REVIEW ARTICLE

Comprehensive Appraisal of COVID-19 Infection and Interaction with Domesticated and Wild Faunae

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Abstract

Corona virus has a wide host range in animal kingdom including humans. Till 2002, the information related to human lethality due to corona virus infection was very scanty and signs were uncommon. But early in 2002, appearance of a syndrome associated with severe acute respiratory syndrome (SARS) has changed the whole scenario in relation to mortality in homo sapiens, and this SARS outbreaks was followed by Middle East respiratory syndrome (MERS) in 2012 and currently in 2019-2020 we are dealing with corona virus disease 2019 (COVID-19) pandemic, caused by corona virus 2 (SARS-CoV-2) which is genetically closely related to SARS-CoV. SARS-CoV-2 spike (S) protein interact with human angiotensin-converting enzyme 2 (ACE2) protein and gain excess to human cells for replication and this action lead to devastating outcome in humans they infect along with excessive cytokine storm. In this current review we have tried to give some update related to COVID-19 infection, major risk factor analysis playing an imperative role in changing the outcome of disease. Further we have detailed the COVID-19 status in domestic and wild animals and how we can deal with understanding the pathogenicity of COVID-19 by using various animal model.

Keywords: Animals, COVID-19, Human, Risk factors, Wild faunae.

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Corona Virus

Viruses either have DNA or RNA as a genetic material. Corona virus belong to RNA virus and mainly effect mucosal tracts such as respiratory and digestive system of various animals including human beings, it leads to symptoms like cold, digestive problems or even more complex disease such as in feline or canine corona virus infections. Usually, this virus was not lethal to adult healthy humans until SARS, MERS and COVID-19 infections are show up. This virus has spike shape S glycoprotein on its outer lipid layer covered protein coat. Corona virus belongs to subfamily Orthocoronavirinae and at present there are more than 45 species of corona viruses (https://talk.ictvonline.org/taxonomy/). SARS (caused by SARS-CoV) is a zoonotic disease that affect the respiratory tract of humans. It first appeared in China and was disseminated rapidly to many countries. This outbreak started in 2002 with 8422 human infections leading to 916 mortalities with case fatality rate (CFR) of 11% across the globe (Chan-Yeung and Xu, 2003). SARS was followed by MERS also known as camel flu, it first appeared in 2012 in Jeddah, a city of Saudi Arabia and spread to other countries. Till January 2020, 2519 cases of MERS were reported, out of which 866 died with CFR of 34.3% (www.emro.who.int). Currently world is fighting against COVID-19, and it is discussed in later sub-section.

Pandemic Corona Virus Disease 2019

COVID-19 is a viral infection which was recently identified as a member of corona virus which come from beta group of *Coronaviridae* family. Member of this family has spikes on their outer surface so it resembles the appearance of crown-like structure under electron microscopic imaging that's why the name corona virus was given to this virus (Shereen *et al.,* 2020). Place of origin of this virus strain was Hunan seafood market of an industrial city in China (Hubei province), *i.e.* Wuhan at the beginning of December 2019. Among all corona virus in *Coronaviridae* family, this current virus (SARS-CoV-2) was 7th member which [229E (alpha coronavirus), NL63 (alpha coronavirus), OC43 (beta

