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Covid 19: The first microorganism ever to cause global lockdown - A Microbiological review

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Abstract

Covid-19 pandemic has caused a public health crisis with millions of infected cases around the globe. The virus allegedly originated in bats in Wuhan city of China and then transmitted to humans. The common symptoms of Covid-19 are fever, cough, breathlessness, fatigue etc that may progress to pneumonia and multi organ dysfunction leading to death. Till March 24, 2021, a total of 128M people were infected including 2.81M deaths worldwide. The mortality rate varies from 2-3%. The molecular diagnosis (RT-PCR) remains the trusted method. The role of antiviral agents is uncertain. Moreover, the first vaccine for Covid-19 is yet to be developed and the impact of preventive measures like social distancing, lockdown etc. is yet to be analyzed.

Keywords: SARS-CoV-2, Pandemic, Respiratory Illness; RT-PCR

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Introduction

Coronavirus belongs to a large family (Coronaviridae) of positive sense, single stranded RNA viruses. The Coronaviridiaefamily is divided into Torovirinae and Coronavirinae subfamilies, which is further divided into alpha, beta, gamma and delta Coronaviruses. Alpha- and beta-coronaviruses usually infect mammals, while gamma and delta coronaviruses usually infect birds and fish. Coronaviruses are named for the crown-like spikes on their surface.[1],[2]

Human coronaviruses were first discovered in the mid-1960s. However, till date, seven coronaviruses that can infect humans have been documented. These are 229E (alpha coronavirus), NL63 (alpha coronavirus), OC43 (beta coronavirus), HKU1 (beta coronavirus), MERS-CoV (beta coronavirus), SARS-CoV (beta coronavirus), SARS-CoV-2 (beta coronavirus).[3]

Most probably,SARS-CoV-2 has its ecological reservoir in bats, and transmission of the virus to humans has likely occurred through an intermediate animal host – a domestic animal, a wild animal or a domesticated wild animal which has not yet been identified. Moreover, coronaviruses that infect animals gets genetically evolved and pose a new threat to public health.[4]

Pathogenesis

Viral entry and Receptors

Viral entry to host cell is an indispensable step to initiate a viral life cycle. Covid-19 spike proteins bind with the great affinity to ACE-2 (Angiotensin converting enzyme 2) Receptor, an enzyme that play a key role to regulate functions in the cell by cutting large protein angiotensionogen.[5] ACE-2 is present in humans, bats, pigs, civet cats etc and may justify the facile transmissibility of this virus.[6]

Nevertheless, additional host interactions may also associate with transmission of Covid-19. It has been noted that a distinct (N-terminal) domain of SARS-

CoV-2spikeproteinsmaybindtoalternativehost-cell receptors.[7],[8] Alternative host cell communications by N-terminal domains permit consideration, as it is known that analogous domains on several human CoVs have significant assisting cell-binding functions.[9] SARS-CoV-2 spike proteins have also acquired several basic residues, forming a furin protease cleavage site. Time-based development of proteolyticscissorsprimes and activate the SARS-CoV-2 proteins to catalyze virus– cell membrane fusion.[10] Thus, the SARS-CoV-2 furin substrate site is probable to facilitate the grooming cleavage step, which sensitizes spike proteins to the subsequent triggering cleavages occurring on susceptible target cells, and enables virus entry and infection.[11]

Pathogenesis of Covid-19 is largely dependent on its genomic structure. Covid-19 is +ssRNA of roughly 30 kb in size with a 5′-cap structure and 3′-poly-A tail.[12] Beginning from the viral RNA, the fusion of polyprotein 1a/1ab (pp1a/pp1ab) in the host is realized.[13] The transcription drives (Figure 1) all the way through replication-transcriptioncomplex

