the infected person [57]. The SARS-CoV outbreak was restricted by quarantining in June 2003. After this only few cases were reported to have SARS-CoV infection. SARS-CoV infected the epithelial cells of the lungs and the immune cells like the dendritic cells and the macrophages. Since these cells produce pro-inflammatory cytokines, infection with SARS-CoV resulted in elevated levels of these cytokines in the patients [58-61].

The next coronavirus outbreak that followed the SARS-CoV outbreak was the MERS-CoV outbreak. This outbreak occurred in 2012 in the Middle East (Saudi Arabia). MERS-CoV resulted in severe infections in the respiratory tract of the infected persons in Saudi Arabia and other Middle East countries [62]. The initial mortality rate of MERS-CoV was about 50%. However, the outbreak did not intensify by the year 2013, and only a few sporadic cases came throughout the year. In April 2014, the number of reported cases increased to over 200 cases and about 40 deaths occurred. This was due to improved diagnostics and reporting of the cases and increased number of births of camels that year. As per the estimates by the European Center for Disease Prevention and Control, by 27 August 2014, there were 855 cases of MERS-CoV and out of which 333 died giving a fatality rate of about 40%. As per the latest news from WHO, the total number of reported cases of MERS-CoV globally were 2519 and out of which 866 died, giving a mortality rate of 34.4% [63].

MERS-CoVs were found to be highly related to two bat coronaviruses, HKU4 and HKU5 [64]. So, it is believed that MERS-CoV originated in bats like SARS-CoV. Studies reported the serological evidence of MERS-CoV antibodies in the dromedary camels in Middle Eastern countries suggesting these camels be the intermediate host for MERS-CoV [65]. Studies also identified identical MERS-CoVs in both humans and camels in Saudi Arabia [66, 67]. One of these studies reported that the infected person had direct contact with the camel found positive for similar MERS-CoV [67].

The most recent coronavirus outbreak was due to a novel SARS-CoV-2 coronavirus. In December 2019, reports of pneumonia-like conditions came in Wuhan, China. The viral spillover is believed to happen in a seafood market in Wuhan, Hubei Province, China [68]. The World Health Organization (WHO) declared COVID-19 to be a "public health emergency of international concern" on 30th January 2020 [69]. Quickly, this disease spread to other parts of China from Wuhan and 66 other countries [70]. Then, reports started coming about confirmed cases from many other countries without a travel history to Wuhan or direct exposure to seafood markets [71].

According to the recent update on 17th March 2020, 179,112 cases of COVID-19 have been reported to WHO, and out of these cases, 7,426 fatalities were reported worldwide [6]. According to this report, the highest reported cases infected with SARS-CoV-2 were in Mainland China with the highest fatalities, followed by Italy and Iran.

Sequence similarity of the novel SARS-CoV-2 with a bat coronavirus suggests that the novel SARS-CoV-2 have originated in bats like SARS-CoV and MERS-CoV [72, 73]. It is still not confirmed whether COVID-19 is transmitted directly from the bats or there are some other intermediate hosts. Recent studies have suggested that snakes can be a possible reservoir for the novel SARS-CoV-2 [74]. Another study has reported that bats and minks can serve as the potential hosts for the novel coronavirus and minks can be the intermediate host [75].

Epidemiology of SARS-CoV-2: Comparison with MERS-CoV and SARS-CoV

The SARS-CoV-2 is a highly infectious virus which can survive in the air for 2 hours. The time of incubation for SARS-CoV-2 is about 4-8 days post-infection [76-78]. Although people from all age groups are vulnerable to infection by SARS-CoV-2, the older adults with comorbidities are at higher risk [76-78]. The people who are infected but are asymptomatic or are in the incubation period of the virus serve as the carriers for the virus [79]. Till date, the respiratory droplets are considered as the primary route of SARS-CoV-2 transmission. However, the faecal-oral route of transmission is also thought to serve as another mode of transmission of SARS-CoV-2, but recent studies show no evidence of viral nucleic acid in the faecal samples of pneumonia patients [80]. Transmission from infected mothers to the newborns is another possible way of virus spread. However, a recent study reported that the newborns born from 9 infected mothers did not have SARS-CoV-2 infection ruling out the possibility of vertical transmission of SARS-CoV-2 from mothers to the newborns [81]. Another possible way of transmission is through the conjunctiva as the conjunctival epithelium can be easily contaminated [82]. Wu et al., reported the R0 for SARS-CoV-2 to be 2.68 closely similar to the reports by the WHO and the Chinese Center for Disease Control [79, 83, 84].