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coronavirus), HKU1 (beta coronavirus), MERS-CoV (beta coronavirus) and SARS-CoV (beta coronavirus) https://www.cdc.gov/coronavirus/types.html)] had infected human beings (Wu *et al.,* 2020[a]). This Hunan sea market is a wet market and was famous for selling live animal and meat of various bats, frogs, snakes, birds, marmots, rabbits, fish, shellfish, hedgehogs and badgers (Tiwari *et al.,* 2020). In initial stage virus had infected about 50 Chinese people and these people presented sign of pneumonia. When samples from these patients were analyzed it confirmed that this pneumonia was related to viral infection, further genomic sequence similarity-based investigation showed that this belong to coronavirus family (Shereen *et al.,* 2020). Earlier it was given name as Wuhan coronavirus or 2019 novel coronavirus (2019-nCov) but after some time its name change to SARS-CoV-2 and the infection related to this virus was called as COVID-19. Earlier in China it wasn't recorded that this virus had human to human transmission or not, later on in Hong Kong it was confirmed that human to human transmission was occurring, moreover they had also confirmed that nosocomial (hospital) transmission was occurring (Chan *et al.,* 2020[a,c]). This virus was first reported in China followed by Thailand, Japan, Italy, USA, France, UAE, Egypt, Algeria (https://www.who.int/ emergencies/diseases/novel-coronavirus-2019/interactive-timeline/#event-88) and the chain of infection goes on across the whole world. Till now 1st November 2020, 190 countries, areas or territories are having COVID-19 cases. Across the globe on whole total 46,245,185 cases had been reported and 1,197,619 patients had died so far with the highest mortality rate in US followed by Brazil and India. India hold 2nd position in total number (8,184,082) of case report of COVID-19 and Maharashtra state hold first place in the number of confirmed (1,678,406) COVID-19 cases (https://www.who.int/emergencies/diseases/novel-coronavirus-2019, https:// gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6). Earlier some researcher believed that this virus came from pangolin or snake etc as an originating animal species. Genetic analysis of SARS-CoV-2 showed that it gives more resemblance to two bat-derived coronavirus strains, *i.e.,* bat-SL-CoVZC45 and bat-SL-CoVZXC21, so it is now believed that this virus is of bat origin (Fig. 1) (Lu *et al.,* 2020). In another study conducted by Chan *et al.* (2020[a]) depicted that nucleotide similarity of 2019-nCoV was 89% and 82% with SARS-like-CoVZXC21 and human SARS-CoV, respectively. Analysis of evolutionary history showed that orf1a/b, spike, envelope, membrane and nucleoprotein resemble very closely to bat (Chan *et al.,* 2020[a]). Moreover, this unique new corona virus has new short protein at orf3b level and this unique orf3b encrypts a secreted protein with an alpha-helix, succeeding with a beta-sheet(s) comprehending six strands (Chan *et al.,* 2020[a]).

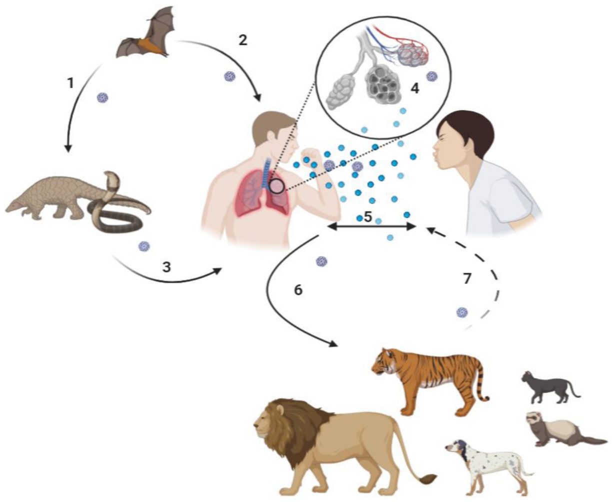

Figure 1: Transmission cycle of COVID-19 between humans and susceptible or virus identified animals

1. Virus originated from bat and could interact with Pangolin and Snake and these animal can act as amplifying host
2. Virus can transmit from bat to human
3. Virus can transmit from Pangolin and Snake to human
4. Virus reach to human respiratory system and hamper the gaseous exchange at alveoli level by killing the infected cells along with other damage to lung tissue
5. Virus mainly via aerosol route is transmitted from infected to uninfected human
6. Virus can be transmitted form infected human to domestic and wild animal
7. Viral transmission form infected animal to uninfected human is not fully documented

Entry of Virus and it's Pathogenicity

As compared to other coronavirus infection, virus had spread across the world like a fire in dry forest, the main reason can be due to genomic modifications in S (spike) protein on envelop of virus receptor-binding domain (RBD) area resulting into high infectivity rate (Shereen *et al.,* 2020; Lu *et al.,* 2020). Mainly, S protein plays important role in binding and entering the host cell. Usually this S protein is present as trimer, this trimer has S1 sub-site which acts as receptor-binding part; a S2 sub-site which acts as membrane fusion part; trans-membrane anchor and intra-cellular tail (Shang *et al.,* 2020). This S1 subunit has RBD that distinguish and bind with ACE2 and this ACE2 acts as host cell receptor during the cellular infection (Lu *et al.,* 2020). RBD frequently changes its position in order to escape from immune system or adaptation to various ACE2 receptors (Shang *et al.,* 2020).

