

Review Article

Covid-19 in pets

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Abstract

The rapid and unpleasant spread of pathogens was exemplified by the COVID-19 pandemic. Throughout history, humans and animals have been affected by numerous significant epidemics and pandemics, including but not limited to the plague, SARS, MERS, H1N1 pandemic influenza, H5N1 avian influenza, and Ebola hemorrhagic fever. Human diseases are mainly caused by animal-human transmission. The COVID-19 pandemic caused by the SARS-CoV-2 virus is the most destructive pandemic of the current century. About 3/4 of all re-emerging and arising human diseases may date back to animals, mainly wild animals. The SARS-CoV-2 virus has been identified as a global health concern as it affects not only humans but also pets and a variety of wild and domestic animals. This finding emphasizes the significant impact of the disease on the health of both humans and animals. Therefore, a "one health" approach is necessary to involve experts from various fields, such as human, animal, and environmental health, as well as other relevant disciplines and sectors, to prevent and manage animal epidemics globally.

Keywords: cat, dog, corona, zoonosis, SARS-CoV-2

Introduction

Rapid and increasing outbreaks of new zoonotic diseases have been reported, including respiratory, hemorrhagic, arthropod, encephalitic, and other viral diseases that kill thousands of people every year. It is undeniable that cats, minks, and ferrets can contract severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), leading to illness, the virus can be transmitted from one animal to another (Shi et al., 2020). The ongoing COVID-19 pandemic, which originated from bats to humans,

has caused a significant alert due to the severity of the disease and its zoonotic recognition (Noor et al., 2020). It is essential to have close collaboration among professionals in animal and human health, as well as stakeholders from other fields, to evaluate the well-being parameters of the planet. Thus, a health principle method must be utilized worldwide for human infectious diseases to prepare for future zoonotic disease pandemics and outbreaks (Jones et al., 2008).

This is due to the identification of SARS-CoV-2 as the root cause of the COVID-19 pandemic global spread. This pathogen, which can easily cross the interspecies barrier, causes respiratory disease (Ramanujam and Palaniyandi, 2022).

It belongs to the Coronaviridae group, which has one of the most giant genomes among viruses and is related to the Orthocoronavirinae subgroup in the Coronaviridae family (Gorbalenya et al., 2020). The virus contains a single-stranded RNA (29.9 kb) and encodes four fundamental developments, including spike (S), nucleoprotein, envelope, and membranes.

The membrane of SARS-CoV-2 virus comprises four primary structural proteins: spike (S) glycoprotein, membrane (M) glycoprotein, small envelope (E) glycoprotein, and nucleocapsid (N) protein (Astuti, 2020).

The virus attaches to host cells through a glycoprotein on its outermost layer, which binds to the Angiotensin-converting Enzyme 2 (ACE2) receptor on the target cells (Luan et al., 2020). SARS-CoV-2 is a member of the Coronaviridae

family and has one of the largest single-stranded RNA genomes (29.9 kb) among viruses. The virus encodes four fundamental proteins, including Spike (S), nucleoprotein, membrane, and envelope proteins (Hoffmann et al., 2020). The S protein is essential for the virus to enter susceptible cells through receptor-mediated pathways. In vitro, studies have shown that ACE2 from 44 different mammals can bind to the RBD (Li et al., 2020b). The M protein is the most abundant protein in the virus and plays a critical role in virus assembly, along with other structural proteins (Schoeman and Fielding, 2019). The N protein is responsible for binding and packaging the genome of viral RNA into a longer helical nucleocapsid structure (Kang et al., 2020). The genome of SARS-CoV-2 has 96% and 79.6% sequence similarity with Bat-CoV and SARS-CoV, respectively (Zhou et al., 2020). This study aimed to investigate the influence of pets on people's well-being during the COVID-19 pandemic and how confinement in isolation affects the relationship between companion animals and humans during a tense event.