Clinical presentation of SARS-CoV-2: comparison with SARS-CoV and MERS-CoV

The data obtained from various groups worldwide and the 31 provinces of China suggest that the clinical symptoms of SARS-CoV-2 are more or less similar to that of SARS-CoV infection [85, 86]. The median age of the infected patients was 47 years; most of them were males (58.2%), the mean incubation time was 3.0 days (range: 0-24.0 days) [85]. The most common clinical symptoms were similar to that of SARS-CoV infection: fever (87.9%), fatigue (69.6%), dry cough (67.7%), and myalgia (34.8%). A few infected patients also presented rhinorrhoea, pharyngalgia, and diarrhoea [24]. Some showed dyspnea and hypoxemia, which eventually could lead to acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndromes (MODS) in one week [77,85].

A recently published case series (n=18) documented the radiographic imaging by chest computed tomography (CT). They reported lung opacities such as ground-glass opacities, rounded opacities, and crazy paving patterns in the infected persons on chest CT scan. The distribution of these opacities was bilateral in the patients [87]. In a more extensive case series (n=138) of COVID-19 in a hospital in Wuhan, China, the most common symptoms observed in these patients were fever followed by fatigue, dry cough, myalgia, and dyspnea. Most of the infected persons were in their late fifties. Most of the patients admitted to the ICU were old adult and with other co-morbid conditions. The mortality report in this study was 4.3% [88]. Another study from Wuhan, China reported 41 laboratory-confirmed cases of COVID-19. Most of these cases were men, had other co-morbidities, and exposed to Huanan seafood market. The symptoms were similar to the previously reported cases [76].

Table 1 describes the epidemiology and clinical presentations of the most important coronavirus outbreaks (SARS-CoV-2, SARS-CoV, and MERS-CoV).

Molecular aspects of SARS-CoV-2, SARS-CoV, and MERS-CoV: genetic similarities/dissimilarities

Roujian Lu et al., recently reported nine patients from different hospitals in Wuhan, China. They were all diagnosed with viral pneumonia, but the cause was not identified. High-throughput

Table 1 - Characteristics of patients with SARS-CoV-2, SARS-CoV, and MERS-CoV.

	Coronavirus		
	SARS-CoV-2	*SARS-CoV*	*MERS-CoV*
Epidemiology			
Outbreak beginning date	December 2019	November 2002	April 2012
Location of the first case	Wuhan, China	Guangdong, China	Saudi Arabia
Confirmed cases	595.800 (Mar 27, 2020)	8096	2519 (From 2012 until January 31, 2020)
Mortality	27.324 (%)	744 (10%)	866 (34.4%)
Time to infect first 1000 people (Days)	48	130	903
Incubation period (Days)	7-14	2-7	5-6
Transmission	Touching or eating an infected, yet unidentified animal. Human-to-human transmission occurs through close contact.	Believed to have spread from bats, which infected civets. Transmitted mainly between humans through close contact.	From touching infected camels or consuming their milk or meat. Limited transmission between humans through close contact.
Clinical Presentation			
Age, years (range)	47.0 (all spectrum of age)	39.9 (1-91)	53 (36-66)
Male: female ratio	1.39:1	1:1.25	2.03:1
Fever	88.7% (%)	99-100%	77±6%
Fatigue	29.4%	31.2%	
Nonproductive cough	67.7%	25%-75%	80±5%
Myalgia	14.8%	49.3%-60.9%	**
Dyspnea	45.6%	40-42%	**
Expectoration	13.3%	NR	**
Sore throat	13.9%	12.5%	39±11%
Diarrhea	6.1%	20-25%	10-20%
Nausea and/or vomiting	5.0%	19.4%-19.6%	**
Dizziness	3.7%	4.2%-42.8%	**
Headache	8.0%	35.4%-55.8%	**
Nausea or vomiting	5.0%	19.4%-19.6%	**

**The average of some clinical presentations for MERS-CoV was not available in the literature.

sequencing (next-generation sequencing) was employed using the bronchoalveolar lavage fluid samples and isolates obtained from cultures. The next-generation sequencing data revealed the infectious agent to be the 2019-nCoV/SARS-CoV-2 [89]. Eight of the viral genomes sequenced showed 99.98% similarity indicating that SARS-CoV-2 has newly emerged in the human population.

