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Review

SARS-CoV-2: Insight in genome structure, pathogenesis and viral receptor binding analysis – An updated review

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ABSTRACT

The novel coronavirus disease (COVID-19) a global pandemic outbreak is an emerging new virus accountable for respiratory illness caused by SARS-CoV-2, originated in Wuhan city, Hubei province China, urgently calls to adopt prevention and intervention strategies. Several viral epidemics such as severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 to 2003 and H1N1 influenza in 2009 were reported since last two decades. Moreover, the Saudi Arabia was the epicenter for Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012. The CoVs are large family with single-stranded RNA viruses (+ssRNA). Genome sequence of 2019-nCoV, shows relatively different homology from other coronavirus subtypes, categorized in betacoronavirus and possibly found from strain of bats. The COVID-19 composed of exposed densely glycosylated spike protein (S) determines virus binding and infiltrate into host cells as well as initiate protective host immune response. Recently published reviews on the emerging SARS-CoV-2 have mainly focused on its structure, development of the outbreak, relevant precautions and management trials. Currently, there is an urgency of pharmacological intervention to combat this deadly infectious disease. Elucidation of molecular mechanism of COVID-19 becomes necessary. Based on the current literature and understanding, the aim of this review is to provide current genome structure, etiology, clinical prognosis as well as to explore the viral receptor binding together functional insight of SARS-CoV-2 infection (COVID-19) with treatment and preventive measures.

1. Introduction

A priority list of epidemic or pandemic pathogens established by World Health Organization (WHO) in April 2018 such as severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and Disease X, elicited by an unknown pathogen [1] (Fig. 1).

The outbreak of novel coronavirus in late December 2019 was identified in Wuhan, a city of 11 million people of Hubei province, P.R. China and in January 2020 the causative agent was identified as beta-coronovirus, same as SARS-CoV, hence named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2]. The infected cases, known initially to exposure, in a wholesale market of seafood in Wuhan. The temporarily name used by the world health organization (WHO) for this pathogen was 2019 novel coronavirus (2019-nCoV) [3,4], and was identified as pathogen able to cause coronavirus disease covid-19 [5]. Furthermore, the first 2019-nCoV whole-genome sequence was unleashed on January 10, 2020, which provides a source for researchers to recognize the virus in patients by reverse transcription polymerase chain reaction(RT-PCR) technique [6]. A group of researchers published first article related with 2019-nCoV on 21 January, which reported that 2019-nCoV is associated to the beta-coronavirus group, sharing 79.5% and 95% with SARS-Cov and a bat coronavirus, SL-CoV-RaTG13, respectively, was renamed SARS-CoV-2 by the Coronaviridae Study Group (CSG) of the International Committee on Taxonomy of Viruses (ICTV) [6,7]. However, it was renamed as HCoV-19, as a standard virus name, by virologist group in China [8–10]. Furthermore, the WHO

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announced the Public Health Emergency of International Concern (PHEIC) on January 30 for 2019-nCoV outbreak. Different groups have submitted 51 whole –genome sequences of 2019-nCoV to GISAID database on 31 January [11]. The WHO on 12th February permanently given a name the 2019-nCoV pathogen as SARS-CoV-2 and noval infected disease as coronavirus disease 2019 (COVID-2019). Unfortunately, SARS-Cov-2 was not controlled and spread rapidly to more than 150 countries. WHO formally recognized the COVID-19 as a pandemic. On 24 February 2020, a total 79,331 of COVID-19 cases were confirmed, including 2618 deaths in China and other 27 countries [12], raising a concern thread globally and calling for pharmacological intervention against this COVID-19 treatment and prevention. The global death rate reached 9,913, with 2,42,650 laboratory-confirmed cases on march 19th 2020. The death rate among infected people varies in different countries. However, the global death rate was around 3.92% in april [13]. WHO reported about 27 million COVID-19 cases and 900 000 deaths On September 6 to date. New cases reached over 1.8 million and 37 000 new deaths were reported on 6 September ending week, a 5% increase in the number of cases and a 2% decrease in the number of deaths compared to the previous week. Over the past week, 4.7 million new cases have been registered worldwide, a 6% decrease from last week, and the number of new casualties has risen to a record high of 93,000, a 9% increase from last week. This takes the total figures since the beginning of the pandemic to over 93 million recorded cases and over 2 million deaths worldwide [14]. On 19th January 2021, total confirmed cases were 95 612 831 and total confirmed deaths were 2 066 176 with 224 countries, areas or territories with cases.

