

# Review Paper: A Review on Transmission of Coronavirus between Humans and Animals: Health Complications and Hazards



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## ABSTRACT

**Objective:** Coronaviruses (CoVs) infections are among the most common diseases in humans and animals. In this paper, the effects of human-animal host interactions of a new coronavirus disease-2019 (COVID-19) emerged from China were reviewed and possible health complications and hazards were investigated.

**Materials and Methods:** Electronic databases including PubMed, Google Scholar, Scopus, and bioRxiv were searched for possible animal hosts of SARS-CoV-2 from the years 2019 to 2022 by following keywords: coronavirus, COVID-19, SARS-COV-2, animal, and transmission.

**Results:** Among different animal species, non-human primates, ferrets, hamsters, and felines are the most susceptible animals to SARS-COV-2 infection and some of them have the ability to transmit the virus to humans.

**Conclusion:** The risk of emerging zoonotic diseases is not far from the mind; hence, the animal populations should be periodically monitored for the possible occurrence and spread of such diseases. It is also recommended to follow hygienic instructions during the COVID-19 pandemic.

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## 1. Background

Coronaviruses (CoVs) are members of the family of Coronaviridae from the order Nidovirales. These viruses were first identified in the late 1960s and were named CoVs because of their crown-like appearance. The genome of these viruses is a single-stranded positive-sense RNA weighing about 30 kb, with a cap structure at the 5' and a tail at the 3' extremities, respectively. CoVs contain a series of structural proteins including spike (S), hemagglutinin (HA), envelope (E), nucleocapsid (N), as well as several nonstructural proteins (Figure 1), which work together to bind to host cells, replicate, and cause viral infections (1, 2).

For decades, CoVs have been thought to cause mild respiratory infections in humans (2, 3); however, two new strains of CoVs (HCoV-NL63 and HCoV-HKU1) caused mild to moderate respiratory infections (4, 5). Later, the other CoV strains that caused acute and fatal diseases and were able to transmit from animals to humans were also identified (2). Severe Acute Respiratory Syndrome (SARS) appeared in Guangdong Province, China in 2002 and its global spread was associated with 8096 cases and 774 deaths (2, 6). Chinese horseshoe bats act as the

natural reservoir host of SARS (7). Transmission of the disease to humans is facilitated by intermediate hosts such as Civet cats and Raccoon dogs, which are often sold as food sources in China (8). In 2012, Middle-East Respiratory Syndrome (MERS) broke out on the Arabian Peninsula and spread to 27 countries. The disease infected a total of 2,499 people during its outbreak and killed 858 cases (9). Similar to SARS, bats were identified as a reservoir of the MERS (10). Camels were also introduced as intermediate hosts between humans and bats (11). Hence, researchers have paid significant attention to these viruses.

In late 2019, new cases of pneumonia were diagnosed in those who were associated with the Hwanan Seafood Wholesale Market in Wuhan City, Hubei Province, China. The researchers' subsequent investigations led to the isolation of a new strain of CoVs from the bronchoalveolar lavage fluid (BALF) in three patients. Due to high genetic similarity, the virus was named SARS-CoV-2 and considered the pathogen of the current outbreak of Coronavirus disease-2019 (COVID-19) (12, 13).

Despite extensive efforts to control the disease, COVID-19 has now spread to more than 200 countries and caused a global pandemic. Currently, the number of infected people, as well as those who have died from COVID-19 has exceeded the total number of people infected with SARS in 2002.