Multiple sequence alignment showed that the SARS-CoV-2 genome was closely related to two viruses that have originated in bats: bat-SL-CoVZC45 (87.99% identical sequence) and bat-SL-CoVZXC21 (87.23% identical sequence). The highest sequence similarity was seen in the E gene (98.7%), and the lowest in the S gene (75%) of the SARS-CoV-2 with bat-SL-CoVZC45 and bat-SL-CoVZXC21. Additionally, most of the SARS-CoV-2 proteins also showed sequence similarity with the bat-SL-CoVZC45 and bat-SL-CoVZXC21 except for the S proteins (only 80%) and protein 13 (73.2%) [89].

When compared with SARS-CoV and MERS-CoV, the SARS-CoV-2 showed less genetic similarity: genetic similarity of 79% with SARS-CoV and 50% with MERS-CoV. However, the coding regions of SARS-CoV-2 had a similar genomic organization as that of the bat coronaviruses and SARS-CoV. At least 12 coding regions were predicted, including 1ab, S, 3, E, M, 7, 8, 9, 10b, N, 13, and 14. The proteins encoded by SARS-CoV-2, bat-SL-CoVZC45, and bat-SL-CoVZXC21 were almost similar in length. The only significant difference was the S protein in SARS-CoV-2 was longer as compared to the S proteins encoded by the bat coronaviruses, SARS-CoV, and MERS-CoV [89].

Phylogenetic analysis based on the S and the RNA-dependent RNA polymerase genes revealed that SARS-CoV-2 is very distant from SARS-CoV, indicating that SARS-CoV-2 is a novel beta coronavirus belonging to subgenus Sarbecovirus [89]. The S2 domain of SARS-CoV-2 showed 93% sequence similarity and S1 showed a sequence similarity of 68% sequence with bat-SL-CoVZC45 and bat-SL-CoVZXC21 S2 and S1 domains, respectively. Although phylogenetic analysis placed SARS-CoV-2 and SARS-CoV in different clades, the two viruses had around 50 conserved amino acids in the S1 domain of the S protein. The receptor-binding domain (S1) of SARS-CoV-2 was closely similar to the S1 domain of SARS-CoV. Protein modelling studies showed that the outer subdomain of the SARS-CoV-2 receptor-binding domain closely related to the SARS-CoV. As discussed earlier, this observation also indicates that similar to the SARS-CoV, the SARS-CoV-2 may also utilize ACE2 as the receptor [89].

The sequencing results highlight the fact that bat-SL-CoVZC45 and bat-SL-CoVZXC21 are not the direct ancestors of SARS-CoV-2 owing to less than 90% sequence similarity and phylogenetic distance. It can be speculated that the natural host for SARS-CoV-2 are the bats similar to that for the SARS-CoV and MERS-CoV and like SARS and MERS CoVs, the SARS-CoV-2 virus is transmitted to humans via some intermediate hosts.

From these observations, it is clear that SARS-CoV-2 shares more similarities in terms of structure and pathogenicity with SARS-CoV than MERS-CoV. Both the CoVs use the same spike (S) protein for binding to the host cells, and both the CoVs utilize similar cellular protease for activating the S protein. The spike protein of SARS-CoV-2 shows a sequence similarity of 76-78% with the spike protein of SARS-CoV. The receptor-binding domain (S2) shows 73-76% sequence similarity with the S2 domain of the SARS-CoV. The receptor-binding motif of the SARS-CoV-2 shows 50%-53% sequence similarity with that of SARS-CoV [90].

CONCLUSIONS

The emergence of recent coronavirus outbreaks has proved that these viruses can mutate or recombine to become pathogenic and cross the species barriers and cause outbreaks in both humans and animals. Since genetic changes are inevitable and a part of the evolutionary process, these viral outbreaks will keep on emerging. It is essential to develop effective antiviral therapeutics and vaccines for these viruses. For this to achieve, we need to understand the detailed molecular mechanisms of the virus life cycle and gain of pathogenicity. A comparative analysis of the recent SARS-CoV-2 outbreak with the previous coronavirus outbreaks can provide us leads to be used for developing therapeutics and vaccines for this virus. Furin inhibitors can serve as potential targets for SARS-CoV-2 vaccine development strategies.

Conflict of Interests

Authors declare no conflict of interests.

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