2. Perspicacity of coronaviral genome and structure

CoVs, a family of Coronaviridae belongs to the subfamily Coronavirinae of the order Nidovirales, which includes four genera: Alphacoronavirus, Betacorona virus, Gammacoronavirus and Deltacoronavirus. Coronaviruses constitute single-stranded positive-sense RNA (+ssRNA) with 5′-cap structure and 3′-poly-A tail (~30 kb) [15]. A single stranded RNA genome of CoVs is constituted of 29,891 nucleotides encoding 9860 amino acids. The tempelate is used genomic RNA that directly translate polyprotein 1a/1ab (pp1a/pp1ab), which encode non structural proteins (nsps) results the replication-transcription complex (RTC) formation in a double-membrane vesicles (DMVs) [16]. Subsequently, RTC synthesiszed subgenomic RNAs (sgRNAs) with discontinuous manner of transcription [17]. A common 5′-leader and 3′-terminal sequences contains these subgenomic messenger RNAs (mRNAs). These minus-strand sgRNAs act as templates for subgenomic mRNAs production [18,19]. Atleast, six ORFs are present in a genome and subgenomes of a typical CoV. The first ORFs (ORF1a/b) , approximately of two-thirds of the whole genome length, encodes 16 nsps (nsp1-16). Between ORF1a and ORF1b is a −1 frameshift, leading to production of two polypeptides: pp1a and pp1ab. Furthermore, chymotrypsin-like protease ($3CL^{pro}$) or main protease (M^{pro}) encoded and processed these polypeptides and one or two papain-like protease into 16 nsps [20,21]. At the 3′-terminus of ORFs, one-third of the genome encodes atleast four structural proteins such as spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins **(**Fig. 2**a).** Apart from these four structural proteins, special structural and accessory proteins are encoded by different CoVs such as HE protein, 3a/b protein, and 4a/b protein. Furthermore, the structural and accessory proteins are translated from the sgRNAs of CoVs [17]. Although, origin of this virus is elusive, however based on genomic analysis, suggests that SARS-CoV-2 possibly be evolved from a strain found in bats **(**Fig. 2**b).** It belongs to the Coronaviridae family. To date, seven coronavirus members in human has been identified including SARS-CoV, MERS-CoV responsible for severe respiratory syndrome. The other four members including HCoV-OC43, HCoV-229E, HCoV-HKU1 and HCoV-NL63 cause mild upper respiratory disease. Although, MERS-CoV was found in Middle Eastern region in 2012, but, it was imported into China [22,23]. For the virion assembly and CoVs infection, four structural proteins are essential for it. Spikes present on viral surface is constituted by the homotrimers of S protein, which is responsible for host cell receptors [24,25]. Function of M protein shapes the virions and is constituted of three transmembrane domain , which promotes membrane curvature that helps to bind the nucleocapsid [26,27]. Moreover, the protein E executes an important role in assembly and release of virus, it is implicated in viral pathogenesis [28,29]. The N protein assembly of two domains, both are able to bind virus RNA genome through different mechanism. Furthermore, N protein is known to interact with nsp3 to help tether the genome to RTC, help to packaging encapsidated genome into virions [30-32]. The CoV-2 surface possess spike (S) protein play a pivotal role in viral attachment, fusion and entry, acts as a hot spot to develop therapeutics. SARS-CoV-2 S protein possesses receptor binding domain (RBD), known to interact strongly with Angiotensin converting enzyme- (ACE2) receptor. [3,6]. Furthermore, study shows that the receptor-binding domain (RBD) in S protein of SARS-CoV-2 possess −10- to 20- fold higher binding affinity than that of SARS-CoV to ACE2, which may confer to the higher infectivity as well as transmissibility of SARS-CoV-2 in contrast to SARS-CoV [33,34]. The proposed mechanisms of SARS-CoV-2 entry into the cells is shown in **(**Fig. 3**).** However, it is poorly understood whether membrane fusion mediated by SARS-CoV-2 surpass the capacity of SARS-CoV. Furthermore, spike (S) protein contains S1 subunit in which receptor binding domain binds to the receptor of ACE2 on target cell, in S2 subunit of S protein contains heptad repeat 1 (HR1) and 2 (HR2) domains known to interact within themselves,

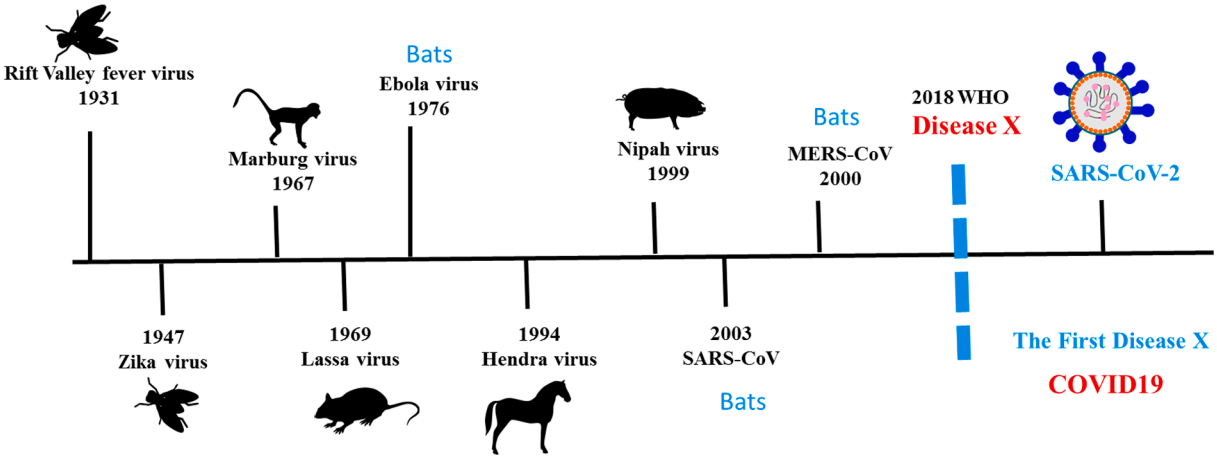

Fig. 1. The timeline for emerging highly pathogenic viruses and the proposed Disease X.