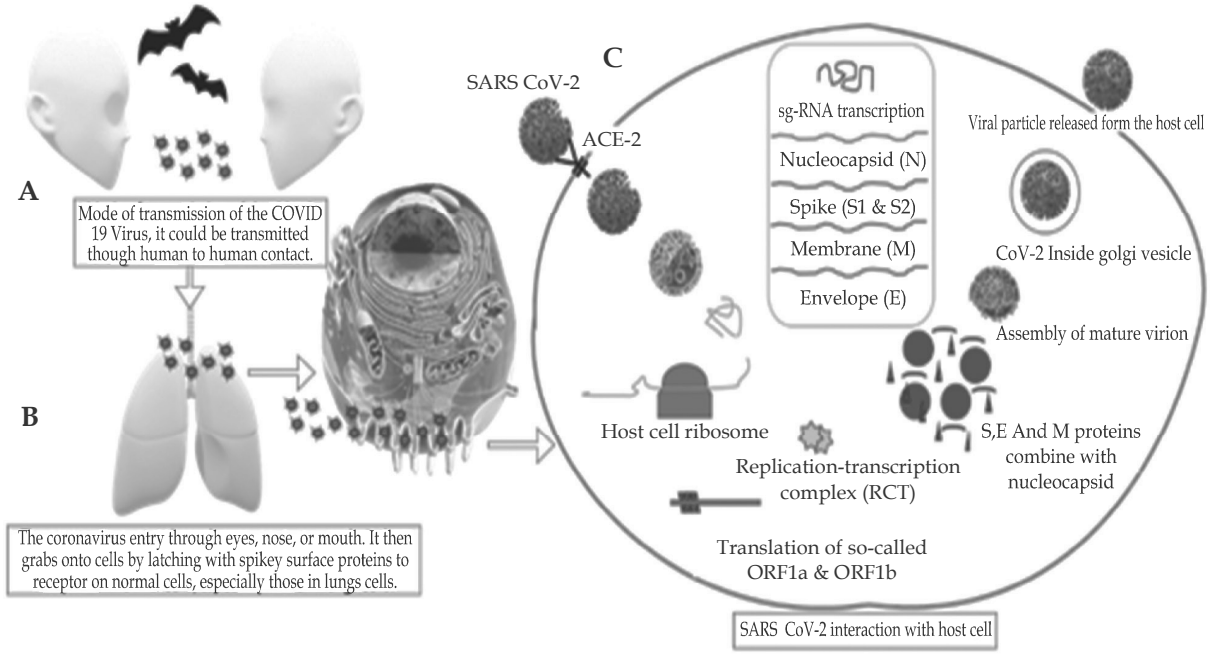

Fig. 1: A. Transmission of the COVID-19 virus by animals or Human to Human close contact. B- Entry of SARS CoV-2 into the lungs, virus attaches with host cell receptors which is mainly present on lungs cells. C- Covid-19 interaction with host cell.

(RCT) organized in double-membrane vesicles and via the manufacture of sub-genomic RNAs structures. Apart from ORF1a and ORF1b, other ORFs encode for structural proteins, including spike, membrane, envelope, and nucleocapsid proteins.[14],[15] Although the pathogenesis of Covid-19 is poorly known, the similar mechanisms of SARS-CoV and MERS-CoV still can give us a lot of knowledge on the pathogenesis of new coronavirus disease to expedite our recognition of Covid-19. It has been analyzed that trans-membrane helical segments in the ORF1ab encoded 2 (nsp2) and nsp3, position 723 presents a serine instead of a glycine residue, while the position 1010 is occupied by proline instead of isoleucine[16]. The matter of viral mutations is key for explaining potential disease relapses.

The virus has high affinity towards the targeting organs that express ACE2, such as the lungs, heart, kidney, liver and gastrointestinal tract.[17],[18] The SARS-CoV-2 found in the fecal samples[19] is more likely for the reason that the virus enters the blood from the lungs and then travels from the blood to the intestines.

Clinical manifestation

Covid-19 is associated with the clinical symptoms like fever, cough, myalgia or fatigue, pneumonia, and complicated dyspnea (Table 1), whereas less common reported symptoms include headache, diarrhea, hemoptysis, runny nose, and phlegm-producing cough[12],[20] or decreased leukocyte counts, and radiographic evidence of pneumonia, which are comparable to the symptoms of SARS-CoV and MERS-CoV infections (Figure 2).[21] Patients with mild symptoms are reported to d

Table 1: Clinical complications due to COVID-19 infection

S.no	Fever	Dry cough	myalgia	headache	Fatigue	Diarrhoea	Dyspnoea/ chest distress	Pharyngeal pain	Haemoptysis	Sputum production	Ref.
1	98.60%				69.60%						[28]
2	87%	60%	11%	13%	39%	14%	16%	13%			[31]
3	81.80%	48.20%	32.10%	9.50%	32.10%	8%	19%				[54]
4	98%	76%	44%	8%	44%	3%	55%		5%	28%	[55]
5	59.40%	34.80%	6.50%	69.60%	10.10%	31.20%	17.40%		26.80%		[56]
6	88.70%	67.80%	14.90%	13.60%	38.10%	3.80%	18.70%	13.90%	0.90%	33.70%	[57]
7	83%	82%	11%	8%		2%	31%	5%			[58]
8	98%	77%	11.50%	6%			63.50%				[36]
range	81.80-98.6%	48.20-82%	11-44%	6-13.8%	32.1-69.6%	2-14%	16-63.50%	9	0.9-5%	26.80-33.7%	

recover within 1 week while severe cases are prone to suffer progressive respiratory failure due to alveolar damage and subsequently leading to death. Mortality rate is comparatively high in elderly patients and all patients with pre-existing conditions (tumor surgery, cirrhosis, hypertension, coronary heart disease, diabetes, and Parkinson's disease etc).[22]

