Comparative Evaluation of the Pathogenesis of SARS-CoV-2 (COVID-2019) with the Pathogenesis of SARS-CoV and MERS-CoV

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ABSTRACT

BACKGROUND

In the present review, three highly pathogenic and deadly human coronaviruses which have emerged within the last two decades are discussed, namely severe acute respiratory syndrome-corona virus-2 (SARS-CoV-2), SARS CoV, and Middle East respiratory syndrome-CoV (MERS-CoV). SARS-CoV-2 is a highly pathogenic and transmissible coronavirus type that emerged in the year 2019 and has caused a worldwide acute respiratory illness, named 'coronavirus disease 2019' (COVID-19), with a high morbidity and mortality. To this end, the present review is based on summarizing the pathogenesis of human coronaviruses, namely SARS-CoV-2, SARS CoV, and MERS-CoV. This review provides a comparative evaluation of the genomic features, origin, transmission, and pathogenicity of these human coronaviruses. The coronavirus pandemic disease 2019 (COVID-19) caused by SARS-CoV-2 is still ongoing, as a result, this comparative evaluation may inform and aid in the knowledge of public health administrators and medical experts to control the pandemic's progression.

KEYWORDS

SARS-CoV-2, SARS-CoV, MERS-CoV

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BACKGROUND

Coronavirus belongs to the subfamily Coronavirinae of the Coronaviridae family and based on genetic properties, it is further subdivided into four genera: α-coronavirus, β-coronavirus, γ-coronavirus and δ-coronavirus. In the last two decades, β-coronavirus genera have been the focus of research due to outbreaks, emerging and re-emerging infections.[1] In the present review, we discuss three highly pathogenic and deadly human coronaviruses which have emerged within the last two decades, namely SARS-CoV-2, SARS-CoV, and MERS-CoV.[2] The SARS-CoV-2 was first detected and diagnosed in several patients who have travelled to Wuhan city, China, or have gone to a seafood market in Wuhan city, China.[3]

These coronaviruses exert a high economic crises and public health burden worldwide. The infections are spreading all across the globe and an increasing number of infections are attributed to the high morbidity and mortality of SARS-CoV-2.[4] The specific medical countermeasures for these human coronaviruses are still under research. Sometimes spread of false information regarding these human coronaviruses is also seen worldwide which results in panic in the general public regarding the infection. The SARS-CoV-2 virus shows many similarities with SARS-CoV and MERS-CoV viruses, however, certain differences also exist as well.[5] Researches were conducted and result obtained during SARS-CoV and MERS-CoV infections are extremely useful for efficiently and effectively managing SARS-CoV-2 disease world-wide. By conducting further research regarding the aetiology and pathogenesis of human coronaviruses, we can fill knowledge gaps and provide potential elements for fighting SARS-CoV-2, controlling its global spread and prepare effective and efficient defence lines against human coronaviruses that may emerge or re-emerge in the near future.[6] The human coronaviruses are positive-sense ribonucleic acid (RNA) viruses and have the largest genome sequence reported among RNA viruses. Structural proteins are essential for the infection and assembly of coronavirus which are spike glycoproteins (S) on the surface of the particle and consists of two subunits S1 and S2. The S1 contains a receptor-binding domain (RBD) and binds with cellular receptors and the S2 facilitates fusion and entrance process. Membrane protein (M) increases the membrane curvature and promotes viral assembly.[7] Envelope protein (E) acts in the release of virus. Nucleocapsid protein (N) is interferon antagonistic (IFN) and acts in viral replication. The non-structural proteins block host immune system for viral replication. RNA-dependent RNA polymerase (RdRp) enzyme has proofreading-activity, so the mutation rate is lower than other RNA viruses, however homologous recombination is frequently seen.[8,9]

To this end, the present review is based on summarizing the pathogenesis of human coronaviruses, namely SARS-CoV-2, SARS-CoV and MERS-CoV. This review provides comparative evaluation of the genomic features, origin, transmission, and pathogenicity of these human coronaviruses. The COVID-19 infection is still spreading worldwide, this comparison of pathogenesis of flu viruses may help in better understanding of clinical specialists to control the pandemic's development.