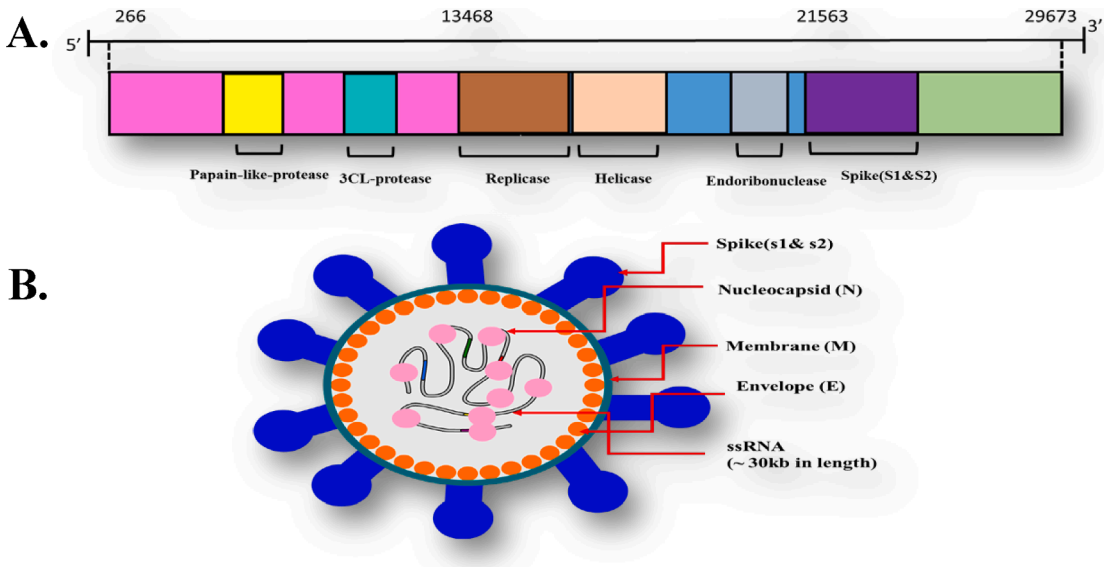

Fig. 2. Schematic representation of RNA genome and Structure of SARS- CoV 2. respectively **(A.)** Singe stranded RNA genome of SARS-CoV2 (~30 kb in length) showing with different components of genome **(B.)** Structure of SARS- CoV 2 is constituted of different elements such as Spike (S1 and S2), Nucleocapsid, membrane, envelope, ssRNA.

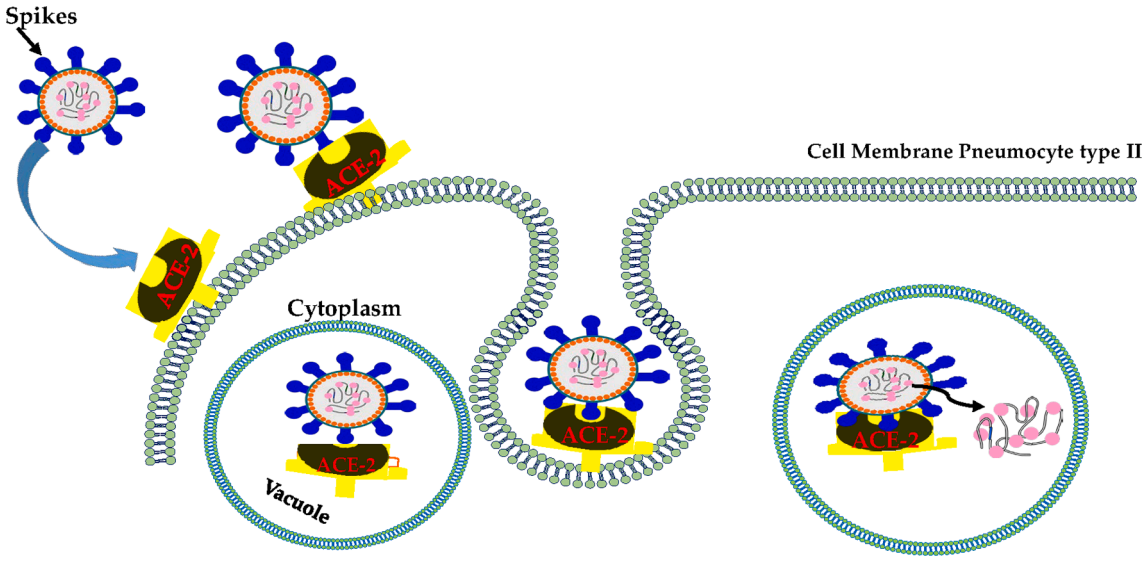

Fig.3. Proposed mechanisms of SARS-CoV-2 entry into the cells. Viral Receptor binding occurred through a densely S-spike protein present on outer surface of virion, responsible entry of genetic material (RNA) , which is then mRNA and host machinery starts translate into protein . The cell is then killed and releases into extracellular milieu after entering the virus into the cell.

results fusion protein of six-helix bundle, consequently bringing into close vicinity for fusion as well as infection [35]. Therefore, the 6-HB fusion core structure of SARS-CoV- 2 and SARS-CoV S proteins should be compared to investigate S proteins mediated structure based membrane fusion ,which will provide the stage for design of coronavirus fusion inhibitors.