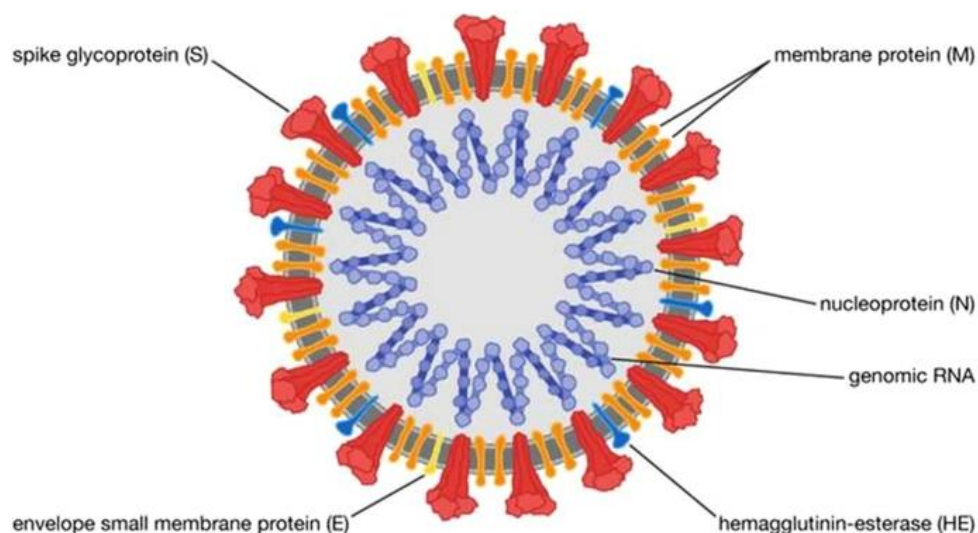


Fig. 1. SARS-CoV-2 Structure (Kiros et al., 2020).

Pathogenesis

The COVID-19 pandemic, which is an acute respiratory syndrome, is resulted by a virus belonging to the Corona family. This virus is also

known to cause hepatic, neural, and enteric disorders in avian and mammalian species (Ramesh et al., 2020). Further studies are still required on the pathogenesis of COVID-19.

Nevertheless, it seems to primarily affect the lung in most patients, as it is a respiratory disease. The ACE2 receptor is used by SARS-CoV-2, found on human and other animal species type II pneumocytes in the lung cells for connection. SARS-CoV-2 entering a cell involves the virus's S glycoprotein binding to the ACE2 receptor. Two pathways for entry have been identified: the endosomal pathway and the non-endosomal path. In the endosomal pathway, the binding occurs after receptor-mediated endocytosis. Cathepsin L is activated by an increase in H⁺ influx into the endosome, which then cleaves the S glycoprotein. This cleavage exposes the fusion peptide near the cleavage site, which then fuses with the host cell membrane, allowing the virus to enter the cell. When using the non-endosomal pathway, the glycoprotein of SARS-CoV-2 S binds to the ACE2 receptor after the S glycoprotein of virus is cleaved by transmembrane protease serine 2 (TMPRSS2) located on the host cell surface. This direct fusion of the viral and plasma membranes leads to the delivery of the viral particle into the cytoplasm (Astuti, 2020; Mahmoud et al., 2020). Once inside the host cell, the virus uncoats its viral genome, leading to its transcription and translation (Mousavizadeh and Ghasemi, 2021).

Epidemiology, ways of transmission, and risk factors

CoVs are famous for circulation in birds and mammals (Abdel-Moneim and Abdelwhab, 2020). Assessing the SARS-CoV-2 genomes has submitted the possible introduction of the virus from the Asian bats related to the *Rhinolopus* species (Lu et al., 2020). An intermediate host may be involved in the transmission to humans, probably the pangolin (Boni et al., 2020; Liu et al., 2020; Wahba et al., 2020; Xiao et al., 2020; Zhang et al., 2020). MERS-CoV and SARS-CoV are viruses that can be transmitted from animals to humans and are mainly found in bats. SARS-CoV was transmitted from bats to palm civet cats and humans, while MERS-CoV was transmitted from bats to dromedary camels and then to humans. The initial human case of SARS-CoV was reported in

China in 2002, where it had spread from palm civets to humans, resulting in a worldwide epidemic that lasted for eight months and caused at least 774 deaths. Ten years later, MERS-CoV was found in Saudi Arabia in 2012 in people who had close contact with camels and became a major public health concern, spreading to 27 countries and killing 858 people (Totura and Bavari, 2019). Nevertheless, the primary origin of the infection is not yet known precisely. SARS-CoV-2 primarily targets the human respiratory system, and as a result, respiratory aerosols and droplets are considered the main routes of transmission.

