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REVIEW ARTICLE

COVID-19: Brief review on pathophysiology and investigational drugs

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Abstract

Though coronaviruses are firstly recognized almost 6 decades back, but only reputed in 2003 and were identified that one of the members is served as the aetiologic vehicle for SARS (severe acute respiratory syndrome). Formerly coronaviruses are well-known as crucial pathogens for causing infections to ventilatory system nothing but respiratory system and enteric system nothing but digestive system of patients, causing common cold in 15% cases of all cases. The coronaviruses are probably human pathogens accomplished with pathological signs in upper and lower respiratory tract. The virological studies particularly coronavirology has been remarkably developed from the last decade. Animal coronaviruses were enlightened during the SARS wide-spread and COVID-19 pandemic brought human coronaviruses (Novel coronavirus-2019) into the spotlight. On 7th July, 2020 WHO technical lead head COVID-19 Dr Maria Van Kerkhove briefed the “evidence emerging” of the transmission of the COVID-19 through air. The potentiality of spread through air in public places particularly in closed, poorly ventilated, crowded places is high. Our review gives an account on investigational drugs and repurposed drugs that are being used for management and treatment of coronavirus disease (COVID-19) with their Id's and mechanism of action against SARS-CoV-2 and data regarding current clinical investigations is also provided.

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Introduction:-**Origin:**

Firstly, SARS-CoV-2 was recognized in patients at Jinyintan Hospital (Wuhan), China on 31st Dec, 2019 [1]. On the basis of clinical signs appeared with the patients, blood sample testing, and chest radiographs, clinicians diagnosed and confirmed that the disease is related to respiratory problem, pneumonia induced by a virus. The epidemiological inspection in the very beginning advised that a large number of cases were linked with local seafood market. Finally, novel coronavirus (2019-nCoV) was recognized in natural specimens of wet market by Center for Disease Control and Prevention, China, depicting the source for outburst. Nevertheless, a determined end was disagreed since the market has not mentioned the connection with first case [2]. Furthermore, two non-identical strains of SARS-CoV-2 were into spotlight not many months prior to COVID-19 outbreak [3]. A recent phylo-epidemiologic study suggested that SARS-CoV-2 would have been imported to seafood market from different places [4]. Yet, it remained mystery regarding the origin of coronavirus; still the epidemiological and etiological investigations are under process.

Description

The phylogenetic studies estimated the evolutionary relationship of coronaviruses as that the genus Coronaviruses is belonged to the family-Coronaviridae under the order-Nidovirales. 2019-nCoV, novel Coronavirus is seventhmember of the family Coronaviridae. Coronaviruses got reputation at epidemic situation occurred in-between 2002 and 2003 for SARS-CoV breakthrough [5]. SARS-CoV in 2003 and MERS-CoV in 2013 demanded a healthcare emergency. Before the SARS breakthrough has emerged, two main pathogens related to human coronaviruses abbreviated as HCoV-OC43 and HCoV-229E are responsible for upper respiratory tract disease and some complicated respiratory diseases with elderly people and people with low immunity [6].

The SARS-CoV breakthrough lead to cause severe respiratory disease associated with inflammation in broncho-alveolar pathway and reported 10% fatality rate. Unlike HCoV-OC43 and HCoV-229E, SARS-CoV has different clinical manifestations affecting GIT, liver, kidneys and even brain which became forefront to wide-spread of virus via different routes. Identification of infected persons and controlling the spread of virus is achieved by the mode of quarantine [7]. Contrastingly HCoV-OC43 and HCoV-229E causes upper respiratory tract infection and common cold [8], but 2019-nCoV causes lower pulmonary infection and develops Acute Respiratory Distress Syndrome (ARDS). Farthest of December 2019, a large number of cases got filed and patients with signs of pneumonitis with no cause of the disease were

admitted in hospitals. Epidemiological reports evaluated that the patients are participants of a wet animal and sea food market in Wuhan, China [9,10]. A pathogen [1, 11-15] named coronavirus, 2019-nCoV was sighted for causing pneumonia. World Health Organization (WHO) on 11th Feb, 2020 named the abnormality as COVID-19, Corona Virus Disease 2019 [16]. Based on the taxonomy and phylogeny, the CSG (Coronavirus Study Group) of (ICTV) International Committee on Taxonomy of Viruses renamed the virus as SARS-CoV-2 stating that 2019-nCoV is kinsfolk to SARS-CoV [17]. A health emergency alert has been activated world-wide by rapid spread of 2019-nCoV. SARS-CoV resulted with 8273 positive cases and 775 deaths and MERS-CoV resulted with 1139 positive cases and 431 deaths, but the COVID-19 reported with 12768307 laboratory-confirmed cases and 566654 deaths till 13th July, 2020 globally [18] with 5.22% fatality rate. The COVID-19 outbreak evolved as a transmissible disease and is being transmitted at a rapid rate universally. This potent virus resulted to global pandemic situation with a serious health risk.

Properties

The coronaviruses are enfolded, single-stranded (ss) RNA viruses which a deliberate natural history. Respiratory, enteric, neurological abnormalities can be caused by these viruses. Serologically and genotypically coronaviruses can be divided to 4 subfamilies namely – alpha (α), beta (β), gamma (γ), and sigma (δ). Both α -CoVs and β -CoVs cause the human virus infections [19, 20]. SARS-CoV and MERS-CoV belongs to sub-family beta-coronaviruses (β -CoVs) [19]. Genome-wide phylogenetic studies reported that SARS-CoV-2 is contributed with identical sequence of 79.5% of SARS-CoV and 50% of MERS-CoV [1,21,22]. 94.6% of sequence is identical in SARS-CoV and SARS-CoV-2 [21], and <90% sequence is identical between SARS-CoV-2 and remaining β -CoVs [1], which implies that SARS-CoV-2 belongs to β -CoVs [23].

