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Review Article

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Review on Newly Identified Coronavirus and its Genomic Organization

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ABSTRACT

Human Coronaviruses (HCoV) exhibit positive single stranded RNA genome with enveloped nucleocapsid. Coronavirus belongs to the family Coronaviridae, originated from avian and mammalian species causes upper respiratory tract infection in humans by novel HCoVs viruses named as HCoV-HKU1, HCoV-NL63 but predominant species is Middle East respiratory syndrome (MERS-CoV) across the world. HCoV-HKU1 sp. is associated with chronic pulmonary disease, while HCoV-NL63 causes upper and lower respiratory tract disease in both children and adults, but most recent one was MERS-CoV, which caused acute pneumonia and occasional renal failure. The novel coronavirus SARS-CoV-2 is a new strain that causes the Coronavirus Disease 2019 (COVID-19) as named by the World Health Organization. According to the recent world statistics report about the COVID-19 cases approx. 101,500 confirmed cases and 3,500 death cases appeared. And mostly, a case of infection with CoV was identified in Wuhan, China. Structurally viral genome constitutes of 2/3rd of replicase gene encoding ORFs regions and rest of the 1/3rd region of genome form the structural proteins. The aim of the study was to understand the viral genetic systems in order to facilitate the genetic manipulation of the viral genome and to know the fundamental mechanism during the viral replication, facilitating the development of antidotes against the virus.

Key-words: Coronavirus, HCoV-HKU1, HCoV-NL63, MERS-CoV, Respiratory tract infection, Structural protein

INTRODUCTION

CoVs are enveloped viruses with (+) ss-RNA genome size of 22–32 kb in length [1]. CoV belong to the subfamily Orthocoronavirinae under the family Corona viridae inside the order Nidovirales, and are categorized into four genera: Alpha-coronaviruses (α), Beta-coronaviruses (β), Gamma-coronaviruses (γ), and Delta-coronaviruses (δ). Usually, CoV infect humans and variety of avian and mammalian species worldwide [2,3]. Considering the clamp of pneumonia cases are unknown etiology in Wuhan, Hubei Province, China, was reported on 31 December 2019, diverse speedy epidemiological, clinical and virological research around the world is working for the genomic analysis [4,5]. The ingenious agent of the pneumonia is prompted to be a novel coronavirus (COVID-19) of the same progeny (however genetically specific) from the coronavirus leads to severe acute respiratory syndrome (SARS) [4]. A recent study reports

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suggested that the CoVs originated from bat, causing severe and fatal kind of pneumonia and bronchiolitis especially in adult, children and immunological weak patients as well. Actually, target site of this virus was respiratory and enteric tracts of both animal and human [3,6,7]. Historically, it was proved the CoV infection in humans have been associated with mild upper respiratory tract sites, caused by the variety of HCoVs-HCoV-229E and HCoV-OC43 [8]. However, the HCOV identification in 2003 year, as novel life-threatening CoV causing the severe acute respiratory syndrome (SARS-CoV) redefined its historical existence [9]. Earlier reports investigated the three novels HCoVs viruses and all three were associated with respiratory diseases, the first one was HCoV-HKU1 which was associated with chronic pulmonary disease [10], second one was HCoV-NL63 that causes upper and lower respiratory tract disease in both children and adults across the world [11], and the third and recent one (April-2012) arising in Middle East respiratory syndrome CoV (MERS-CoV), and their symptoms is associated with acute pneumonia and occasional renal failure [12]. These findings suggest that the CoV exists in nature as potential human pathogen hence, it is necessary to study their genetic systems to facilitate the genetic manipulation of the viral genome to know the fundamental mechanism of viral replication, and take a preventive action against this virus to develop antidotes.

Epidemiological and Pathological Sense of Coronavirus

Epidemiological sense- Health and Human Services (HHS) department of US declared the risk of novel CoV (nCoV) in the year 2020. But jeopardy of nCoV is very low in US. In year 2019 [13], World Health Organization (WHO) publicized a notice of the CoV [14]. The first case of CoV appeared in Chinese people in December 2019 diagnosis as in the form of pneumonia. First 425 nCoV case report was published in "The New England journal of medicine", included characteristics and transmission of the nCoV [15]. The journal concluded that nCoV also transmitted through human to human, which are closely contact with infected peoples.

Here, in this report discussing about the epidemiological and pathological study of HCoV classes summarized in Table 1.