Regarding pets' role in disease transmission

In February 2020, the first instance of COVID-19 in a companion animal was communicated in Hong Kong, China, involving a Pomeranian dog with no relevant symptoms (Kiros et al., 2020). A cat in the same country with no clinical signs of illness was also reported to have COVID-19 in March 2020, with both pets' owners testing positive for the virus (Parry, 2020). The Hong Kong's experts University confirmed the Pomeranian dog's positive RT-PCR result, and the World Organization for Animal Health verified it as a genuine positive case. It was further supported for any positive suspected cat or dog, which should be confined and quarantined at government kennels (Kiros et al., 2020). The potential for human-to-animal transmission was indicated by SARS-CoV-2 genetic sequence similarities between the pets and owners. In some studies, (e.g., Singla et al., 2020), it was claimed that both serological tests and viral culture examined whether a dog was negative or positive. Such tests, without any signs or symptoms, can help to understand that the dog has not transmitted the infection to other people or animals (Almendros, 2020). Despite the WHO's claims that pets are not susceptible to COVID-19 and cannot effectively transmit the disease, several instances of pet infection have been reported worldwide (Csiszar et al., 2020). These pets were primarily from households with infected individuals, whole genome sequencing (WGS) indicated that the sequences obtained from both pets and humans

were identical, demonstrating that the infection was transmitted from pets to humans (Hamer et al., 2020; Neira et al., 2021; Zoccola et al., 2021). Cats are more sensitive to COVID-19 infection than dogs and can transmit the disease to other cats, including those who have not previously been infected (Shi et al., 2020). Following the initial report of COVID-19 in a cat, several other cases were reported in various countries, including Belgium, Russia, Germany, France, and the USA (Yilmaz et al., 2021). Much effort has been made to recognize the association between SARS-CoV-2 infection and pet ownership. Additionally, cats are highly sensitive to COVID-19 and can potentially act as a reservoir for transmitting the virus to other cats, while dogs are less vulnerable (Shi et al., 2020). A case of natural infection in a cat was reported in Belgium, with the virus detected in collected samples through PCR (Garigliany et al., 2020). The cat showed symptoms such as respiratory distress, diarrhea, and vomiting, indicating active viral replication (Dzieciatkowski, 2020; Jurgiel et al., 2020). In addition to dogs and cats, experiments have shown that Syrian hamsters are also sensitive to SARS-CoV-2 and can transmit the disease back to humans. SARS-CoV-2-exposed golden hamsters can infect and efficiently ship the virus to naive hamsters through direct contact and aerosols (Sia et al., 2020; Chan et al., 2020). All pets living with individuals infected with COVID-19 are at risk of contracting the disease and spreading it to other susceptible pets. Therefore, companion animals need to be protected by owners from infection. Thus, COVID-19 can be effectively prevented. Otherwise, problems will be created for the complete control and prevention of the disease. Pets might transmit the virus potentially to humans

since they lead to the expression of the same cell receptor, ACE2. Therefore, continued standard prudent measures are required. The dogs and cats infected with covid 19 infects will defiantly transmit the disease to humans. According to Bakhraibah (2022), it is believed that toxoplasmosis can elevate immunological and immunosuppressive factors, leading to an increased susceptibility to SARS-CoV-2 infection and more severe cases of COVID-19.

Clinical signs

There has been a rise in epidemiological surveys examining dogs residing in households with confirmed cases of SARS-CoV-2 or in areas impacted by COVID-19. However, there are currently no clinical reports describing disease manifestations in dogs. In one case report, a six-year-old Cavalier King Charles spaniel was referred for acute exercise intolerance and syncope that had been ongoing for two months. The clinical signs worsened during a local COVID-19 outbreak, two weeks after members of the dog's family showed symptoms of the viral disease and tested positive for SARS-CoV-2. The cardiologic evaluation demonstrated myocardial injury complicated by systolic dysfunction (Romito et al., 2021).

According to Rudd et al. (2021), intratracheal inoculation of SARS-CoV-2 in a Cat SARS-CoV-2 Infection Model resulted in significant lethargy, dyspnea, fever, and dry cough, consistent with the early exudative phase of COVID-19. However, studies suggest that dogs (*Canis lupus familiaris*) are only mildly susceptible to SARS-CoV-2 contamination and do not exhibit any clinical signs, indicating that they are less likely to progress to COVID-19 in vivo (Shi et al., 2020).