The genome size of SARS-CoV-2 virus is of 29.9-32 kb which is similar to remaining β -CoVs [24]. It owns a nucleo-capsid made of phosphorylated nucleo-capsid protein (N) and genomic RNA. The nucleo-capsid protein is enfolded within the bilayered phospholipids and two distinct typed spike proteins are surrounded, the hemagglutinin-esterase (HE), the spike glycoprotein (S) which is present in all coronaviruses. The viral envelop with glycoprotein trimmer protein locates the envelope protein (E) and membrane protein (M) [23]. Typically like the β -CoVs, genome of SARS-CoV-2 is held with 50 and 30 terminal sequences with 265 and 229 nucleotides (nt) at 50 and 30 terminal regions respectively, along with a gene order 50 -replicase open reading frame (ORF) 1ab-S-envelope (E)-membrane (M)-N-30. SARS-CoV-2 has various genes such as S with 3822 nt, ORF3a with 828 nt, E with 228 nt, M with 669

nt, and N with 1260 nt. A suspected gene ORF8 is found between M and N ORF genes with 366 nt in length, which resembles SARS-CoV [23].

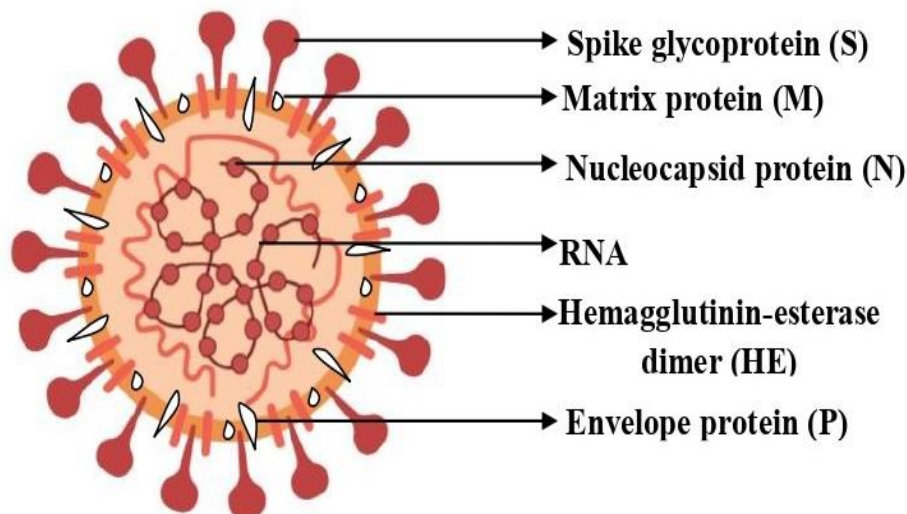


Figure 1 Structure of SARS-CoV-2

Structural proteins	Protein features
Nucleo-capsid protein (N)	Binds with RNA to make spiral ribonucleoprotein
Membrane protein(M)	Transmembrane envelop and it determines the shape of the protein
Envelop protein(E)	Interacts with M protein to form the surrounding envelop and essential for the virus infectivity nature
Spike protein(S)	Binds to the ACE2 receptors of the host cells which facilitates the entry of virus into the host cell and is targeted by antibodies secreted by the host cells

Table 1:- Structural proteins of SARS-CoV-2 and their properties.

The viral particulate is oval shaped with 60~100 nm diameter [25]. Most of the information regarding CoVs is acquired from SARS-CoV and MERS-CoV. SARS-CoV-2 can be degraded by ultra-violet light or can be desensitized by heating at 56° C for 30 minutes and disinfectants like peracetic acid, diethyl ether, 75% ethanol, chloroform and chlorine can disinfect the virus [25]. The novel corona virus, SARS-CoV-2 has high stability on stainless steel and plastics than on cardboard and copper, the live virus was screened out 72 hours after accommodated to the surfaces. The continuance of SARS-CoV-2 is lengthier compared to SARS-CoV and lengthiest lively time is reported on plastic and stainless steel [26].

Transmission

Since the COVID-19 outbreak has begun and is still continuously evolving the globe, everyday a new thing is spotlighted regarding the virus. SARS-CoV-2 is mainly transmitted when an infected person sneezes, coughs or comes in contact directly with mucous layers. People are prone to be infected when they go in contact with contaminated surfaces and when they touch their nose, mouth with those contaminated hands.

Pre-symptomatic transmission is the transmission of virus from an infected person who is non-symptomatic till then. The time lapse between infection and occurrence of symptoms is known as incubation period, averagely 5-6 days which may hold out to 14 days. This is also considered as presymptomatic session for the reason that infected person is symptomless. And these symptomless people play a key role in the transmission of the virus which is more contagious [27-32]. There is highest possibility of transmission of the virus through these symptomless people who are tested and confirmed as positive for SARS-CoV-2 [33,34]. Though it can easily be transmitted, virus needs a particular route for transmitting, which is now being transmitted through droplets that come out while sneezing, coughing and why not contaminated surfaces. On 7th July, 2020 WHO technical lead head COVID-19 Dr Maria Van Kerkhove briefed the “evidence emerging” of the airborne spread of the COVID-19 after a group of scientists urged the global body to update its supervision on how the respiratory disease passes between people, but that it was not definitive. The possibility of airborne transmission in public settings - especially in very specific conditions such as closed, poorly ventilated, crowded places. Furthermore, the evidence needs to be gathered and interpreted. **Symptomatic transmission** is the transmission of virus from an infected person with proper symptoms after the SARS-CoV-2 infection. Proper epidemiologic reports are depicting that people being infected are in contact with those who are already positive for infection [35-41]. A varied virological and clinical report confirms that in the early stage of infection (before onset of symptoms) virus is discharged from nose and mouth in higher amounts [42-45]. **Asymptomatic transmission** is defined as the condition where transmission is from a confirmed positive case of SARS-CoV-2 virus infection, with no symptoms. People with absence of symptoms but infected with virus are treated as super spreaders of the virus.