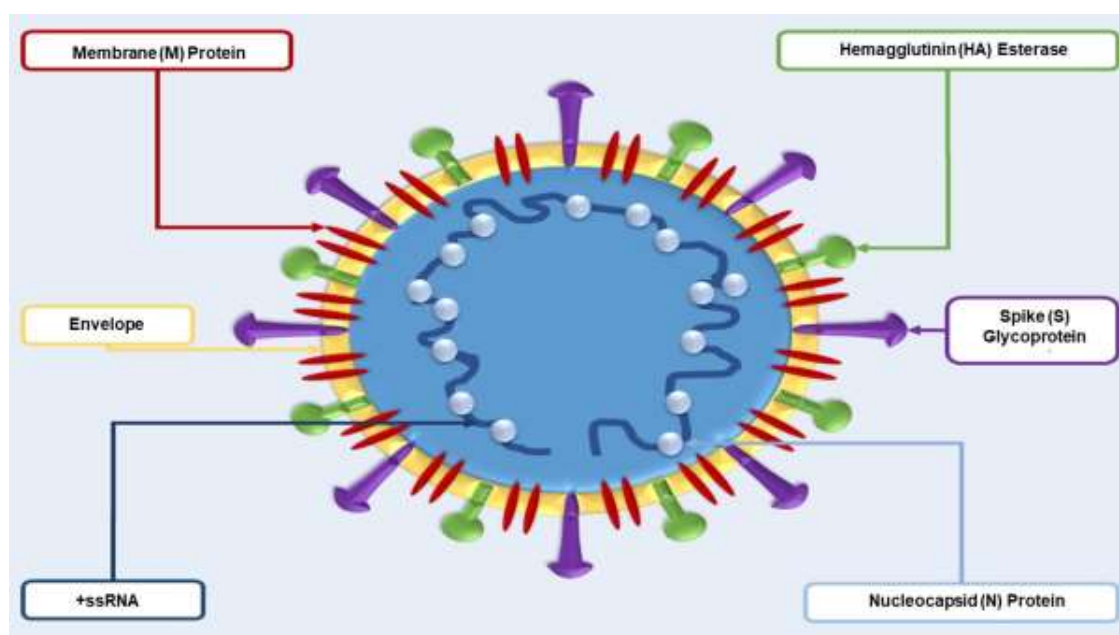


Figure 1. The schematic structure of CoVs

According to the latest World Health Organization (WHO) report, as of this writing, more than 392 million people worldwide have been infected with the disease, and at least 5.7 million of them have died (14). There is emerging public health concern about the possible transmission of SARS-CoV-2 to other animal species, and its subsequent potential to become reservoirs of infection (15).

## 2. CoVs Classification and Their Hosts

Based on phylogenetic relationships and the genome structure, CoVs are divided into four categories, called alpha, beta, gamma, and delta. Alpha and beta CoVs can infect humans and other mammals. Gamma CoVs can infect birds and marine mammals, such as whales and dolphins. Delta CoVs are mainly observed in birds and sometimes in mammals (1, 2). Infections caused by these viruses in animals generally lead to intestinal diseases and a lesser extent cause respiratory, hepatic, and central nervous system problems (1).

## 3. SARS-Cov-2 Phylogeny and Its Possible Origin and Intermediate Host(s)

SARS-CoV-2 is a genus of beta-CoVs that along with the bat-like SARS (BatCoV RaTG13), belongs to the subgenus Sarbecovirus (16, 17). The SARS and MERS-CoVs differ genetically from newly discovered CoV, but they are also belonging to beta-CoVs. According to a study by Malik et al. (16), SARS-CoV-2 is approximately 50% similar to MERS and approximately 79% similar to SARS.

The origin of SARs-CoV-2 is not yet identified and researchers are trying to find the origin and possible intermediate animal hosts. As mentioned earlier, the first cases were those who worked in and/or visited the Huanan Seafood Wholesale Market; however, none of the subsequent cases were related to this market. Hence, the human-to-human transmission or the presence of extensive animal resources should be considered. It has been reported on social media that besides seafood, some wild animals such as snakes, marmots, and bats were also sold on the market. WHO has reported that environmental samples taken from the Huanan market have been positive for SARS-CoV-2, but no specific animal association has been identified (18).

Scientists believe that like the two previous epidemics of the CoVs, the bat is the reservoir of

the new CoV. Studies have shown that SARS-CoV-2 has a 96.3% genetic similarity to bat-like SARS (BatCoV RaTG13) (19). It is also thought that like SARS and MERS, other species of animals have roles as intermediate hosts between humans and bats (20). Early reports based on genetic analysis suggested that snakes may be a possible source of transmission to humans (19, 20), but this claim has been questioned by others as snake infection with CoVs has not been reported so far (21). A more plausible hypothesis is that the scaly anteater (pangolin) is the intermediate host for SARS-CoV-2. Studies have shown that SARS-CoV-2 has about 90% genetic resemblance to the CoV in the pangolin. Due to more similarity between S1 glycoprotein of SARS-CoV-2 and pangolin CoV (in comparison to bat CoV), researchers have suggested that the bat CoVs may have first entered to the pangolin body and after evolution, it entered into humans (22-26). Third hypothesis suggests that stray dogs may have acted as intermediate hosts in the transmission of SARS-CoV-2 to humans (27).