3. Etiology

Since last two decades, potent infectious pathogen emerged increasingly like SARS-CoV in 2003 and MERS-CoV in 2012 [36-38]. CoVs are positive-stranded RNA viruses. Under an electron microscope, CoVs appear crown like structures due to the presence of densly spike glycoprotein on the envelope. The members of Coronaviridae known to cause various diseases such as respiratory, enteric, hepatic, and neurological diseases in different animal species like camels , cattle ,cats and bats. In mid-1960 s, some HCoVs were identified, whereas others were identified in new millennium. Overall, estimates propose thatpopulation of 2% are robust carriers of a CoV and are responsible for around 5% to 10% of acute respiratory infections [39]. So far, seven human CoVs (HCoVs) that can infect humans have been identified. The seven CoVs that can infect humans include HCoV-OC43, and HCoV-HKU1 (betaCoVs of the A lineage); HCoV-229E, and HCoV-NL63 (alphaCoVs). They are responsible for the common colds and upper respiratory infection in weak immunocompetent individuals. Lower respiratory tract infection occur in immunocompromised and elderly people. On the other end, SARS-CoV, SARS-CoV-2, and MERS-CoV (betaCoVs of the B and C lineage, respectively) are other human CoVs. These are responsible for epidemic with variable severity features of respiratory manifestations. The mortality rates are about 10% and 35% for SARS-CoV, MERS-CoV respectively.

SARS-Cov-2 is associated with betaCoVs category. The diameter is

about 60–140 nm with round or elliptical appearance and present often in pleomorphic form. Exposure to ultraviolet rays and heat minimize its function. Lipid solvents including 75% ethanol, chlorine-containing disinfectant and peroxyacetic acid effectively inactivate the virus. Furthermore, Chan *et al.,* demonstrated that new HCoV genome isolated from different patients with atypical pneumonia possessed 89% nucleotide identity with bat SARS-like CoVZXC21 and 82% to that of human SARS-CoV, hence named as SARS-CoV-2 [40]

4. Dynamics of transmission of novel coronavirus

The Wuhan, Hubei province of china became epicenter of novel coronavirus (nCoV-2019–infected pneumonia(NCIP) in December 2019 and January 2020 [3].Li and colleagues evaluated data on 425 confirmed cases to demonstrate epidemiologic properties of NCIP in Wuhan [41]. Li and colleagues further found that confirmed cases of first 425 patients were of the median age group with 56% male. The confirmed cases onset before January 1, 2020, were associated with wholesale market of seafood, in contrast with 8.6% of subsequent cases. Based on this information, human-to-human transmission evidence were confirmed among close association since December 15, 2019 [42] **(**Fig. 4**).** A cluster of five members of patients in a family confirmed COVID-19 transmission person-to-person [43]. Moreover, preventive measures should be implemented in population and awareness as well. Furthermore, requiring diagnosis of pneumonia, , basis on case definition approximately 2% case fatality rate is evidenced [44].

The important implications for containment and mitigation strategies have related to the transmission efficiency for any deadly virus. The recent report by Fauci and group reveals the estimated basic reproduction number (R_0) is 2.2, indicating the spread of infection from infected person to more than two persons. In addition to,authors also show that until this number reduces below 1.0, it is probably that the outbreak spreads continue. Moreover, recent reports show that high loaded titers of virus in early course of oropharynx disease with minimal symptoms arose concern about the rapidly infectivity in such patients [45,46].

China, United states, South Korea and other several countries restricted the travel of people, to control the slow down of expand of this new disease within the epicenter and the worldwide. United States and South Korea has witnessed a dramatic reduction in travelers from china, mostly from Wuhan, Hubei province. The rapid action taken by Chinese authorities prevent them to control COVID-19 in China.

Moreover, 14 cases has been detected in the United states on February 26, 2020, travelledl from china or in close associate with travelers. Three of them were U.S. citizen back from China, and 42 among U.S. passengers returned from a cruise ship,associated with spread of infection [47].Consideration the current report about the efficiency of transmission, one should be ready for Covid-19 to gain a foothold throughout the world. In United States, a shift of community spread could require from containment to mitigation strategies such as social distancing to prevent minimum transmission of this virus as well as strategies to isolating ill persons, school closure and other important means [48].

Main route of transmission is droplet associated with respiration in addition to aerial transmission [49]. However, asymptomatic cases should not ignored as it playcrucial role in process of transmission [50]. From faeces of confirmed patients, a new coronavirus was detected in Shenzhen, Wuhan as well as in United states, which exists in human digestive track and replicates which provide evidence of fecal-oral transmission [51]. In the early stage of COVID-19 cases, a fruitful examination using Chest *X-ray* provide images with multiple patchy shadows as well as interstitial changes [52], exceptionally in the lung periphery [53]. In nutshell, COVID-19 image findings reported similarity to those with SARS [54,55], and MERS [56,57].

5. Clinical prognosis of coronavirus disease

Data from affected patients have been need required on clinical characteristics. A study done by Guan *et al.,* reported 1.4% mortality rate among 1099 patients with laboratory-confirmed Covid-19; these patients possesses wide spread of disease severity [58]. Furthermore, the median age group of patients was 47 years in which 41.9% were female. The history of direct contact with wildlife had only 1.9% patients. Whereas, 72.3% of non-residents of Wuhan had contact with residents of Wuhan, including 31.3% people visited the Wuhan city. Patients have seen with common symptoms like fever (43.8% on admission and 88.7% during hospitalization) and cough (67.8%). The 83.2% of the patients have seen Lymphocytopenia on hospitalization. Moreover, initially first two months of current outbreak, Covid19 spread rapidly with varying