Diagnosis

COVID-19 can be diagnosed by Polymerase chain-reaction (PCR) which is the main method for the detection of SARS-CoV-2 [46]. The sensitivity of testing of naso-pharyngeal swab becomes high by the onset of symptoms. Testing of sputum samples increases sensitivity than testing the naso-pharyngeal

swabs, laboratories are also accessible for sputum testing lower pulmonary tract samples and sputum samples are may be easily obtained [47]. Centers for Disease Control and Prevention (CDC) recommended that oropharyngeal swab can be used in case of unavailability of naso-pharyngeal swab [48]. On-site self-collection of nares specimens present anteriorly is recognized by the Food and Drug Administration (FDA) and accepted it as method of collection [49] which reduces the exposure of health workers for infection.

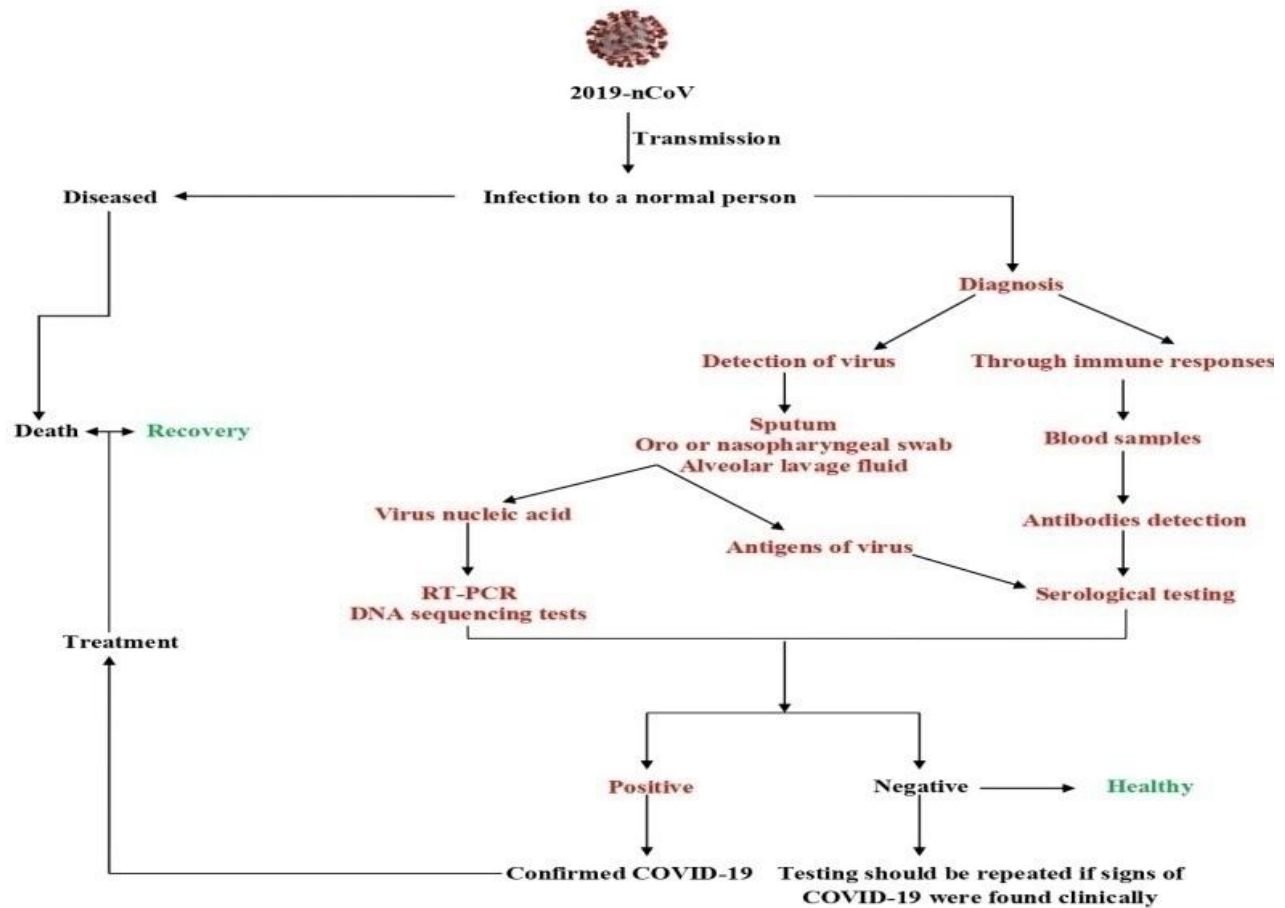


Figure 2:- Diagnosis of COVID-19

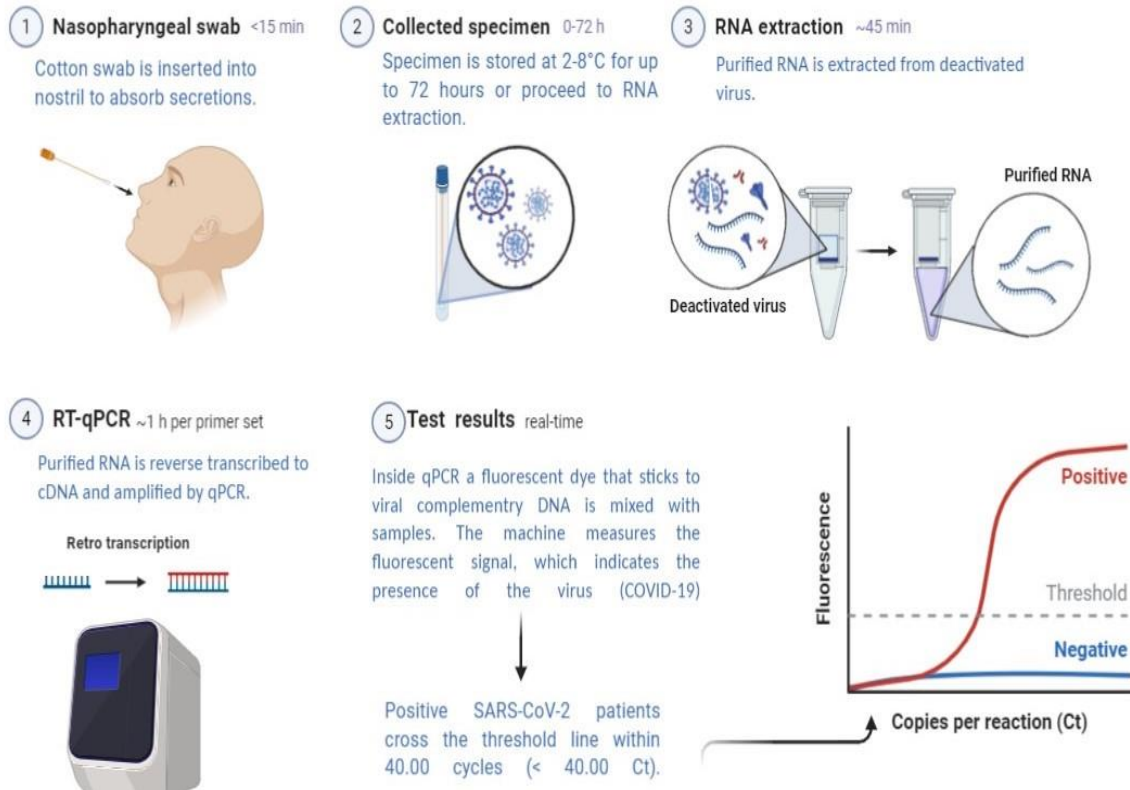


Figure 3:- Steps involved in RT-qPCR

Risk factors-Symptoms- Clinical manifestations

The clinical signs of attack of 2019-nCoV are appearing post incubation period of roughly 5.2 days [50]. Depending upon the severity of virus and immunity of the patient, the life span remained after the beginning of symptoms is 6 - 41 days [51].

Ailments that occur usually are:

1. Fever
2. Cough
3. Fatigue
4. Headache
5. Haemoptysis
6. Diarrhoea
7. Dyspnoea
8. Lymphopenia [14,51,52,53]

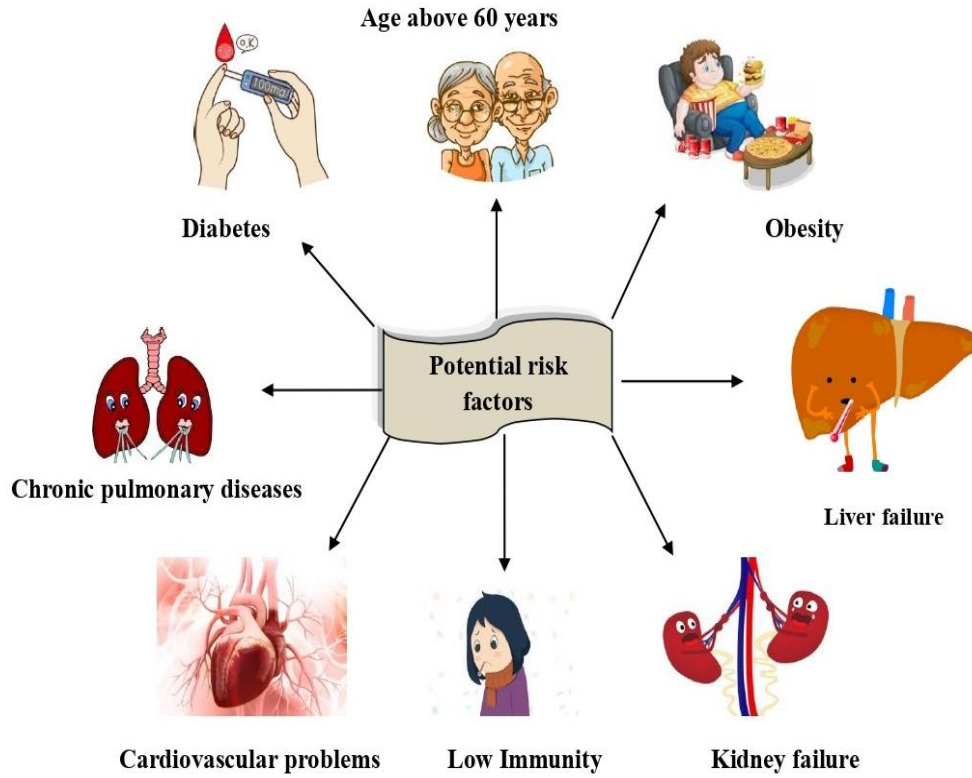


Figure 4:- Risk factors for COVID-19

- Mild
- Severe
- Critical

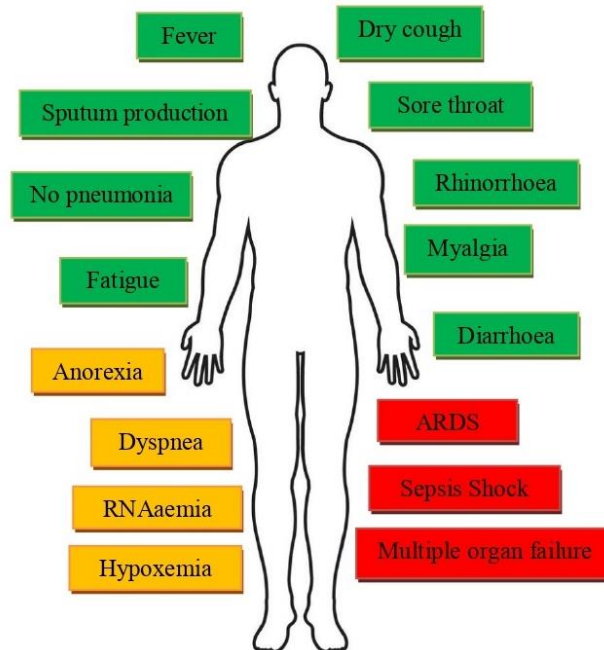


Figure 5:- Symptoms according to severity of the infection

Apart from pneumonia which was revealed by CT scan of chest, various abnormalities that lead to death are RNAemia, ARDS, and acute cardiac injury [52]. Some cases reported ground-glass opacities peripherally in sub-pleural areas of lungs [54] lead to constrained and systemic immune triggering which increases inflammatory responses. Symptoms associated with upper respiratory tract such as sneezing, sore throat and rhinorrhoea are noticeable for lower respiratory tract infection which is idiosyncratic clinical characteristic of 2019-nCoV [55,56]. Patients with COVID-19 positive also began to develop GIT infections like diarrhoea where a few cases of SARS-CoV and MERS-CoV had resembling digestive upset. CT scan of chest resulted with increased dyspnea in the upper lobe of lungs [57]. Methods should be developed to recognize the transmission through various discharges and a new therapeutic strategy is needed to evolve new therapies against 2019-nCoV.