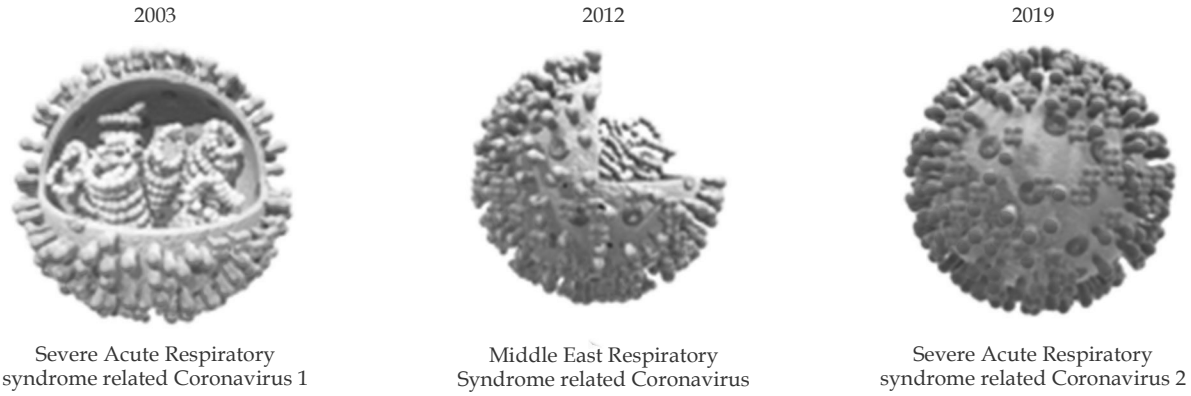

Fig. 2: The diagram showing clinical sing and symptom of COVID-19 and other similar virus (MERS-CoV, SARS-CoV-1)

Clinical symptoms	SARS-CoV-1 (2003)	MERS-CoV (2012)	SARS-CoV-2 (2019)
Fever or chills	YES	YES	YES
Dyspnea	YES	YES	YES
Muscle pain	YES	YES	YES
Headache	YES	YES	YES
Cough	Dry	Dry or productive	Dry
Diarrhea	YES	YES	Uncommon
Nausea or vomiting	YES	YES	Uncommon
Sore throat	Y	Uncommon	Uncommon
Arthralgia	YES	Uncommon	Unknown

Diagnosis

Several diagnostic methods have been developed for the detection of Covid-19. Reverse Transcriptase Polymerase Chain Reaction (RT PCR) remains the most trusted method as it directly detects the viral RNA in nasopharyngeal & oropharyngeal swabs, tracheal aspirate or bronchoalveolar lavage (BAL) samples. Several studies have shown that SARS CoV2 RNA can also be detected in blood and stool

specimens.[23],[24],[25][26] Charité Berlin, from Germany, was the first to develop the assay and standardize the protocol for real time RT-PCR.[27] The test detects the presence of three genes- E, S, RdRp and N.RT-PCR shows very high sensitivity and specificity. However, the time and type of specimen collected for RT-PCR play an important role in the diagnosis of Covid-19. It has also been suggested that in the early days of infection, patients have high levels of virus in spite of the mild symptoms.[28]

The few molecular based sample-result devices have been developed for the detection of Covid-19 target gene directly in the samples (Table 2).[29],[30]

Table 2: Performance of molecular based closed system for the detection of Covid-19

Manufacturer	Device name	Clinical Sample	Target gene	TAT	Ref
Cepheid	Xpert Xpress SARS-CoV-2	Nasopharyngeal & Oropharyngeal swab	NG	45 minutes	[59]
Qiagen	QIAstat-Dx Respiratory SARS-CoV-2	Nasopharyngeal swab	Orf1b and RdRp genes	1 hour	[60]
Roche	Cobas SARS-CoV-2	Nasopharyngeal & Oropharyngeal swab	ORF1ab gene	3 hours	[61]
Hologic	Panther Fusion SARS-CoV-2	Nasopharyngeal & Oropharyngeal swab	ORF1ab gene	<3 hours	[62]
Abott	Abott Real Time SARS-CoV-2	Nasopharyngeal & Oropharyngeal swab	RdRp and N genes	470 samples in 24 hours	[63]
	Abott ID NOW Covid-19	Nasopharyngeal & Oropharyngeal swab	RdRp gene	5-13 minutes	[64]
Becton, Dickinson (BD)	BioGX SARS-CoV-2	Nasopharyngeal & Oropharyngeal swab	N gene	<3 hour	[29]