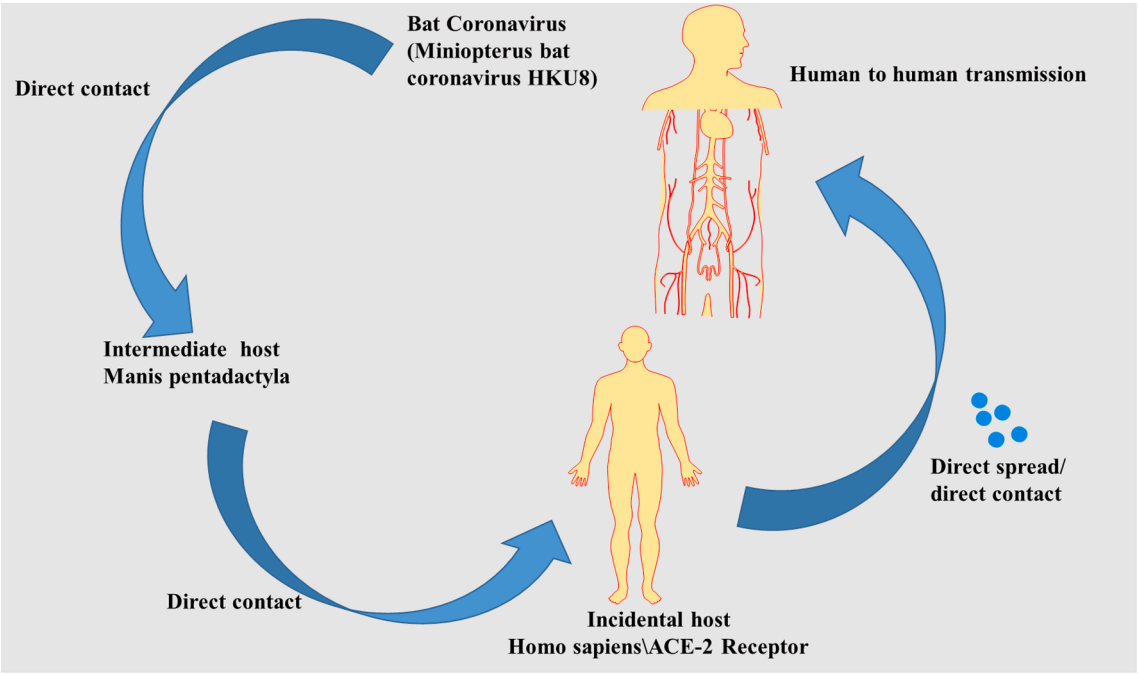

Fig. 4. Transmission Cycle of SARS-CoV2.

percent of illness throughout China. Patients admitted often present without fever, and many have no abnormal findings. Study also reported that Covid-19 mimic those of SARS-CoV, dominant symptoms were fever and cough **(**Fig. 5**),** however, symptoms related to gastrointestinal were rare, reveals distinct viral tropism in contrast to SARS-CoV, MERS-CoV, and seasonal influenza [59,60].

There is no new coronavirus infected patients in Tibet and Qinghai provinces up to now [61]. The confirmed cases together with clustered cases without travel history to Wuhan City, Hubei province, China emerged as the center of this disease [50]. Iran, Italy, Republic of Korea and Japan epidemics became the concern of WHO [62]. The assessment on COVID-19 daily risk, according to the European Centre for Disease Prevention and Control (ECDC) [63], have considered it now high level risk from moderate risk.

6. *In vitro* effective inhibition of novel coronavirus (2019-nCoV) by remdesivir and chloroquine

Chinese authorities have reported 2835 confirmed cases including 81 deaths on January 27, 2020. In addition to, 19 confirmed cases from different countries such as Hong Kong, Macao and Taiwan, and 39 imported cases were identified in Thailand, Japan, South Korea, United States, Vietnam, Singapore, Nepal, France, Australia and Canada. However, currently no specific antiviral treatment against this new virus is available; therefore, researchers need to identify urgently effective antiviral agents or drugs to combat the disease.

Various drugs including ribavirin, interferon, lopinavir-ritonavir, corticosteroids were given to patients suffering from SARS or MERS; however, potency of several drugs remains dubious [64]. One of the scientific groups demonstrated antiviral competence of ribavirin, penciclovir, nitazoxanide, nafamostat, chloroquine together with remdesivir (GS- 5734) and favipiravir (T-705), against a clinical isolate of 2019-nCoV *in vitro* were approved by FAD [65].

Remdesivir have been experimented in various animal models viz., mice, *in vitro* cell culture, and nonhuman primate (NHP) models, to act as potent antiviral drug against large number of RNA viruses (including SARS/MERS-CoV5) [66]. In current scenario, it is in clinical consideration to combat Ebola virus infection. Structurally, Remdesivir represents an adenosine analogue. It gets into nascent viral RNA chains resulting into pre-mature termination. Furthermore, Warren *et al.*, reported inNHP model that under 10 mg/kg dose when injected intravenously, reported its active form in the blood (10 μM) for prolonged time. It confer 100% defense against Ebola virus infection. [67]. The group reported that in Vero E6 cells, the EC 90 value of remdesivir against 2019-nCoV was 1.76 μM, which suggest that its functional concentration is probable to be reached in NHP. They further experimented Remdesivir on human liver cancer Huh-7 cells, that being sensitive to 2019-nCoV 2. Their results showed that it inhibits virus infection efficiently. Moreover, the possible molecular mechanism for the inhibition of RNA synthesis of SARS-CoV-2 by remdesivir has been described recently [68].