In relation to lifecycle briefly in humans, spike protein of SARS-CoV-2 bind with cellular receptor, *i.e.,* ACE2. Lysine 31 residue of ACE2 receptor of human cell recognize the 394 glutamine residue at RBD region of SARS-CoV-2 (Wan *et al.,* 2020). This result in fusion of envelop of virus with host cell membrane and an endosome is formed and virus reach to the cytoplasm of cell. In the cytoplasm of host cell genomic RNA form orf1a/orf1b, and result into production of many protein molecules. These bigger protein molecules are then cleaved to smaller particle with the help of viral protease enzyme. Moreover, further mRNA form more viral protein. These viral RNA and various protein form many small virions in endoplasmic reticulum and Golgi body mainly located at endoplasmic Reticulum-Golgi bodies intermediate compartment and form various small vesicle which contain new virions from parent virus. These vesicles then go to cell membrane and in last many new virus particles are released to the surrounding environment by budding from the host cell.

Course of SARS-CoV-2 infection or pathogenicity can be divided into 3 stages:

A. After initial infection asymptomatic phase remains for 1-2 days (Mason 2020).

B. After first phase end, second stage starts, in this phase virus reach to the lower respiratory tract and host immune system (T and B cells response) is also initiated. It can lead to release of various interferon along with release of some chemokine, *i.e.* CXCL10 (Mason 2020).

C. After second phase ends, last stage, *i.e.,* third stage starts. This stage leads to acute respiratory distress syndrome (ARDS), hypoxia and other lethal conditions. Virus reach to the level of lung alveoli and start affecting the gaseous exchange capability of infected human pulmonary system (Fig. 1). In pulmonary alveoli this virus mainly attacks alveolar type II cells and starts its replication to produce more virions, this process leads to death of infected cell and the viral replicative cycle goes on in new cell and in the end large number of lung alveolar cells get infected. During all these changes, host defense systems try to compensate and make many membranes which are rich in fibrin and hyaline, these type of host responses further aggravate the condition and lead to ARDS (Mason, 2020). Third stage also lead to various degree of pulmonary consolidation, pulmonary interlobular septal thickening mainly under the pleural region (Wu *et al.,* 2020[b]). Virus infection also causes the formation of more cellular fibromyxoid exudates, and edema formation in the lung of infected person. Flow cytometry analysis showed that due to COVID-19 infection CD8 T cells had high level of perforin and granulysin, moreover there was high level of TH17 cells, these changes can lead to severe lung injury via causing cytokine storm in infected patient (Xu *et al.,* 2020).

At present there is still controversy that immune system is good or bad guys in COVID-19. Some researchers state that in initial infection, physician in hospital should boost immune system. But in later stage they should try to suppress the immune system in order to avoid further lung damage like by giving vitamin B3 (Chowdhury *et al.,* 2020; Shi *et al.,* 2020[a,b]).

Risk Factor Analysis of COVID-19

COVID-19 severity varies among people and depends upon various factors which can easily influence the mortality rate. Various risk factors like age, sex, cancer, cardiovascular disease, respiratory disease, immuno-suppression caused by HIV, renal disease, hepatic disease, metabolic disease, stroke, neurological conditions, organ transplant and rheumatoid arthritis, lupus or psoriasis (Williamson *et al.,* 2020; Richardson *et al.,* 2020) were studied in many epidemiological studies across the world which can affect the outcome of infection. Some main and critical factors affecting the COVID-19 related mortality rate along with the country of study are shown in Table 1. The detail analysis of epidemiological data show that people with some pre-existing condition have higher mortality rate or need more ICU related health care facility, so these people should take extra care as compared to normal human being.