Based on severity of disease, COVID-19 is at 4 levels, they are:

1. Mild
2. Moderate
3. Severe
4. Critical

Mild patients don't have serious symptoms and have no characteristic radiographical changes in the broncho-alveolar region. Patients with moderate infection suffer with respiratory problems, fever and have characteristic change in the radiographical aspect of lungs. Patients affected severely will definitely have one of the three conditions like dyspnea with respiratory rate more than 30 times per minute where a healthy adult being needs 12-16 breaths per minute, hypoxemia where oxygen saturation less than 93 percent where the normal condition needs 95-100 percent and partial pressure of oxygen (PaO₂) less than 300 mmHg when the normal range is 400-500mmHg. Critically infected patients suffer with arrest of respiration, respiratory sepsis and collective organ abnormalities. Patients suffering with simultaneous health issues such as hypertension, diabetes, chronic pulmonary diseases (emphysema and chronic bronchitis), cardiac arrests and cancer lead to report higher fatality rate when compared to patients with no such co-morbid conditions, which also implies that they are highest risk factors for patients infected with 2019-nCoV.

Pathophysiology

Entry of the virus

ACE2 receptor facilitates the entry of SARS-CoV-2 host cells. Though SARS-CoV-2 is present inside the gastro-intestinal cells it mainly infects the type-2 pneumocyte cell present in the lungs. Type-2 pneumocyte cell with secretes dipalmitoyl phosphatidylcholine which is a surfactant lowers the surface tension of lungs. SARS-CoV-2 with the help of S protein present on the surface binds to receptor ACE2. This association between ACE2 receptor and S protein lead for a conformational change and it allows the enzyme called serine protease, TMPRSS2 to cleave the viral structure which cleaves the S protein at S1, S2 domains facilitates the attachment of membranes of virus and host cell and virus enters into host cell. Viral replication is primarily suppose to take place in epithelium of nasal cavity and pharynx lined by a mucosa (upper respiratory tract) followed by multiplication of virus takes place in gastro-intestinal mucosa and lower respiratory tract [58], with small amounts of viremia. Some people infected with SARS-CoV-2 also experienced with acute liver injury, diarrhoea, kidney failure and heart failure which are not related to pulmonary infection [2,59–61], making clear that all organs are involved.

Pathological changes

The pathological reports found that COVID-19 patient shows a pulmonary isobilateral diffused alveolar injury with cellular fibromyxoid excretes [62]. A suspension of pneumocytes, formation of hyaline membrane in the right lung and pulmonary edema in left lung implies the acute respiratory distress syndrome (ARDS). The mono-nuclear inflammatory subverts controlled by lymphocytes are recognized in both the lungs. A cytopathical change is observed with multinucleated syncytiatic cells with unusual expansion in pneumocytes with huge nuclei, amphophilous granulated cell protoplasm and intra-alveolar spaces filled with eminent nucleoli impling the pathological changes in the function of cell. Acute Respiratory Distress Syndrome (ARDS) is a life threatened condition which the oxygen is prevented for the entry into lungs and also into circulation which leads to severe respiratory disorders and lung injuries [63]. Across 40 genes including ACE2, vascular endothelial growth factor (VEGF), tumor necrosis factor (TNF) and interleukin 10 (IL-10) are reported to be associated with the development of ARDS [64].

Dysfunctioning of immune system

Reduction and hyperactivation of CD4 and CD8 T cells is observed peripherally. Increase in the concentration of the proinflammatory CD4 cells and cytotoxic granular CD8 cells triggers immune responses antivirally and T cells get overactivated [62]. Lymphopenia emerged as a feature of COVID-19 [1,2], which suggests that it is important factor for accounting the disease severity and mortality.