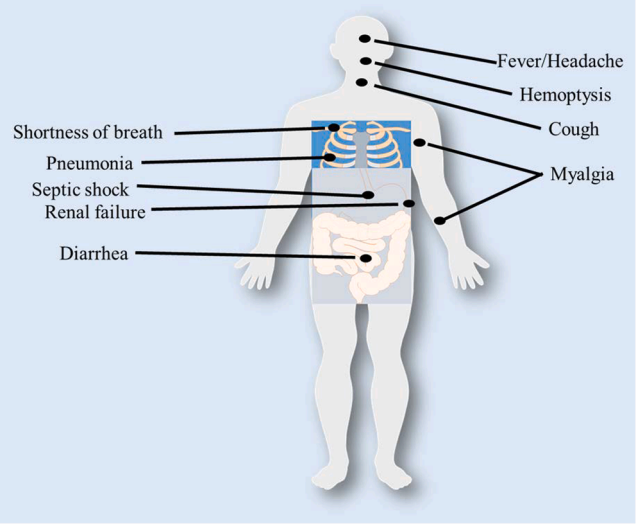

Fig. 5. Clinical presentation of patients with COVID19.

Chloroquine,is commonly used as anti-malarial drug and as autoimmune disease drug. It has shown to act as potent broad spectrum antiviral drug [69]. It is reported to increase endosomal pH which is needed for virus/cell fusion. Moreover, SARS-CoV associated with receptors involved in glycosylation interfere with chloroquine, hence blocking virus infection. The authors suggested that chloroquine in Vero E6 cells, worked at both levels of entry of the 2019-nCoV infection [70]. Apart from this, chloroquine posses immune-modulating activity, which might add to its antiviral effect in *vivo*. Chloroquine, after taken orally, gets in full body, which includes lung also. In Vero E6 cells, 6.90 μM was the EC90 value of chloroquine against the nCoV-2019, which can be achieved clinically as reported in the plasma of rheumatoid arthritis patients who received 500 mg administration [71]. Chloroquine is a cost friendly and safe drug, which is employed since 70 years and thus is potential target against the 2019- nCoV.

The study has shown that remdesivir and chloroquine are potent in controlling of 2019-nCoV infection *in vitro* studies [72]. These drugs are used in humans with no safety concern, and reported to be effected against several diseases, they could be experimented in human patients, which suffer the novel coronavirus disease.

7. Designing protein dependent vaccine

Recently, spike glycoprotein was described to acquire immunogenic epitopes. They performed immunoinformatics analysis to provide a quick immunogenic profile of these epitopes so that the rapid production of the vaccine could put an earlier end to this catastrophic situation. Furthermore, it detects possible coronavirus epitopes (SARS-CoV-2) as well explains the docking complex of the construction vaccine and TLR5, developed peptide-based vaccine followed in silico validation. There are popular coronavirus epitopes (SARS-CoV-2) listed against B-cells and T-cells [73]. In another study they tried to find the S-protein epitopic portion that could act as key targets for the production of vaccines and also seeks to explain the adaptive immunity molecular mechanism of epitopes and the TLR4/MD-2 complex [74]. However, while formulating the vaccine to resist COVID-19, these immunoinformatic investigations require multiple *in vitro* and *in vivo* validations.

8. Preventive measures/ treatment

At present, no vaccine or treatment for novel coronavirus COVID-19 has been identified.To limit the spread of cases, preventive measures are the current strategy. There is a risk, epidemic will increase as long as R0 is greater than 1 (COVID-19 is 2.2), reducing this value to less than 1 must focus on preventive control. It includes the isolation of patients and careful infection control together with appropriate measures to be adopted and clinical care of an infected patient provisionally. For instance, during specimen collection precautions like droplet, contact and airborne should be adopted and sputum induction should be avoided. WHO have issued the general recommendation including, (1) Avoid close contacts with acute suffering respiratory infection subjects (2) wash hands frequently, especially during contact with infected person (3) unprotected contact with farm or wild animals should be avoided (4) symptoms of acute airway infected person should keep their distance, use disposable tissues to cover cough and fever and wash their hands (5) and avoid public gatherings of immunocompromised individuals **(**Fig. 6**).** The bed rest as well as supportive treatment, including antiviral therapy [75], antibioics application, immunomodulating therapy [76], bronchoalveolar lavage (BAL), respiratory support, organ function support blood purification and extracorporeal membrane oxygenation