The mammalian body contains an antiviral protein called Zinc-Finger Antiviral Protein (ZAP), which can stop pathogen replication and destroy the virus genome. Viruses in their genome contain a specific sequence of building blocks known as CpG dinucleotides that help the immune system to search for and eliminate the pathogen. This sequence is known by the ZAP protein in the lungs, but viruses can also ingeniously circumvent this defense mechanism. Single-stranded CoVs can get rid of the ZAP-dependent defense mechanism by reducing the number of their CpG dinucleotides (28). It was found that SARS-CoV-2 and a similar bat CoV (BatCoV RaTG13) had the lowest CpG levels among all close CoV relatives. Only the CoV genome in dogs that causes highly contagious intestinal disease in these animals has similar CpG levels to those found in SARS-CoV-2 and BatCoV RaTG13. Accordingly, researchers suggest that SARS-CoV-2 originally entered the body of stray dogs through the consumption of bat meat, and then, the virus evolved in the animal intestine and reduced its CpG genome. Ultimately, the acquisition of this trait enables the virus to escape from the immune response mediated by ZAP and turn it into a dangerous pathogen for humans (27). Findings from other studies sparked speculation that turtles may act as a potential intermediate host for SARS-CoV-2 (29). However,

Luan et al. (30), showed that the ACE2 receptor of the turtle is unable to bind to S protein RBD of SARS-CoV-2.

#### 4. COVID-19 in Animals

##### 4. 1. Laboratory Animals

###### 4. 1. 1. Laboratory Rodents and Lagomorphs

Among rodents used as animal models in experimental studies, the golden Syrian hamster is naturally susceptible to SARS-CoV-2 infection (31, 32). The ACE2 receptor of hamsters and humans are structurally similar to each other and the spike protein of SARS-CoV-2 has a high affinity to binding to this receptor. Syrian, Roborovski Dwarf and Chinese hamsters have manifested clinical and histopathological signs similar to humans. The inoculation of SARS-Cov-2 infection to hamsters caused weight loss and respiratory distress accompanied by mild to severe pneumonia (32). The percentage of disease transmission from infected animals to naive co-housed hamsters is high. Also, experimental infection is lethal in the Roborovski Dwarf strain (33, 34).

Due to differences in key amino acid residues of the ACE2 receptor in mice, SARS-CoV-2 is incapable to bind ACE2 receptors (35); therefore, mice have low sensitivity to SARS-CoV-2 infection (31). Experimental infection results in transient weight loss and mild to moderate pneumonia in BALB/c and C57BL/6J mice (36). Infection to SARS-CoV-2 was not detected in guinea pigs (37).

###### 4. 1. 2. Laboratory Ferrets

Ferrets are commonly used as animal models for viral respiratory infections. SARS-CoV-2 can replicate in the upper respiratory tract of ferrets and is effectively transmitted to naive ferrets by direct contact (38). Experimental infection of ferrets had no clinical signs of COVID-19 such as that observed in humans. Histologically, thickened respiratory mucosa and exudate of polymorphonuclear cells, lymphocytes, and some macrophages are reported. Damage to the epithelial lining was characterized by hypertrophy, hyperplasia, and squamous metaplasia (39).

###### 4. 1. 3. Non-Human Primates

The primate models have yielded helpful insights into SARS-CoV-2. Studies have shown that non-

human primates including African green monkey, Rhesus macaques, Cynomolgus macaques, and Common marmosets can be experimentally infected with SARS-CoV-2, but Common Marmosets are relatively resistant to SARS-CoV-2 as compared to other two species (31). In general, experimental infection of African green monkeys, Rhesus macaques, and Cynomolgus macaques with SARS-CoV-2 caused weight loss and reduction of appetite. Besides, interstitial pneumonia can be seen in histopathological sections of their lungs (32).