COVID-19 in Domestic and Wild Faunae

Usually animals rarely suffer from COVID-19. But recently many report came into light that pet and other animals can be infected by COVID-19, it can be due to rapid mutation that can occur at RBD section of S gene of virus and it can lead to broaden the host range (Tiwari *et al.,* 2020). First case of pet animal, *i.e.,* dog infected with SARS-CoV-2 came from Hong Kong (Sit *et al.,* 2020). SARS-CoV-2 RNA was detected in five nasal swabs collected over a 13-day period from a 17-year-old neutered male Pomeranian. A 2.5-year-old male German Shepherd dog was also positive for SARS-CoV-2 RNA on two occasions and virus was isolated from nasal and oral swabs. The dogs remained asymptomatic during quarantine. In Utah (USA) minks from 2 farm were found to be infected with SARS-CoV-2. The persons who were in close contact with these minks were also found positive for the virus. In Netherlands also many minks from 40 different farms were found positive for SARS-CoV-2. Cats near the Netherlands infected mink's farms were also found to be positive for SARS-CoV-2 (www.wur.nl/en). Similar cases of infected minks were also reported from European country like Spain and Denmark (www.aphis.usda.gov). In New York state a German Shepherd dog along with his owner were reported positive for SARS-CoV-2 and dog showed pneumonia like symptom (www.aphis.usda.gov). Three Lions and 4 tigers which are kept in Bronx Zoo of New York were also tested positive for SARS-CoV-2 (www.aphis.usda.gov), it is speculated that the infection to big cats was from infected human but this finding was not confirmed. In a recent research it was also experimentally documented that ferrets and cats are extremely vulnerable to SARS-CoV-2; dogs have stumpy vulnerability; and other animals like pigs, chickens, and ducks are not vulnerable to the SARS-CoV-2 (Shi *et al.,* 2020[a]). Many researchers have a feeling that in all these animal infection, SARS-CoV-2 virus was transmitted from humans to animals. Inside of the cat and dog communities these animals already falling in Feline-CoV (FCoV) and Canine-CoV circulation. However, it`s obvious that these corona viruses are relatively distinct from SARS-CoV-2. Feline infectious peritonitis (FIP) is a complicated infection which is caused by FCoV and proposed by antibody-dependent enhancement (ADE) mechanism. It`s not clear yet that ADE is responsible with for the enhancement or

Table 1: Crucial risk factors in COVID-19

S.No.	*Risk factor*	*Data from major epidemiological study*
1	Age	In Mexico, out of 89,756 patients 13.6% were over 65 year of age (Giannouchos *et al.,* 2020). In China, out of 2044 patients 57. 58% were over 60 year of age (Liu *et al.,* 2020). In Italy, out of 3988 patients 25% were over 69 year of age (Grasselli *et al.,* 2020).
2	Sex	In USA, out of 5700 patients 60.3% were male (Richardson *et al.,* 2020). In Mexico, out of 89,756 patients 56.4 % were male (Giannouchos *et al.,* 2020). In China, out of 2044 patients 48% were male (Liu *et al.,* 2020). In Italy out of 3988 patients 79.9% were male (Grasselli *et al.,* 2020). In USA study out of 2215 patients 64.8% were male (Gupta *et al.,* 2020).
3	Diabetes	In USA out of 5700 patients 33.8% were diabetic (Richardson *et al.,* 2020). In Mexico, out of 89,756 patients 17.5% were having diabetes (Giannouchos *et al.,* 2020). In China, out of 2039 patients 16.7 were having diabetes (Liu *et al.,* 2020). In Italy, out of 3988 patients 12.8% were diabetic (Grasselli *et al.,* 2020). In USA study out of 2215 patients 38.87% were diabetic (Gupta *et al.,* 2020).
4	Hypertension	In USA, out of 5700 patients 56.6 % had hypertension (Richardson *et al.,* 2020). In Mexico, out of 89,756 patients 20.9% were having hypertension (Giannouchos *et al.,* 2020). In China, out of 2039 patients 39.7% had hypertension (Liu *et al.,* 2020). In Italy, out of 3988 patients 41.1% had hypertension (Grasselli *et al.,* 2020). In another USA study out of 2215 patients 59.7% were having hypertension (Gupta *et al.,* 2020).
5	Obesity	In USA, out of 5700 patients 41.7% were obese (Richardson *et al.,* 2020). In Mexico Out of 89,756 patients 20.5% had obesity (Giannouchos *et al.,* 2020). In USA, out of 3615 individuals 21% were obese (Lighter *et al.,* 2020).
6	Asthma	In Mexico, out of 89,756 patients 2.9% had asthma (Giannouchos *et al.,* 2020). In another USA study out of 2215 patients 11.6% were having asthma (Gupta *et al.,* 2020).
7	Smoking	In Mexico, out of 89,756 patients 91.7% were current non-smoker (Giannouchos *et al.,* 2020). In another USA study out of 2215 patients 29.6% were current or former smoker (Gupta *et al.,* 2020).
8	Heart disease	In Italy, out of 3988 patients 13.3% had heart disease (Grasselli *et al.,* 2020). In USA study out of 2215 patients 8.8% were having Congestive heart failure (Gupta *et al.,* 2020).

susceptibility of SARS-CoV-2 like symptoms in cats. This concept is far from dog communities since dogs do not resemble the FIP like complex disease with ADE (Stout *et al.,* 2020).