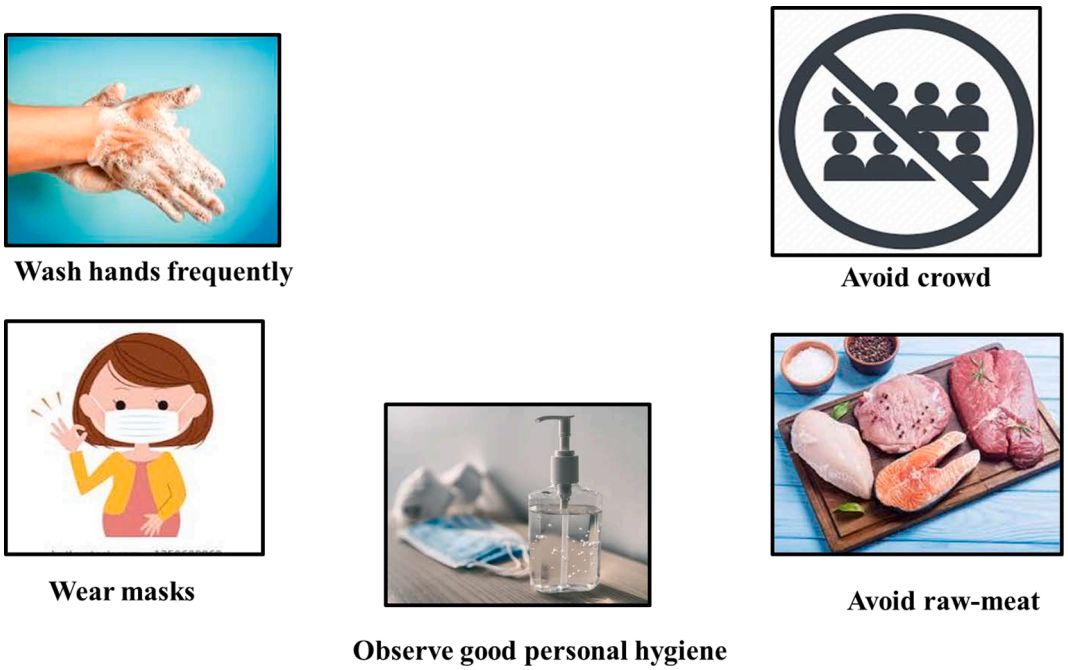

Fig. 6. Preventive measures.

(ECMO) [77] are included in general strategies.

However, scientific community in China is growing to develop a coronavirus vaccine. Recently, China has announced first animal test, and university of Queensland in Australian researchers announced that, after the three-week *in vitro* study completion, they will start working on animal models. Moreover, Washington State of U.S., a novel coronavirus immunization in the National Institute for Allergy and Infectious Diseases (NIAID) has started a phase 1 trial.

Solidarity, an international clinical trial initiated by the World Health Organization and its collaborators to help identify an appropriate cure for COVID-19. It is one of the largest global randomised trials for the treatment of COVID-19, participating approximately 12,000 patients in over 30 countries at 500 medical centers [78]. The key effects of mortality, introduction of ventilation and period of hospitalisation were not specifically reduced by every drug-study. The main goal was to help assess if in-hospital mortality was at least moderately affected by any of the four re-used antivirals, and whether any effects ranges between mild and serious illnesses [78]. The observations are to be considered in the sense of all the mortality data from properly randomised trials, this analysis presents more than three-quarters of the evidence for Remdesivir and Interferon. Four experimental trials comparing remdesivir with control were performed: the Solidarity Study (604 deaths in 5451 randomly allocated patients), the Adaptive Covid-19 Treatment Trial (ACTT-1) (136 fatalities in 1062 patients; mortality was a secondary outcome), and two smaller studies (41 deaths) [78-82].

For Hydroxychloroquine and Lopinavir, no clear proof of gain or hazard was found by Solidarity in either subgroup. The only other major trial for such two drugs is treatment, which is greater than Unity for these drugs. The results of both are consolidated by a combination of log-rank analyses from these two relatively large trials [83,84]. The use of higher doses of hydroxychloroquine for prophylaxis is likely to be linked with enhanced safety issues, so focusing on other specific alternatives may be worthwhile [85]. The combined mortality RR (combining Unity, Rehabilitation and the only insightful smaller trial) for Lopinavir (always co-administered with Ritonavir) was 1.02, 95 percent CI 0.91–1.14. While ventilated patients were unable to swallow Lopinavir tablets, no apparent benefit was seen in studies limited to those who were not already ventilated at admission.

Hardly any large mortality trials have been recorded for Interferon-β1a. The mortality RR in Solidarity was 1.16, 0.96–1.39 on the basis of about 4000 patients; p = 0.11 (or 1.12, 0.83–1.51, without co-administration of Lopinavir. This does not show risk, but in these situations the lower satisfaction limit prevents a moderate reduction in mortality. Subcutaneous and intravenous interferons have different pharmacokinetic properties [86,87], and interferon signaling [88,89] can be impaired by glucocorticoids, however the clinical importance of both problems is uncertain. Corticosteroids were obtained by about half of the interferon-allocated patients (and half of their controls), but the interferon seemed unaffected by corticosteroids.

Numerous thousand patients have now been randomised in separate trials in each of these 4 repurposed non-specific antivirals. Lower confidence intervals (particularly for Remdesivir) would be beneficial, but better care is the primary need. Approximately 2000 patients per month are still recruited by Solidarity, and successful factorial designs would enable it to test more therapies, such as immune modulators and unique monoclonal anti-SARSCoV-2 antibodies [78].

9. Production of vaccine

There are three vaccines for COVID-19 that have been approved for use by some national regulatory agencies. Sputnik V is the first registered vaccine developed by Russia. The first to gain emergency confirmation from WHO is the Pfizer/BioNTech Comirnaty COVID-19 mRNA vaccine. The Emergency Usage Listing opens the door for countries to facilitate receiving and distributing the vaccine through their own regulatory approval processes. It also makes it possible for UNICEF and the Pan American Health Organization to acquire distribution of the vaccine to nations truly needy [90].

In addition, Covishield (the local name for the Oxford-AstraZeneca vaccine produced in the UK) and Covaxin, locally manufactured by the pharmaceutical company Bharat Biotech, were granted permission by India's drug regulator. Bharat Biotech, a 24-year-old vaccine manufacturer, that has a pipeline of 16 vaccines and exports to 123 countries, has produced the domestic government-backed vaccine. It is an inactivated vaccine, which means that it consists of coronaviruses that are destroyed, making it easier to administer into the body. A coronavirus sample, extracted by India's National Institute of Virology, was used by Bharat Biotech.

Wide studies of the efficacy and safety outcomes of 5 vaccine candidates, including these three (and for Moderna and AstraZeneca), were publicly announced in official statements, but only one (AstraZeneca) published results in peer-reviewed literature. We expect more news of this nature in the near future. Additional applicants are likely to be submitted for approval by regulatory bodies. There are several possible candidates for the COVID-19 vaccine currently in production.