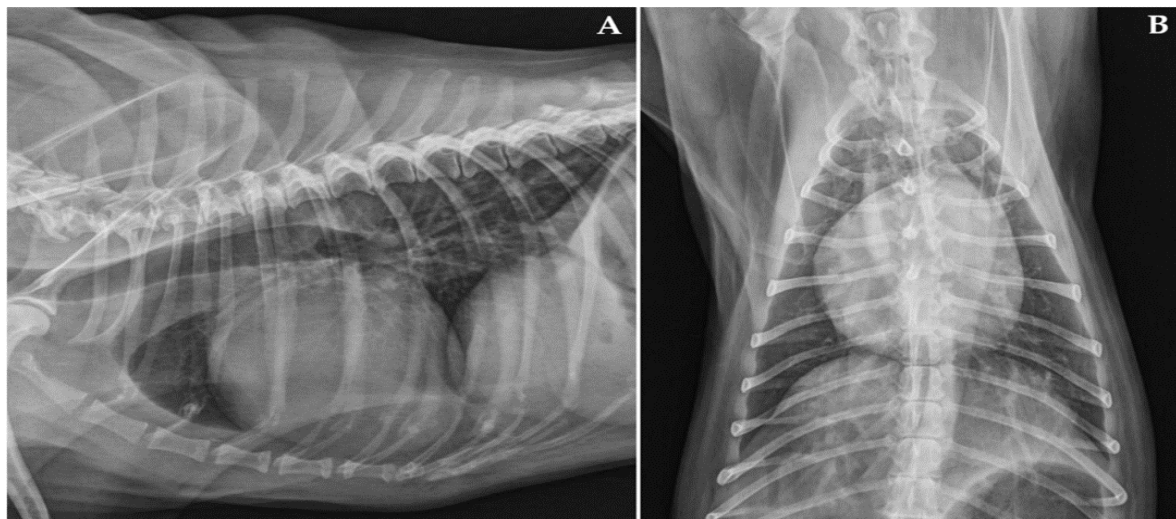


Fig. 2. The figure displays the right lateral (A) and dorsoventral (B) thoracic radiographs of a COVID-19-positive dog. The images clearly show a cardiac silhouette mild enlargement, but no abnormalities in the lung parenchyma (Romito et al., 2021).

Laboratory diagnosis

The process of diagnosing SARS-CoV-2 in animals experimentally is comparable to analyzing the virus in humans. To analyze the virus, samples from the respiratory tract, such as the nasal turbinate, tonsils, and soft palate, are crucial (Singla et al., 2020). The samples from these sites are desirable. However, other samples from other sites can also be used, such as rectal swabs, if direct sampling is impossible owing to dangers to the animal or experiment staff (OIE) (Infection with SARS-CoV-2 in animals). The molecular test was advanced for human specimens. Real-time reverse-transcription polymerase chain reaction (RT-PCR) is considered the gold standard for diagnosing SARS-CoV-2 in animals (Richard et al., 2020; Rani et al., 2021), it is commonly used with the respiratory tract samples mentioned earlier. Other methods for detecting SARS-CoV-2 in animals include viral genome sequencing, isolation of virus in cell culture, and various molecular tests like reverse transcription loop-mediated isothermal amplification (RT-LAMP) (Baek et al., 2020). The OIE has reported that rapid immunochromatographic tests and other serological immunoassays, such as virus neutralization and enzyme-linked immunosorbent

assay (ELISA), can detect antibodies against SARS-CoV-2 in animals. Younes et al. (2020) discussed SARS-CoV-2 infection in animals.

Treatment

Several antiviral drugs and vaccines have been examined, although no definitive cure has been known for COVID-19 in modern medicine. Thus, it is essential to use supportive treatment frequently. Viral infections heavily affect human health. Owing to the urgent requirement to discover a cure for different viruses, searches have been performed on an extensive range of drugs. Other effects have been shown by Azithromycin (AZT), categorized as a macrolide, and various widespread viruses like severe acute respiratory syndrome coronavirus (SARS-CoV), Enterovirus (EVs), Zika, Ebola, Influenza, and Rhinoviruses (RVs) (Khoshnood et al., 2022). It was indicated that these viruses inducing global concerns are the objective for AZT's different actions. Owing to the history of AZT in the treatment of viruses mentioned above, with the emergence of COVID-19, AZT is considered a promising candidate for the treatment of COVID-19 due to its antiviral and immunomodulatory properties. AZT usage instructions are highly controlled to medicate viral

infections such as COVID-19. Using AZT in the treatment of COVID-19 is still debated. Though, finally, WHO was convinced by novel research to proclaim the stop of AZT use (alone or combined with hydroxychloroquine) in treating SARS-CoV-2 infection. In the present work, the structure of all of the viruses as mentioned above, and the clinical and molecular effects of AZT against the virus were studied (Khoshnood et al., 2022).