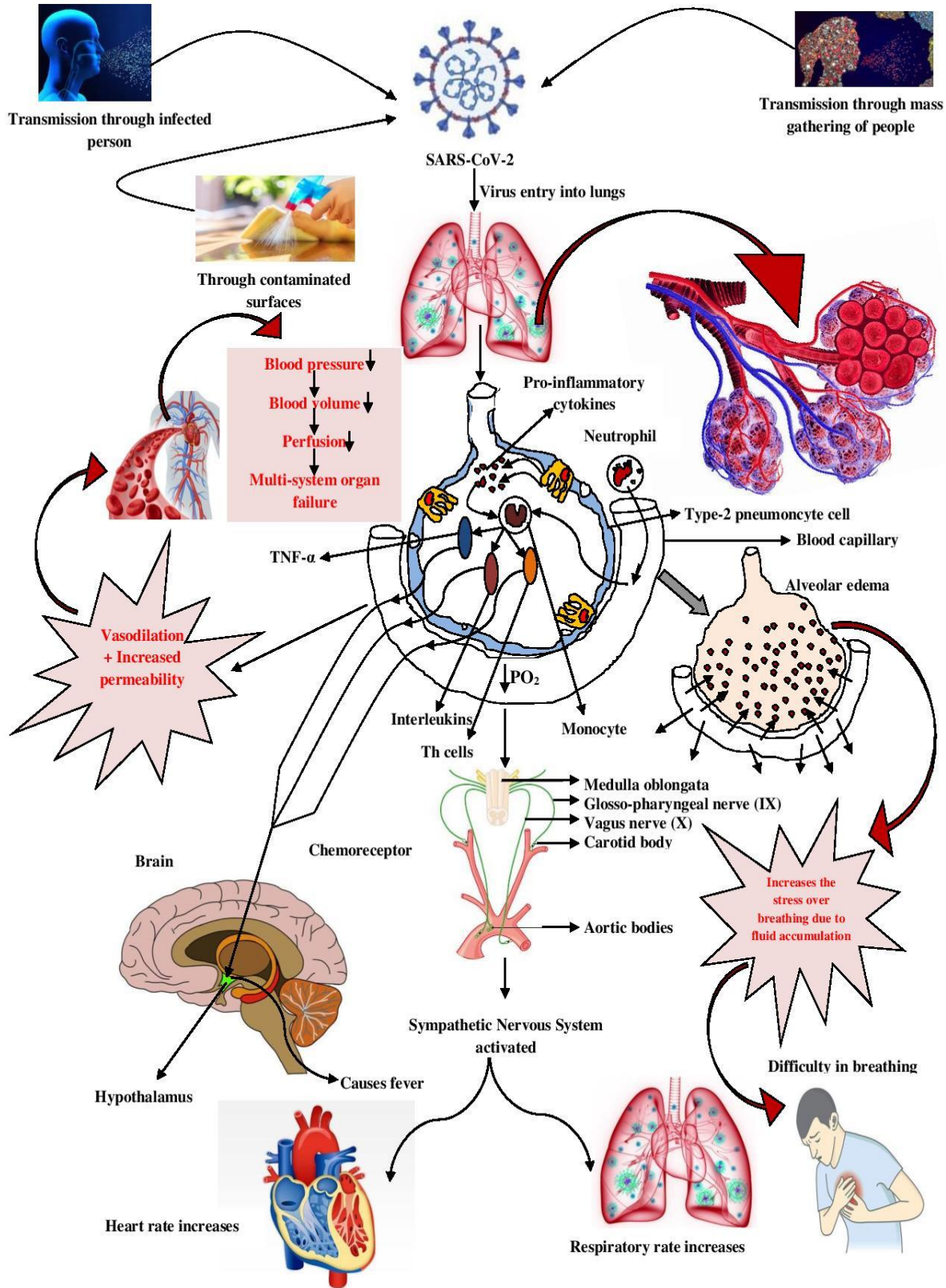


Figure 6:- An illustrated pathophysiology of SARS-CoV-2

Pharmacological treatment for COVID-19

Investigational Antiviral Agents

Remdesivir

Remdesivir is a monophosphate prodrug officially called as GS-5734 which is metabolized to an active C-adenosine nucleoside triphosphate analogue. It was discovered when it is under screening procedure for anti-microbial activity against RNA virus family like Flaviviridae and Coronaviridae. During the peak stage of outbreak of Ebola virus research activity of this agent promised for host polymerase selective activity against Ebola virus with a very low EC₅₀ [65]. Right away, remdesivir with its broad spectrum is hopefully promising the potent therapeutic activity against SARS-CoV-2 and a *in vitro* action against many novel coronaviruses with EC₉₀ value of 1.76 $\mu\text{M/L}$ and EC₅₀ value of 0.77 Mm/L [66,67].

Evaluation of the pharmacokinetic properties and safety factors of remdesivir were done in both multiple-dose and single-dose phase I trials [68]. Saphenous (intravenous) infusions halfway between 3 mg and 225 mg were accepted across the any evident for kidney and liver toxicity. Remdesivir indicated linear pharmacokinetic results in a bordered dose range with an intra-cellular half-life of higher than 35 hours. Firstly, remdesivir has been used clinically used in the treatment of Ebola virus [69]; yet, case reports suggests that a fortunate result has been reported by the use of remdesivir for COVID-19 [70,71]. Still clinical trials are under process to assess the safety parameter and activity against the virus in COVID-19 patients.

Favipiravir

Favipiravir, a prodrug of nucleotide “purine”, ribofuranosyl-5'-triphosphate. Favipiravir halts replication of the virus by inhibiting the enzyme RNA polymerase viral. Yet it indicated the broad activity against RNA viruses its preclinical data is derived from anti-influenza and Ebola activity [72]. EC₅₀ value against SARS-CoV-2 Vero E6 cells was 61.88 $\mu\text{M/L}$ [67].

There is probable dose variation for the reason of low EC₅₀ value with influenza when compared to SARS-CoV-2 and Ebola [73, 74]. So for COVID-19, consideration of doses should be at higher range [74]. A loading dose with 2 doses of 2400 mg to 3000 mg for every 12 hours followed by maintenance dose of 1200 mg to 1800 mg for every 12 hours are recommended. Half-life is nearly 5 hours [75]. A limited adverse affect profile with higher dose regimens is found and is well tolerable [74,76-78].

Selected Repurposed Drugs

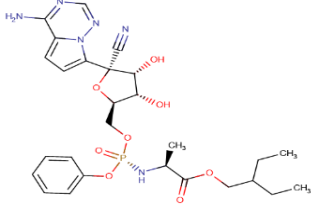
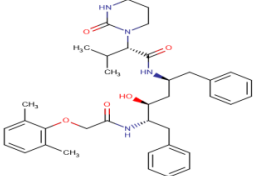
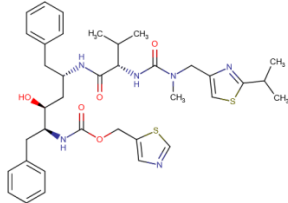
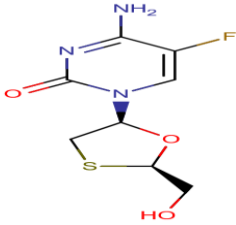
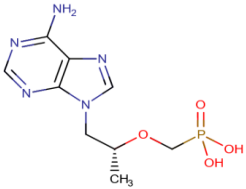
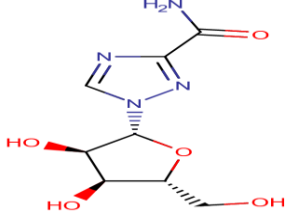
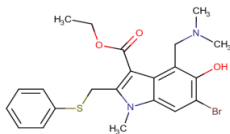
Hydroxychloroquine (HCQ) and Chloroquine