Over 50 vaccine candidates for COVID-19 are presently in trials. Through the ACT Accelerator, WHO works in partnership with scientists, industry, and global health organisations to allow faster the pandemic response. COVAX (led by WHO, GAVI and CEPI) will promote the equal access and dissemination of such vaccines to protect individuals in all countries when a safe and efficient vaccine is found. People who are most at risk will be given priority. While we work fairly to introduce a safe and efficient vaccine, we need to continue the vital efforts of public health to suppress transmission and reduce mortality.

10. SARS-CoV2 mutant analysis

One of the recent study have analysed a total of 10 022 genomes of SARS CoV-2 (sequences are accessible from the data repository) from 68 countries [91]. Most genomes came from the United States of America (3543 samples), followed by the United Kingdom of Great Britain and Northern Ireland (1987 samples) and Australia (760 samples; 65,776 variants with 5775 separate variants were identified in total. The 5775 separate variants consist of 2969 missense mutations, 1965 synonymous mutations, 484 non-coding area mutations, 142 non-coding de de variants 36 stop-gained versions, 11 deletions for frameshift and two insertions for in-frame [91].

The D614G variant was perhaps the most specific clade found, which is situated in an epitope of B cells with a highly immuno-dominant region and consequently, vaccine efficacy can be affected [92]. Although amino acids in this epitope are very conserved, in addition to D614G, other 14 variants were identified. Nearly all D614G mutation strains also have a replication-responsible protein mutation (ORF1ab P4715L; RdRp P323L), which can affect the speed of replication of the virus [93].

Mutations in the spike protein receptor binding domain indicate that such variants are unlikely to reduce ACE2 binding affinity, since that would decrease the virus' fitness. V483A and G476S are mainly observed in U.S. samples, while V367F is found in Chinese, Hong Kong Special Administrative Area, France and the Netherlands samples. In order to improve the structural stability of the spike protein, the variants V367F and D364Y have been documented to allow more effective binding to the ACE2 receptor. In short, specific structural changes concomitant with spike protein mutations must be closely studied during the design and implementation of therapy [94]. Furthermore, the RBD-ACE2 complexes for wild-type, V367F, and S494P, acquired from the protein–protein docking refinement, were then analysed with the assistance of GROMACS 2018.1 package [95] by molecular dynamics simulation using the AMBER-ILDN force field [96]. Whereas the population variants V367F and S494P demonstrate a greater binding affinity to human ACE2, compared to the Wild-type spike protein. In all the complexes, binding affinity does not correlate well with the protein–-protein interface region between the RBD and ACE2. The altered binding affinity is, therefore, largely determined by the altered basic interactions in each mutant between RBD and ACE2. Interestingly, the population variants of V367F and S494P exhibit a higher binding affinity towards human ACE2. During ACE2 detection, the improved binding affinity of S494P is due to better interfacial complementarity, whereas the variant of V367F interacts with ACE2 facilitated by a higher number of hydrogen bonds. The reorientation of Lys31 promotes the formation of two additional hydrogen bonds in V367F, which increases its binding free energy contribution.

A new emergent variant also known as lineage B.1.1.7 and UK COVID version, Variant of concern is a strain of SARS-CoV-2, the COVID-19-causing virus, one of many causing concerns. It was found in November 2020 from a data obtained in September, during the COVID-19 pandemic in the UK, reported to be between 30% [97] and 80% [98] more transmissible and 30% more lethal [99] than wild-type SARS-CoV-2. The variant is also noteworthy because it has more mutations than commonly seen [100]. Some mutation have potential biological effects. Mutation N501Y is one of six primary receptor-binding domain (RBD) contact residues and has already been reported as rising human and murine ACE2 binding affinity.

11. Concluding remarks

Emerging infectious diseases poses a global public threat due to its rapid spread throughout the world. Previously unknown pathogen detected in Wuhan city, Hubei province of China caused respiratory distress including fever and cough [3]. WHO named it as COVID19 [3]. After two months, initially the hospitalized patients were found with unknown severity. Studies by different research groups initiated to work, understand the possible etiology of this novel virus (COVID19), and confirmed as epidemic. Due to the current mayhem caused by the rapidly emerging virus, special attention is given to COVID-19, its genome updates and infectivity. The first 2019-nCoV whole-genome sequence contains 29,891 nucleotides encoding 9860 amino acids was unleash on January 10, 2020, which provides a source for researchers to recognize the virus in patients through a techniques known as reverse transcription polymerase chain reaction(RT-PCR) [101]. Although, origin of this virus is elusive, however based on genomic analysis suggests that SARS-CoV-2 possiblyevolved from a strain found in bats. Based on sequence, SARS-Covid- 2 shows higher ancestral homology with SARS-Covid. Furthermore, the prominent homology with the SARS-CoV $3CL^{pro}$ structure, the SARS-CoV-2 $3CL^{pro}$ substrate binding site shares few critical differences, highlighting the requirement of fast-track drugdiscovery, which might address the alarming COVID-19 pandemic. Future Future prospectsp include the dynamics of transmission, and serosurveys to understand the subclinical infections would be valuable.

Ethical statement

Ethics approval and consent to participate:

13. Consent for publication

Not applicable

14. Availability of data and materials

Only available by contacting the corresponding author.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authors contribution

EAB searched the literature and wrote the main manuscript ; EAB, NS made figures; EAB, NS, JK, AA, FMA, AM, MSA, SR edited the manuscript. All the authors read and approved the manuscript.

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