##### 4.2. Companion and Pet Animals

Due to close contact between companion animals and humans, their susceptibility to SARS-CoV-2 is an important issue in public health. Generally, cats are highly susceptible to infections. Some evidence has shown that cats are susceptible to airborne transmission of SARS-CoV-2 (40). Cats in Wuhan have also been seropositive for SARS-CoV-2 (36). They shed viral agents through their mouths and noses. Shi et al. (15), have reported the existence of the infectious virus in the upper respiratory tract of cats. Infection is not accompanied by clinical signs and is capable of direct contact transmission to other cats. A few cases have been identified in different countries where cats were infected with SARS-CoV-2 from their owners. Cats can develop neutralizing antibodies that prevent reinfection. Recent studies show that cats may be a good model for vaccine development (40). In a feline SARS-CoV-2 infection model study, significant lower respiratory disease and features of diffuse alveolar damage and acute respiratory distress syndrome analogous to those seen in the early exudative phase of human COVID-19 were reported. SARS-CoV-2-infected cats exhibited clinical signs of lower respiratory disease characterized by increased respiratory effort and coughing in addition to signs of systemic involvement such as pyrexia and lethargy. Histologic features included vascular injury, pulmonary edema/exudate, perivascular inflammatory infiltration, alveolar histiocytosis and necrosis, intra-alveolar fibrin, fibrinoid vasculitis, and vascular thrombosis (41). Unlike cats, dogs have low susceptibility to SARS-CoV-2 (15). Dogs do not shed virus following infection but do seroconvert and mount an antiviral neutralizing antibody response. Infection of pet animals following exposure to human patients is possible. Experimental infection

of domestic dogs and cats with SARS-CoV-2 shows no gross lesions. Histological findings in cats include ulcerative, suppurative lymphoplasmacytic rhinitis, lymphoplasmacytic tracheitis, alveolar histiocytosis with edema, and mild interstitial lymphocytic pneumonia with peribronchiolar and perivascular lymphocytic cuffing (40).

Also, according to a recent genomic and epidemiologic study, pet hamsters caused two independent zoonotic infections of the Delta variant of SARS-Cov-2 in humans and at least one further human-to-human transmission event in Hong Kong (42). There is no evidence to confirm that horses are susceptible to infection with SARS-CoV-2 (31).