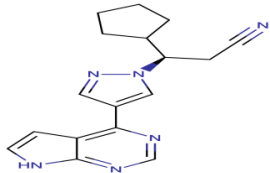
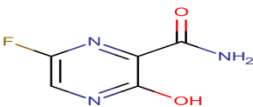
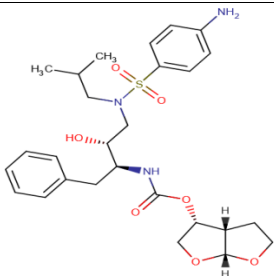
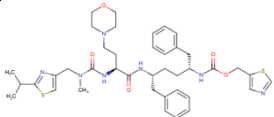
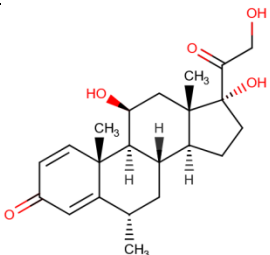
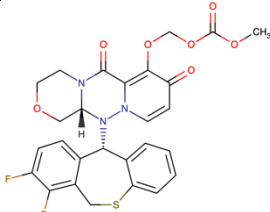
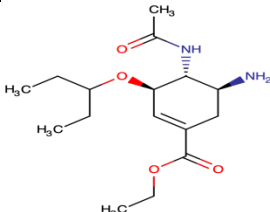
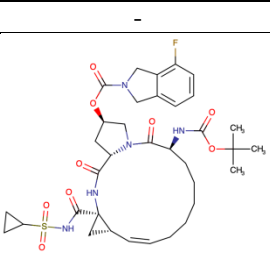
Hydroxychloroquine and Chloroquine have a long history for treating and preventing malaria and several chronic inflammatory diseases which include rheumatoid arthritis and systematous lupus erythematosus (SLE) [79]. Chloroquine and HCQ blocks entry of virus into the cells by the inhibition of glycosylation of receptors, it allows proteolytic transformation, and endosomal acidification. Immunomodulatory effect by diminishing the production of cytokines and also inhibits the self-eating of host cells (autophagous effect) and inhibits the activity of lysosomes of host cells [80,81]. Chloroquine in vitro inhibits SARS-CoV-2 in low range of EC50. After one day, hydroxychloroquine shows lower EC50 when compared with chloroquine where hydroxychloroquine shows EC50 of 6.14 $\mu\text{M/L}$ and chloroquine shows EC50 of 23.90 $\mu\text{M/L}$ [82]. It's not evident that HCQ and chloroquine are efficient for treating SARS-CoV and MERS-CoV. China briefed in the new bulletin that chloroquine was successful in treating more than 100 COVID-19 patients and radiological reports suggested that there is viral clearance and decreased disease severity [83]. Dosing of chloroquine to treat COVID-19 has consisted of 500 mg orally once or twice daily [84,85].

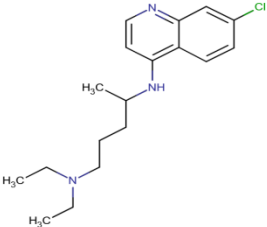
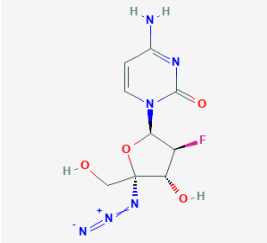
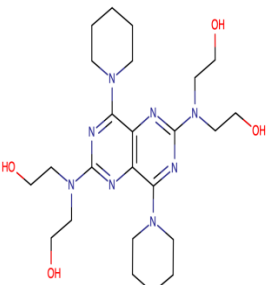
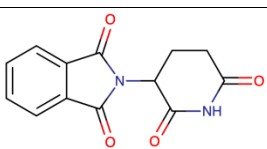
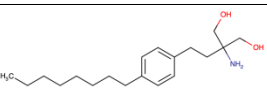
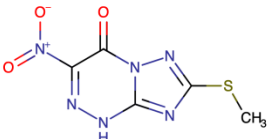
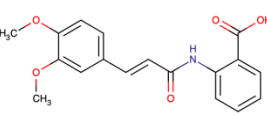
Nevertheless, serious adverse events are caused by both the agents that includes prolonged Q-T interval, retinopathy, hypoglycemia [86,87]. No adverse events are reported for chloroquine treatment for COVID-19 [83].

Lopinavir/Ritonavir/Ribavirin

Lopinavir/ritonavir is a US FDA approved drug treating HIV, indicated activity against different coronaviruses by inhibiting 3-chymotrypsin [75,88]. No published data exists that implies that lopinavir/ritonavir is active against SARS-CoV-2 [89]. Many case reports, small retrospective studies and non-randomized cohort studies made hard to discover the effect of lopinavir/ritonavir [90,91]. Lopinavir/Ritonavir dosing regimen of 400 mg/100 mg twice daily for 14 days is suggestible [85,92]. Ribavirin is a guanine analogue which inhibits viral RNA-dependent RNA polymerase. It is smacked as drug candidate against different nCoVs and treating COVID-19. It's not evident that ribavirin can treat covid and pulmonary syncytium data suggests that inhaled administration gives no benefit compared to intravenous administration [93].