AETIOPATHOGENESIS OF SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS INFECTION

Severe acute respiratory syndrome coronavirus was the viral agent for the pandemic SARS infection that occurred from 2002 to 2003 involving 33 countries and resulted in approximately 8096 cases and 774 deaths.[10] It was reported in various studies that bats were the potential natural reservoir for the pandemic outbreak of SARS in 2003. Coronavirus belongs to the subfamily Coronavirinae of the Coronaviridae family and based on genetic properties, it is further subdivided into four genera: α-coronavirus, β-coronavirus, γ-coronavirus and δ-coronavirus. In the last two decades, β-coronavirus genera have been the focus of research due to outbreaks, emerging and re-emerging infections.[1] A study conducted in 2006 by Li et al. found that significant genetic changes have been reported in the spike(S) glycoprotein of the bats SARS-CoV to infect humans. The sequence data of human SARS-CoV report 87 – 92 % similarity with bats SARS-CoV.[11] Moreover, other than bats, intermediate hosts (civet cats and raccoon dogs) have also transmitted SARS-CoV to humans and subsequently, person-to-person transmission resulted in the pandemic of SARS-CoV.[12] SARS-CoV can infect the respiratory tract of individuals in all age groups. However, several risk factors including old age, diabetes, and heart disease increase the risk of morbidity and mortality. SARS-CoV infection occurred principally through droplet transmission and it was associated with fever, myalgia, malaise, chills, and diarrhea.[12] A study conducted by Holmes et al. in 2003 reported that the sudden outbreak of SARS-CoV was not due to the mutation or recombination in previous human coronaviruses. Epidemiologic reports revealed that SARS-CoV was not similar to previously known human coronaviruses.[13] Supporting this, genomic sequencing of SARS-CoV was reported to be similar to animal isolates. Various serological studies reported that animal traders had specific antibodies (IgG) against SARS-CoV infection. These results stated that SARS-CoV was a zoonotic virus strain and originated from bird and animal species.[14]

The entry of human SARS-CoV into cells is facilitated by binding of S glycoprotein to angiotensin converting enzyme2 (ACE2) receptors, thereafter, the changes in S glycoprotein take place by cellular serine protease cathepsins L and B in the endosome microenvironment to facilitate its fusion process.[12] A study conducted by Li et al. in 2005 found that 318 – 510 residues of the S1 domain encode the RBD. The adaptation of ACE2 with S glycoprotein permits the infection of human cells and is also responsible for the severity of SARS-CoV.[15]

The ACE2 receptors are found on epithelial cells of the lung, heart, kidney, liver, and tongue. The binding of S glycoprotein to ACE2 receptors of the respiratory tract causes loss of cilia, increase in the number of macrophages

in the alveoli, and squamous metaplasia. These changes lead to diffuse alveolar damage in the lungs.[16] Furthermore, SARS-CoV also produces 3a and 7a proteins that lead to cellular apoptosis in the lungs, liver and kidneys cells. Also, increasing inflammatory cytokines, activation of TH1, and increasing inflammatory interleukins such as IFN-γ, IL-10, IL-6, IL-1B, IL-8, IL-12 and MCP-1 have been reported in SARS-CoV infection.[17] The present review is based on summarizing the aetiology of human coronaviruses, namely SARS-CoV.

AETIOPATHOGENESIS OF MERS-CoV INFECTION

In 2012, Middle East respiratory syndrome-related coronavirus presented in the Middle East with approximately 2494 confirmed cases and 858 deaths.[18] It is also a zoonotic infection. Initially, the origin of MERS-CoV was reported to be from bat as the reservoir of MERS-CoV due to its phylogenetic similarity with strains of bat coronaviruses. Coronavirus belongs to the subfamily Coronavirinae of the Coronaviridae family and based on genetic properties, it is further subdivided into four genera: α-coronavirus, β-coronavirus, γ-coronavirus and δ-coronavirus. In the last two decades, β-coronavirus genera have been the focus of research due to outbreaks, emerging and re-emerging infections.[1] Various phylogenetic and serological studies reported that dromedary camels suffer from the human-MERS-CoV-like disease. Thereafter, various other studies linked camel–human contact and human-to-human transmission especially in healthcare communities.[18]