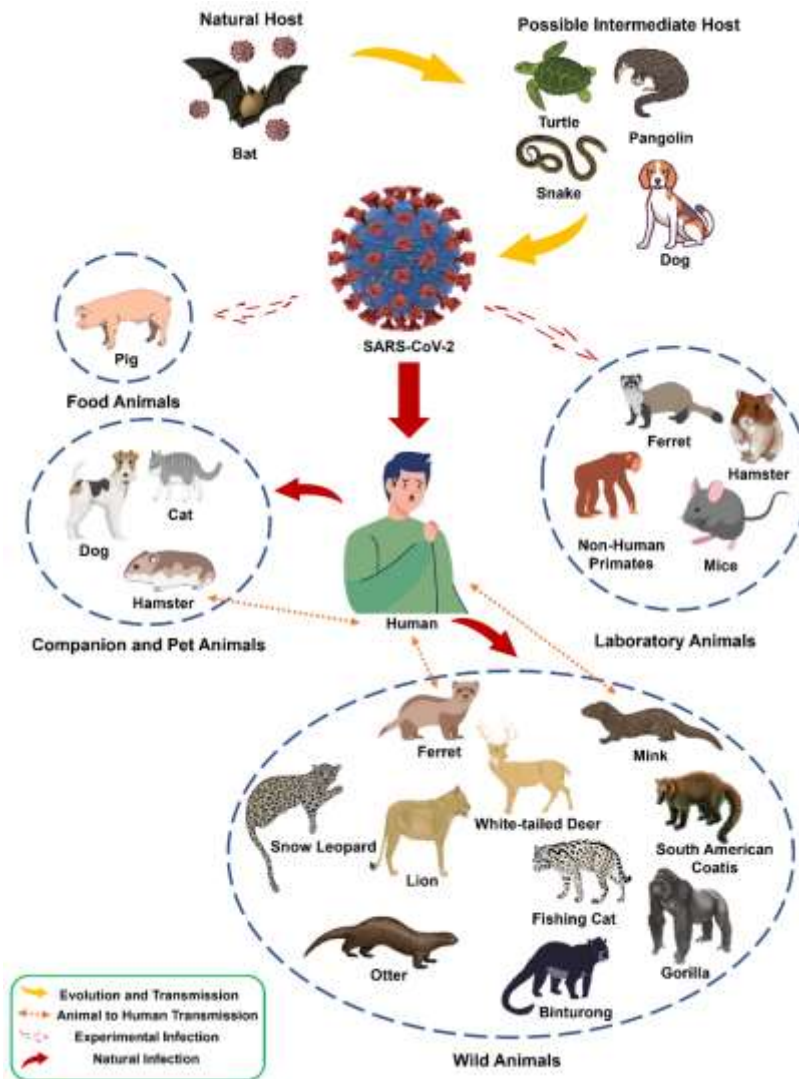


Figure 2. Schematic summary of SARS-CoV-2 hosts and susceptible animals

### 4. 3. Food Animals

COVID-19 pandemic caused unexpected detrimental effects on livestock and aquaculture production, supply chain, and trading (43-45). However, SARS-CoV-2 showed poor replication in livestock species such as pigs, chickens, and ducks. There was no detection of viral RNA after the

animals were deliberately inoculated with the virus or exposed to the infected animals (15). In pigs, high inoculating dose results in mild susceptibility to SARS-CoV-2 as demonstrated by viral RNA and antibody detection in oral fluids and nasal wash in some inoculated pigs (46). Besides, SARS-CoV-2 neutralizing antibody response was observed in pigs

inoculated parenterally (47). However, pigs are not likely to participate in the transmission and spread of SARS-CoV-2 (48). While farm animals are unlikely to transmit SARS-CoV-2, extensive outbreaks have been documented at meat processing plants because of the close working conditions among human workers. These observations suggest that food production will likely remain a concern throughout the pandemic (49).

**4. 4. Wild Animals**

The first cases of COVID-19 in wild animals were reported in lions and tigers on April 5, 2020, in the Bronx Zoo (New York City, United States).

They have suffered from mild to moderate upper respiratory clinical signs (coughing and wheezing) accompanied by anorexia. Infection to SARS-Cov-2 was confirmed by detection of viral RNA in samples taken from their respiratory organs; however, all animals recovered spontaneously (50). Afterward, the positive cases were reported in other wild animal species including binturongs, otters, white-tailed deers, fishing cats, gorillas, minks, snow leopards, and South American coatis (51). The major concern is related to minks and ferrets because both animals are kept as exotic pets and are bred on farms (37). It was suggested that mink-to-human transmission occurred in breeding farms (52).

**Table 1.** Susceptible animals to SARS-CoV-2 infection

Animal Specie	Type of Infection	Susceptibility	Reference
Mice	Experimental	Low	(35, 36)
Hamster	Experimental and Natural	High	(33, 34, 42)
Cat	Experimental and Natural	High	(40, 41)
Dog	Experimental	Low	(40)
Ferret	Experimental and Natural	High	(38, 39)
African green monkey	Experimental	High	(31, 32)
Rhesus macaques	Experimental	High	(31, 32)
Cynomolgus macaque	Experimental	High	(31, 32)
Common marmoset	Experimental	High	(31, 32)
Pig	Experimental	Low to Mild	(46-48)
Lion	Natural	High	(50)
Tiger	Natural	High	(50)
Gorillas	Natural	High	(51)
Mink	Natural	High	(52)
Snow leopards	Natural	High	(51)

## 5. Discussion

In this review, the last studies on the possible origin and susceptible animal hosts of SARS-CoV-2, as well as evidence on its cross-species transmission between humans and other animals have recapitulated (Table 1 and Figure 2). After SARS and MERS, COVID-19 is the third zoonotic disease caused by a member of Coronaviridae and is classified as the first pandemic in this family that leads to heavy fatal infections in humans (53). The virus primarily originated from various domestic or wild animal species such as bats and/or pangolins. Targeted and retrospective surveillance should be extensively performed to identify the reservoirs for SARS-CoV-2 and other related viruses before they are transmitted to humans. Due to the high rate of infection with SARS-CoV-2, farm minks and ferrets have the potential to become a source of new CoV variants. Therefore, strict surveillance and monitoring should be ruled on their farms (52). Regarding companion animals, raising public awareness about the transmissibility of SARS-coV-2 between humans and animals will help prevent the virus from spreading in the human population (54).