Li et al. have reported that various studies have shown that traditional herbal medicine can relieve COVID-19 symptoms (Li et al., 2020a). Shiri et al. (2021) suggested that a combination of Sugarcane, Black Myrobalan, and mastic may be an effective treatment for COVID-19 symptoms, as it has been shown to reduce treatment duration and has been confirmed as safe. Terminalia chebula contains various molecules that provide it with antiviral, antifungal, and antibacterial activity. According to Hongbo et al. (2010) and Lopez et al. (2017), Terminalia chebula is effective against swine flu type A, HSV-1, and HIV-1 as an antiviral agent. Mastic has been shown in animal model studies to have the potential to develop pulmonary fibrosis. In an animal model of asthma, the use of mastic reduced the expression of TNF- α , IL-4, and IL-5, increased lung inflammation, and reduced respiratory tract inflammation (Zhou et al., 2009). Giamarellos-Bourboulis et al. (2020) have reported that TNF- α has potential action in the cytokine storm triggered by COVID-19 (Giamarellos-Bourboulis et al., 2020). Of course, these herbal compounds should be further investigated in terms of not causing severe side effects and drug interactions.

Prevention and control

Strategic management and effective control measures, such as privacy protection, temperature screening, public distancing, quarantine of individuals with suspected or confirmed infection and travel history, early testing, and preventing global spread, are crucial in reducing human-to-human transmission (Gasmi et al., 2020; Lipsitch et al., 2020; Hellewell et al., 2020). Studies suggest the virus may have originated from a caged wild

animal and was transmitted to humans at the Huanan Seafood Wholesale Market. Another means to control infection may be identifying the transmission cycle from the susceptible animal sources. Considering the vulnerability of pets and other animals to SARS-CoV-2, people positive or suspected of COVID-19 are suggested to limit their contact with these animals to decrease animal infection from human sources. Social distancing, surveillance, and quarantine are yet considered as final effective ways to control the human-to-human spread. A sustained and significant effort is required by the nation's health to hinder illness and support the one-well-being method in their control and prevention planning. Thus, people and animals can be protected against sickness to control the disease. Continuous viral circulation is particular between people and animals. Continuous monitoring of animals is crucial.

Developing a vaccine for various animal species and getting it into the pipeline is a difficult and lengthy process. However, Russia has initiated the development of Karni-Kov, an early vaccine for carnivorous animals. This vaccine aims to safeguard carnivores against SARS-CoV-2 and has undergone successful trials in arctic foxes, cats, rats, and mink (Chavda et al., 2021).

A linear DNA vaccine candidate that encodes the receptor binding domain of SARS-CoV-2 was used, and it induced protective immunity in domestic cats. Regulatory approval for this vaccine has been granted by the United States Department of Agriculture (USDA). Zoetis has experimentally developed a vaccine candidate that was used to vaccinate eight great apes against SARS-CoV-2 at the San Diego Zoo. Additionally, researchers in Korea have developed a COVID-19 vaccine for dogs that prevents the reverse zoonotic disease (Ga et al., 2022). Of course, the covid-19 vaccines made for dogs and cats should be further investigated and researched to ensure they do not cause severe side effects in the short or long term.

Conclusion and future perspective

The SARS-CoV-2 outbreak has been detected in various animal species thus far. More detailed

investigations are required on the virus, and it is essential to implement a Health approach and dynamic risk assessments along with targeted control programs to decrease the disease. The transmission of SARS-CoV-2 infection could be significantly influenced by animals. The COVID-19 cases linked to minks in the Netherlands provide evidence of animal-human viral spillover. It is plausible for COVID-19 to be contracted by humans from animals, including pets and other domesticated species. Therefore, it is crucial to incorporate standard precautionary measures in disease prevention planning when interacting with or spending time with companion animals. It is also essential to track the pets SARS-CoV-2 infection, especially those with owners who have tested positive and isolate them to prevent the spread of COVID-19. Abandoning pets should be avoided at all costs. To prevent further transmission, it is crucial to trace infected individuals and animals. Further research is necessary to evaluate the total zoonotic risks of SARS-CoV-2 and determine the probable intermediate host to prevent the virus from re-emerging. This study presents a health strategy for animal epidemic control and prevention in countries like the Netherlands, Spain, China, and the USA.

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Not applicable.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Ethical approval

Not applicable.

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