The mean incubation period for MERS-CoV infection is around 5 – 7 days but it was reported to be 2 – 14 days in some studies. MERS-CoV infection showed male preponderance. Symptoms of diseases vary from asymptomatic to mild symptoms and are sometimes presented with severe disease which leads to multi-organ failure. Some studies reported precipitation of metabolic syndromes in MERS-CoV infection including diabetes mellitus and cardiovascular diseases. These lead to decreased innate and humoral immune responses and make patients more prone to infectious diseases.[19] Researches were conducted and result obtained during MERS-CoV infections are extremely useful for efficiently and effectively managing disease worldwide. By conducting further research regarding the aetiology and pathogenesis of human coronaviruses, we can fill knowledge gaps and provide potential elements for fighting and controlling its global spread and prepare effective and efficient defense lines against human coronaviruses that may emerge or re-emerge in the near future.[6] CD26 and DPP4 are the receptors for the binding of MERS-CoV to the epithelial cells of the respiratory tract and pneumocytes. The human coronaviruses are positive-sense RNA viruses and have the largest genome sequence reported among RNA viruses. Structural proteins are essential for the infection and assembly of coronavirus, which are spike glycoproteins (S) on the surface of the particle and consists of two subunits S1 and S2. The S1 contains a receptor-binding domain and binds with cellular receptors and the S2 facilitates fusion and entrance process. Membrane protein (M) increases the membrane curvature and promotes viral assembly.[7] MERS-CoV also has a specific RBD which has 231-amino-acids in S glycoprotein and helps in binding at DDP4 on host target cells. DPP4 affects T cell activation, cytotoxic modulation, glucose metabolism, cell adhesion, and apoptosis. The co-restructures of MERS CoV and SARS-CoV are highly similar and their RBMs are highly divergent which leads to different receptor specificities.[20] Envelope protein (E) acts in the release of virus. Nucleocapsid protein (N) is interferon antagonistic (IFN) and acts in viral replication. The non-structural proteins block the host immune system for viral replication. RNA-dependent RNA polymerase (RdRp) enzyme has proofreading-activity, so the mutation rate is lower than other RNA viruses, however homologous recombination is frequently seen.[9] The present review is based on summarizing the aetiology of human coronaviruses, namely MERS-CoV.