Overall, studies showed that COVID-19 is a human-animal disease (zoonosis) in which the main reservoir of the causative virus (SARS-CoV-2) is likely to be the same as the previous two CoVs (SARS and MERS). Due to the strong genetic similarity of this virus with the Bat SARS-Like CoVs, it is unlikely that the virus is man-made (19). However, more evidence is still needed.

An intermediate animal host (possibly scaly anteaters) may also have acted as an intermediate host between humans and bats. Given the evidence that cats and minks can be infected with the SARS-CoV-2 (15), it is not far-fetched that these animals may act as intermediates. For this reason, serological studies of the population of these animals near the primary foci of the disease (such as the city of Wuhan) are useful. On the other hand, given the evidence of infection of urban stray animals such as cats and the presence of anti-virus antibodies in their blood (36), it is necessary to conduct extensive research on the possibility of these animals as the SARS-CoV-2 reservoir. On the other hand, the determination of the molecular pathways of the evolution of animal CoVs, their spectrum of hosts, and their pathobiology can help us to better understand the mechanisms that lead to the emergence and adaptation of zoonotic

CoVs in humans (55). It has been shown that SARS-CoV-2 is transmitted from human to human through respiratory droplets. Stronger evidence needs to be found as to whether the SARS-CoV-2 can be transmitted to humans or other animals through food, packages, or other animals, especially pets such as dogs and cats. However, it is important to follow the relevant health tips.

Bats have now been identified as hosts in 7 of 11 species of alpha-CoVs and 4 of 9 species of beta-CoVs (56). Given the role of bats as a repository of CoVs, it is suggested that the population of these animals periodically be monitored.

The interconnectivity of human health with that of animals and the environment is captured in the "One Health" concept, which is defined as "the collaborative efforts of multiple disciplines working locally, nationally, and globally to attain optimal health for people, animals, and our environment". The concept of One Welfare extends One Health to recognize the interconnections between animal welfare, human well-being, and the environment (57, 58). The emergence of COVID-19 serves as a model for the existence of strong relationships between human and animal health, ecological conditions, and human habits. Admittedly, many viruses have been around for a long time in animals that are natural reservoirs. The transmission of viruses from their natural hosts to humans and other animals is largely due to human activities, including new methods of agriculture and urban planning. Therefore, the most effective way to prevent the emergence of zoonotic viral diseases is to maintain the distance between natural resources and human society in accordance with the concept of "One Health".

All health hazards in recent years have been caused by zoonotic agents. But how worrying is a particular zoonotic disease? Is it possible to prioritize zoonotic diseases? To answer these questions, health officials must consider how widespread a particular disease can be, how severe its impact on humans and animals can be, and whether it can be considered a potential contributor to bioterrorism. In all these cases, the role of veterinarians is very important. Veterinarians work in the public health system, and human health and well-being are one of their main concerns. It is important to note that veterinary virologists are not only responsible for examining viruses and their pathogenicity in domestic and wild animals but also for detecting human zoonotic diseases. In this perspective, the efficiency of new diagnostic

technologies and metadata management in public medicine's health institutions is the first line of defense for human health. This goal requires training a new generation of veterinarians based on the current needs of society. This can be achieved with a profound revolution in the curriculum of veterinary schools. Bioinformatics, genomics, statistics, ecology, social sciences, and communication are among the basic skills for veterinarians who will face the next epidemic of zoonoses in the future (59).

## 6. Conclusions

Due to the climate of four seasons, the diversity of animal species, and the increasing proximity of humans and animals to each other, the risk of emerging zoonotic diseases in Iran is not far from the mind. Hence, it is necessary to establish infectious disease control centers with the cooperation of the Ministry of Health and veterinary and environmental organizations. Besides, the animal populations should be periodically monitored for the possible occurrence and spread of such diseases. On the other hand, training researchers who can make comparative researches on emerging infectious diseases in addition to establishing comparative medical centers will help the development of vaccines and drugs. Surveillance for emerging zoonotic diseases should not focus exclusively on livestock and should instead enable data and expertise to be shared across medical, veterinary, and environmental health services and professions. It is also recommended to follow hygienic instructions during the COVID-19 pandemic.

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## Conflict of Interest

The authors declare no conflict of interest.

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