Several studies have documented other diagnostic method like Isothermal nucleic acid amplification that detects viral RNA much faster than PCR as there is no requirement of repeated heating and cooling cycles.[31],[32] ELISA and rapid immunochromatographic tests have also been developed for the detection of Covid-19 spikes protein antigen and Covid -19 IgG/IgM antibodies in various clinical samples[33],[34] These tests are cheaper, easy to perform and require no expertise. However, the accuracy of these tests remains uncertain. A study revealed that the sensitivity of SARS-CoV N-based IgG ELISA (94.7%) was significantly higher than that of SARS-CoV S-based IgG ELISA (58.9%).[35]

The radiographic imaging also plays a key role in diagnosis of Covid-19. The typical CT images show bilateral pulmonary parenchymal ground-glass and consolidative pulmonary opacities, sometimes with a rounded morphology and a peripheral lung distribution. Lung involvement with a peripheral predominance is also seen in patients with SARS-CoV and MERS-CoV infections. Thus, a combination of CT scan and RT PCR are found to be helpful. [36],[37],[38]

Prevention and treatment

There is, no specializedtreatment for COVID-19 is available till date. Some antiviral drugs such as ribavirin, lopinavir-ritonavir have been used based on the knowledge with SARS and MERS, whereas, the role of corticosteroids is unverified[39],[40],[41] In a historical control study in patients with SARS, patients treated with lopinavir-ritonavir with ribavirin had better consequences as compared to those given ribavirin alone.[42] Supportive treatment for complicated patients has included continuous renal replacement therapy (CRRT), invasive mechanical ventilation, and even extracorporeal membrane oxygenation (ECMO). The first reported patient with 2019-nCoV infection in the USA was treated with remdesivir[43], and others have used antiretrovirals like ritonavir, with trials of both in progress.[44] A recent study conducted by the "front-line" health care providers combating COVID-19 in Wuhan indicated that systemic corticosteroid treatment did not show significant benefit.[45] Baricitinib has been suggested as a potential drug for the treatment in the hope that it might reduce the process of both virus invasion and inflammation.[46] One recent study shows, that monoclonal

antibody (CR3022) binds with the spike RBD of SARS-CoV-2. This is likely due to the antibody's epitope not overlapping with the divergent ACE2 receptor-binding motif. CR3022 has the potential to be developed as a therapeutic candidate, alone or in combination with other neutralizing antibodies for the prevention and treatment of COVID-19 infection.[47],[48] Several studies have also reported Hydroxychloroquine (antimalarial drug) as a potent anti Covid-19 agent.[49],[50],[51],[52]

The guidelines focusing on the preventive measures have been published by every country depending on the number of active cases, mortality rate and their health facilities. However, the preventive measures like social distancing, lockdown, quarantine etc. were implemented by most of the countries. Lockdown was used as the biggest preventive experiment against covid-19. Till June 16, 2020, a total of 78 Countries have put lockdown with an average of 51 days and maximum 90 days[53] The effect of lockdown on Covid-19 cases are mainly affected by the environmental factors, health facilities, Federal and state government policies, public awareness, country economy etc. Thus the global data with and without lockdown has still to be analyzed.

Conclusion

Covid-19 has become a global issue ever since it had first emerged and caused the outbreak in China. Now, it has turned to pandemic, infecting more than 7.82 million people worldwide so far. Antiviral agents like Lopinavir, Ritonavir etc do not appear to be effective. However, some studies shows that the antimalarial drug, Hydroxychloroquine (HCQ), has some therapeutic effect against this deadly virus but more scientific research need to be conducted to prove its efficacy. it is a highly pathogenic human virus, possibly a zoonotic agent, it is critical that countries around the world are taking preventive steps like lockdown and home-quarantine to stop transmission and save lives. However, some universal public health guidelines, focusing on combating Covid-19, are urgently needed to be developed.

Compliance with Ethical Statement: This work does not require institutional ethical approval.

Conflict of interest: The authors declare no conflicts of interest.

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