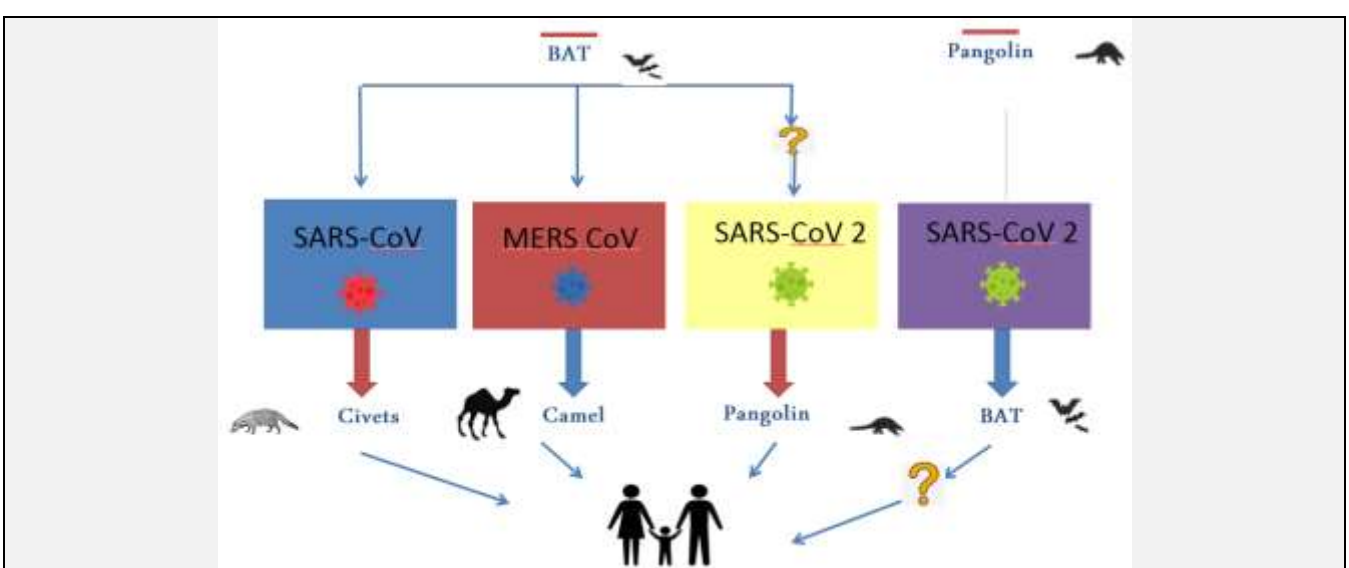

Figure 1. The Potential Animal Hosts, Bio-Distribution of SARS-CoV, MERS-CoV, and SARS-CoV-2

AETIOPATHOGENESIS OF SARS-CoV-2 INFECTION

SARS-CoV-2 is a highly pathogenic and transmissible coronavirus type that emerged in the year 2019 and has caused worldwide acute respiratory illness, named 'coronavirus disease 2019' which leads to high morbidity and mortality. Coronavirus belongs to the subfamily Coronavirinae of the Coronaviridae family and based on genetic properties, it is further subdivided into four genera: α-coronavirus, β-coronavirus, γ-coronavirus and δ-coronavirus. In the last two decades, β-coronavirus genera have been the focus of research due to outbreaks, emerging and re-emerging infections.[1] The SARS-CoV-2 was first detected and diagnosed in several patients who have travelled to Wuhan city, China, or have gone to a seafood market in Wuhan city, China.[3] The SARS-CoV-2 belongs to β-coronaviruses genera and it infects the upper and lower respiratory tract. Symptoms of the SARS-CoV-2 are milder than SARS-CoV and MERS-CoV but in transmission from human to human, it is reported to be faster than SARS-CoV and MERS-CoV. However, the mortality rate of SARS-CoV-2 is reportedly lower than that of SARS-CoV and MERS-CoV.[9]

Various studies reported that diabetes mellitus and hypertension may down regulate the host innate immune response and play a role in the pathogenesis of SARS-CoV-2 by interfering with the function of macrophages, lymphocytes, IFN-γ, and interleukin.[21]SARS-CoV-2 affects all ages with high severity of disease among middle-aged and older people with underlying disease. Children show less severe infection which may be due to their relatively healthy respiratory tract and active immune system compared with middle-aged and older people. These coronaviruses exert a high economic crises and public health burden worldwide. The infections are spreading all across the globe and an increasing number of infections are attributed to the high morbidity and mortality of SARS-CoV-2.[4] The specific medical countermeasures for these human coronaviruses are still under research. Sometimes spread of false information regarding these human coronaviruses is also seen worldwide which results in panic in the general public regarding the infection. According to recent studies, the SARS-CoV-2 pandemic was reported to cause the highest number of deaths globally. The incubation period, epidemiological, laboratory, radiological, and clinical findings of patients with SARS-CoV-2 were similar to SARS-CoV in 2003 and MERS-CoV in 2012. However, phylogenetic tree analysis reported that the SARS-CoV-2 is different from SARS-CoV and MERSCoV.[10]

A study conducted by Wei Ji et al. using genomic sequence analysis of different strains of human coronavirus revealed that SARS-CoV-2 is a recombinant virus strain between the bat coronavirus and a source-unknown coronavirus. They proposed that possible intermediate host of SARS-CoV-2 is the pangolin.[16] Envelope protein (E) acts in the release of the virus. Nucleocapsid protein (N) is interferon antagonistic (IFN) and acts in viral replication. The non-structural proteins block the host immune system for viral replication. RNA-dependent RNA polymerase (RdRp) enzyme has proofreading-activity, so the mutation rate is lower than other RNA viruses, however homologous recombination is frequently seen (8). Therefore, reports indicate the SARS-CoV-2 outbreak in Wuhan city was a zoonosis disease similar to SARS-CoV in 2003. The viral and S2 genome sequencing reported that SARS-CoV-2 is 96.2 % similar to bat coronaviruses and also very distantly correlated with SARS-CoV and MERS-CoV.[17]