S.No.	Drug	Drug Bank Id	Structure	MOA	Current clinical investigations	Evidence/ Indication	References
1	Remdesivir	DB14761		RNA polymerase inhibitor	In Vitro Assay, Clinical report, Clinical trial	Phase III passed for Anti-Ebola, Phase III-COVID-19	94
2	Lopinavir	DB01601		Protease inhibitor	Clinical Trial	Approved for Anti-HIV, COVID-19	95
3	Ritonavir	DB00503		Protease inhibitor	Clinical Trial	Approved for Anti-HIV, COVID-19	96
4	Emtricitabine	DB00879		Nucleoside reverse transcriptase inhibitor	Clinical Trial	Approved for Anti-HIV, anti-HBV	97
5	Tenofovir	DB14126		Nucleoside reverse transcriptase inhibitor	Clinical Trial	Phase III for Anti-HIV, anti-HBV	98
6	Ribavirin	DB00811		Inhibitor for protein synthesis and Viral mRNA	Clinical Trial	Anti-HBV, Anti-HCV, Anti-influenza, Anti-SARS, COVID-19	99
7	Umifenovir	DB13609		S protein/ACE2, membrane fusion inhibitor	Clinical Trial	Approved for Influenza, In Phase IV trial for COVID-19	100

8	Ruxolitinib	DB08877		Kinase inhibitor	Clinical Trial	In Phase 0 trial for COVID-19	101
9	Favipiravir	DB12466		RNA polymerase inhibitor	Clinical Trial	Approved for Anti-influenza, In phase II for anti-Ebola	102
10	Darunavir	DB01264		Protease inhibitor	Clinical Trial	Approved for Anti-HIV	103
11	Cobicistat	DB09065		Inhibitor of cytochrome P450 3A isoform	Clinical Trial	Approved for Anti-HIV	104
12	Methylprednisolone	DB00959		Corticosteroid	Clinical Trial	In phase II for COVID-19, rheumatic disorders and allergic asthma approved	105
13	Baloxavirmarboxil	DB13997		Polymerase inhibitor	Clinical Trial	Approved for anti-influenza approved	106
14	Oseltamivir	DB00198		Inhibitor for Neuraminidase, Sialidase	Clinical Trial	Approved for Anti-influenza, Phase III for COVID-19	107
15	IFN alpha-1b		-	Immunomodulation	Clinical Trial	Interferon	108
16	Danoprevir	DB11779		Protease inhibitor	Clinical Trial	In phase III for Anti-HCV, Phase IV for COVID-19	109

17	Peginterferon α -2a	DB00008	-	Immunomodulation	Clinical Trial	HCV approved, COVID-19 Phase IV	110
18	Chloroquine	DB14761		Inhibits glycosylation of host receptors.	In Vitro Assay, Clinical trial	Approved for Antimalarial, In phase III for anti-HIV anti-HCV, In phase IV for COVID-19	111
19	Azvadine	PubChm 24769759		Reverse transcriptase inhibitor	Clinical Trial	Approved for Anti-HIV	112
20	Dipyridamole	DB00975		Adenosine deaminase and phosphodiesterase inhibitor	Clinical Trial	In phase IV for COVID-19, Phase IV completed for coronary arteriosclerosis, Phase IV completed for stroke prevention.	113
21	Thalidomide	DB01041		TNF- α inhibitor	Clinical Trial	Phase III completed for cancers; Phase II completed for COVID-19;	114
22	Fingolimod	DB08868		-	Clinical Trial	In phase II for COVID-19; Completed Phase IV trial for Multiple Sclerosis	115
23	Triazavirin	DB15622		RNA synthesis inhibitor	Clinical Trial	In phase III for COVID-19	116
24	Tranilast	DB07615		Inhibits Hematopoietic and prostaglandin D synthase	Clinical Trial	Completed phase IV for Conjunctivitis; In Phase IV for COVID-19	117

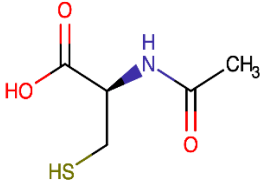
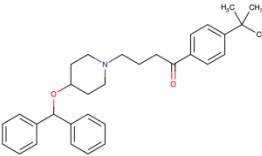
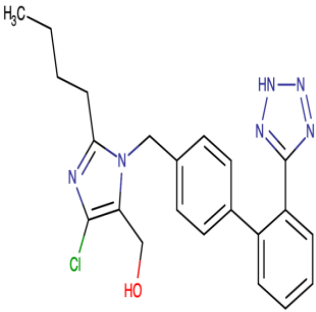
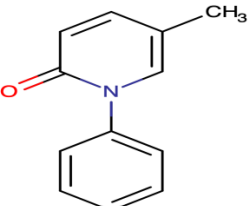
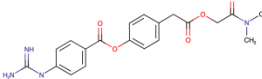
25	Acetylcysteine	DB06151		Mucolytic agent	Clinical Trial	Completed Phase IV trails for Drug Overdose, Bipolar disorder, AMI, lung diseases; In Phase IV for COVID-19	118
26	Ebastine	DB11742		H1 inhibitor	Clinical Trial	Completed phase IV trails for IBS, urticaria; Phase IV for COVID-19	119
27	Losartan	DB00678		Angiotensin II receptor blocker	Clinical Trial	Completed Phase IV trails for high blood pressure, diabetes mellitus, hypertension, kidney diseases, stroke; Phase IV for COVID-19	120
28	Pirfenidone	DB04951		Profibrotic cytokine down-regulator and Inhibitor for Collagen synthesis,	Clinical Trial	Completed Phase IV for IPF; completed Phase III for DFU and Phase 0 for COVID-19	121
29	Camostat	DB13737		TMPRSS2 inhibitor	Clinical Trial	COVID-19 Phase I	122

Table 2:- Updated list of investigational drugs against SARS-CoV-2

Conclusion:-

The whole universe is worried about the COVID-19 pandemic and the main groups of people getting affected by this virus are the elder group and those having severe comorbid conditions. There is still no specific therapeutic antiviral treatment or vaccine available. The novelty of the disease made scientists aim towards discovering a new therapeutic target to combat the disease. Investigation of therapeutic targets is needed and fastness and accuracy in clinical trials are demandable. Therapies emerged till date are just to manage the symptoms and save the affected people from life threat as there is no effective therapy emerged to date.

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