Animal Model for Further Study on Pathogenicity of COVID-19

Usually in the field of virology and immunology various mouse models are used for experimental studies in initial stages before trying the research trail on non-human primates. Normal mouse strains like C57BL/6, BALB/6 etc. model can't be used for SARS-CoV-2 because mouse ACE2 does not efficiently attach with viral S protein (Wan *et al.,* 2020). Moreover, as we all know that virus gain entry by ACE2 receptor, so transgenic mouse model with human ACE should be developed to study effect of SARS-CoV-2 on mouse model (Wan *et al.,* 2020). So at present some advance strategies can be used to modify the mouse so that interaction between S protein and ACE in mouse could be increased. Human SARS-CoV-2 virus strain S protein can be genetically modified, which can be further used to enhance interaction with mice ACE. Transgenic mouse model having human ACE can be made by genetic modification, recently transgenic mice expressing human ACE2 was made and after giving SARS-CoV-2 it was seen that virus effectively replicated in lung of mice (Bao *et al.,*2020; Sun *et al.,* 2020). In normal mice, pulmonary infection to lungs can also be made by modifying SARS-CoV-2 with adenovirus 5 (Ad5) or adeno related virus that express human ACE2. Use of humanized mice having human ACE2 had also been used and it support replication for SARS-CoV-2 (Muñoz-Fontela *et al.,* 2020).

Other animal model can also be used like recently Syrian hamster had been used to study SARS-CoV-2 and this animal showed viral titer in lung at 10^5-10^7 TCID50/g (Chan *et al.,* 2020^b). Recently in Germany, it was recorded that animals like normal pigs and chickens can't be used to study SARS-CoV-2 (Schlottau *et al.,* 2020). At present many studies are also showing that non-human primates can be used as a model to study SARS-CoV-2. Among non-primate rhesus monkey can be used as a potent model, in rhesus monkey SARS-CoV-2 infection showed viral titer in swab taken from nasopharyngeal and throat area, moreover rectal shedding of virus was also noted (Munster *et al.,* 2020). In another study macaque were also used to study pathogenicity and course of COVID-19 disease (Rockx *et al.,* 2020), furthermore crab-eating macaques (*Macaca fascicularis*) were also seen to be an effective model for SARS-CoV-2 infection (Finch *et al.,* 2020). As we know that mink, cat and dog can also show COVID-19 infection, so these animals can also be used as a model to study current pandemic. Currently there are preclinical studies completed on rhesus macaques as a primate animal model to show vaccine immunogenicity and protective efficacy with challenge studies before begin human phase clinical trials (Mercado *et al.,* 2020).

Various *in-vitro* cell line and organoid have also been used to propagate the virus. Among all susceptible cell lines, the most commonly used cell lines for SARS-CoV-2 are Human airway epithelial cells, Vero cells, Caco-2 cells, Calu-3 cells, HEK293T cells and as an organoid model mainly studied organoids are Human bronchial, Human lung, Human kidney, Human liver ductal, Human intestinal and Human blood vessel organoids (Takayama, 2020).

Concluding Remarks

From the outcome of 3 major epidemics in last 2 decades, we can speculate future expectations based on current knowledge on animal fauna and we could suggest that wild animals should be kept in wild areas and should be separated from domesticated animals both in farming or marketing areas including spaces where humans are residing. There are many take home message from current epidemic as it shows that diagnostic studies are much important to take action and defining the zoonotic potential of infectious agent for estimation of future pandemics. Screening of animals or epidemiological studies are much important for controlling the emerging zoonotic diseases and at least can provide information about update of existing outbreaks and it`s situation. This pandemic also clearly showed that almost 10% of human species could die if the pathogenicity was similar to SARS. Moreover, adequate health management along with access to supportive therapy also play crucial role in controlling the outbreaks. Vaccine studies are time taking and financially consuming experiments. So urgent medications such as development of wide range anti-viral or molecular compounds having protease activity are much favorable. Other lessons such as reducing unnecessary contact and maintaining distance between live animal and human or human and human will be important to controlling the outbreaks in limited areas including reducing the movements from where outbreaks are occurred.

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