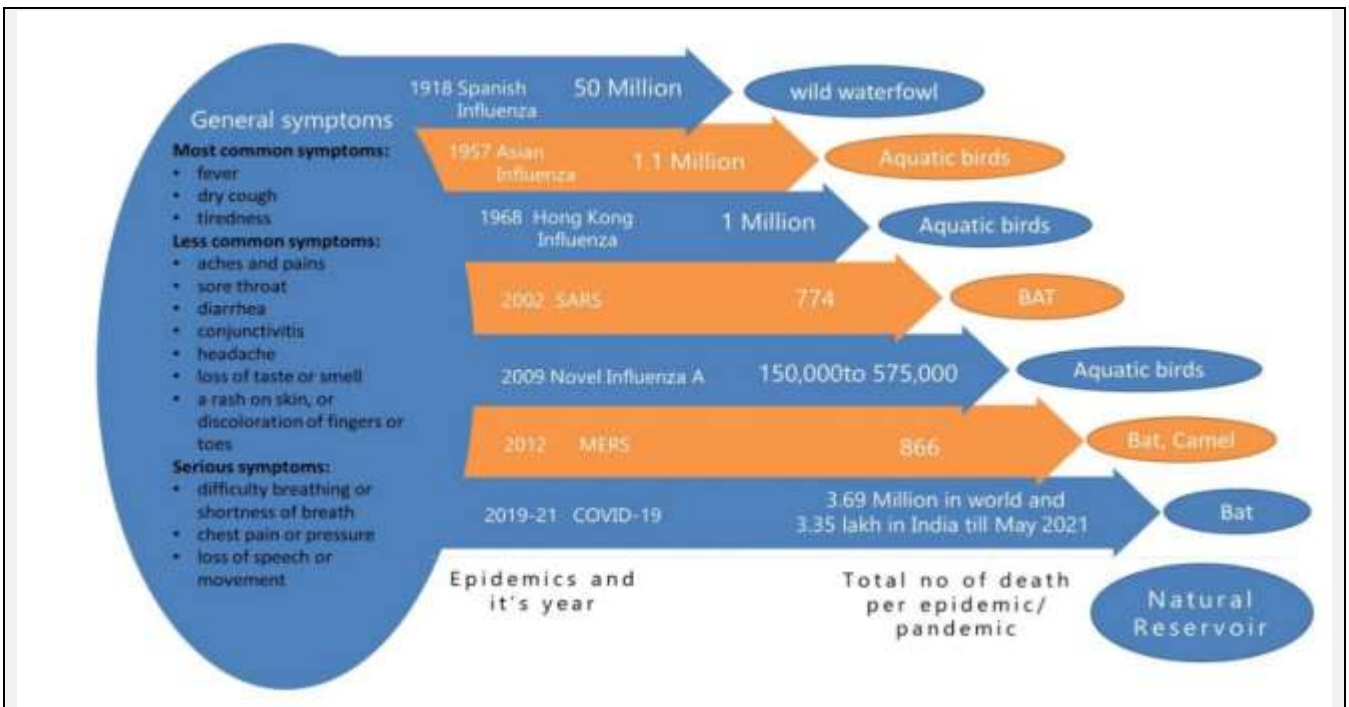

Figure 2. Epidemics of SARS-CoV-2, SARS-CoV, MERS-CoV, and Influenza A Viruses. The Timeline, Natural Reservoirs, Total Number of Deaths, and Symptoms of the Patients Infected with These Viruses

The human corona viruses are positive-sense RNA viruses and have the largest genome sequence reported among RNA viruses. Structural proteins are essential for the infection and assembly of coronavirus which are spike glycoproteins (S) on the surface of the particle and consists of two subunits S1 and S2. The S1 contains a receptor-binding domain and binds with cellular receptors, the S2 facilitates fusion and entrance process. Membrane protein (M) increases the membrane curvature and promotes viral assembly.[7] It is also reported that SARS-CoV-2 and SARS-CoV have distinct genome sequences of RNA-dependent RNA polymerase (RdRp). That's why SARS-COV-2 was clustered within an independent subclade in the β-coronavirus genus.[19] Other studies of phylogenetic analysis of RBD reported that the SARS-CoV-2 was similar to SARS-CoV located in lineage B. Moreover, SARS-CoV-2 can infect BHK-21 cells. These findings indicate that SARS-CoV-2 utilizes the ACE2 as a cell receptor and cellular proteases like TMPRSS2 for S glycoprotein priming.[22]

A study conducted by Lu et al. reported that various residues in RBD of SARS-CoV, S glycoprotein were found to be variable in SARS-CoV-2.[19] It is also reported that biophysical and cryo-EM structure evidence showed that the affinity of SARS-CoV-2 S protein to ACE2 receptors is 10 – 20 folds higher than the SARS-CoV. These reports solidify the theory of the higher pathogenicity of SARS-CoV-2 in comparison with SARS-CoV.[23] Researches were conducted and result obtained during SARS-CoV infections are extremely useful for efficiently and effectively managing of SARS-CoV-2 disease worldwide. By conducting further research regarding the aetiology and pathogenesis of human coronaviruses, we can fill knowledge gaps and provide potential elements for fighting SARS-CoV-2, controlling its global spread and prepare effective and efficient defense lines against human coronaviruses that may emerge or re-emerge in the near future.[6] Among healthy adults and children, ACE2 modulates the renin-angiotensin system via cleaving angiotensin II to angiotensin-1–7 to prevent acute lung failure. Various studies reported that acute lung injury from a viral infection is associated with ACE2 deficiency and increase in angiotensin II.[24] The specific medical counter measures for these human coronaviruses are still under research. Sometimes spread of false information regarding these human coronaviruses is also seen worldwide which results in panic in the general public regarding the infection. The SARS-CoV-2 virus shows many similarities with SARS-CoV and MERS-CoV viruses, however, certain differences also exist as well.[5] A study conducted by Zhou et al. reported that Asians are more susceptible to SARS-CoV-2 infection compared to other races due to the expression of the ACE2 receptors.[25] The ACE2 receptors are physiologically related receptors during SARS-CoV-2 infections and accounts for the localization of viruses. The infection efficiency correlates with the ACE2 receptors of each species to support viral replication.[26]

CONCLUSIONS

In the present review, we discuss three highly pathogenic and deadly human coronaviruses which have emerged within the last two decades, namely SARS-CoV-2, SARS-CoV, and MERS-CoV. We concluded that bat seems to be the common natural origin of SARS-CoV-2, SARS-CoV, and MERS-CoV. SARS-CoV-2 is a highly pathogenic and transmissible coronavirus type that emerged in the year 2019 and has caused a worldwide acute respiratory illness, named 'coronavirus disease 2019' (COVID-19), with a high morbidity and mortality. The clinical features are similar; however, SARS-CoV-2 spreads more rapidly than SARS-CoV and MERS-CoV. The S glycoprotein adaptation and its affinity for ACE2 receptors determine the severity of infection. Hence, a vaccine containing inactivated SARS-CoV-2 or S glycoprotein could have the potential to prevent COVID-19. Extensive research is needed on genetic diversity and recombination events of SARS-CoV-2 to present an effective treatment. The present review is based on summarizing the pathogenesis of human coronaviruses, namely SARS-CoV-2, SARS-CoV, and MERS-CoV. This review provides comparative evaluation of the genomic features, origin, transmission, and pathogenicity of these human coronaviruses. The coronavirus pandemic disease 2019 (COVID-19) caused by SARS-CoV-2 is still ongoing, as a result, this comparative evaluation may inform and aid in the knowledge of public health administrators and medical experts to control the pandemic's progression.

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