Table 1: Epidemiological and Pathological study of HCoV classes

Classes of HCoV	Symptoms of HCoV	Fatality Ratio (%)	Incubation period (Days)	Median death Time (Days)	References
229E	Malaise Headache, Nasal discharge, Sneezing, Sore throat, Fever and cough	–	2–7 days	–	Jones *et al.* [16]; Sharma *et al.* [55]
OC43	Headache, Malaise, Nasal discharge, Sneezing, Sore throat, Fever and Cough	–	2–7 days	–	Walsh *et al.* [17]; Lee *et al.* [61]
SARS-CoV	Fever, Headache Malaise, Chills, cough Dyspnea Respiratory distress, Diarrhea	9%	2–13 days	24 days	Mc-Bride *et al.* [9]; Gorse *et al.* [18]
NL63	Cough, Rhinorrhea Tachypnea, Fever Hypoxia, Obstructive laryngitis	–	2–6 days	–	Graham *et al.* [19]
HKU1	Fever, Running nose Cough, Dyspnea	–	2–6 days	–	Liu *et al.* [20]; Favreau *et al.* [50]
MERS-CoV	Fever Cough, Chills Sore throat, Myalgia Arthralgia, Dyspnea Pneumonia, Diarrhea and vomiting	36%	2–11 days	15 days	Kim *et al.* [14]; Kvansakul and Hinds [39]; Schoggins and Rice [74]

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The most prevalent classes existing across the world are as follows: HCoV-229E, HCoV-OC43 and HCoV-NL63 and HCoV occurrence usually during the winter season of temperate countries. The worldwide statistics reported that the total number of cases of coronavirus was 101,500 appeared till date, while the total number of recovered cases count was 51,187 and rest 3,490 death cases appeared. A recent study reported that the human coronavirus COVID-19 is affecting 89 countries and territories around the world [21,22]. COVID-19 Real time data of top 10 affected worldwide graphical representations with the country graph is presented in Fig. 1. Real time status board of COVID-19 data in Table 2 was updated by the following source: http://infographics.channelsnewasia.com/wuhan/gmap.html, https://wuhanvirus.kr/, WHO.

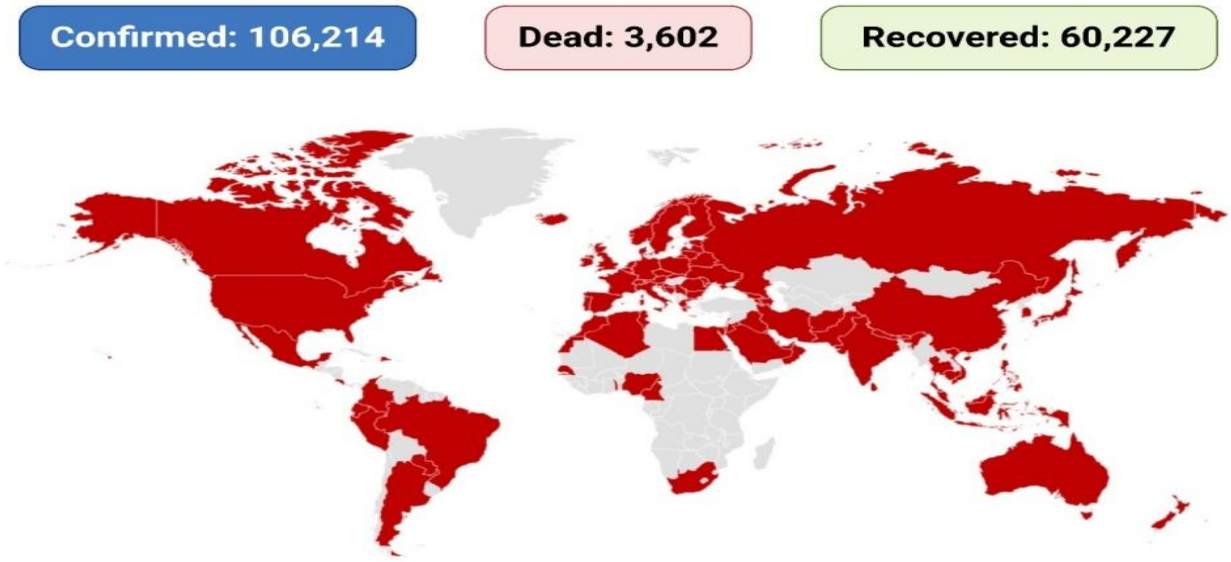

Fig. 1: COVID-19 Real time worldwide graphical representation with the country wise status

Table 2: Worldwide confirmed and death cases of Human Coronavirus in 2020 year

Countries	H-CoV Cases	Death Cases
China	80,651	3,070
South Korea	6,767	42
Iran	4,747	124
Italy	4,636	197
France	613	9
Germany	534	0
Spain	365	8
Japan	348	6
Switzerland	181	1
United Kingdom	163	2
United States	148	12
Singapore	130	0
Netherlands	128	1
Hong Kong	106	2
Malaysia	83	0
Australia	66	2
Kuwait	58	0
Thailand	48	1

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Taiwan	45	1
UAE	42	0
Vietnam	17	0
Pakistan	5	0

Genomic organization of HCoV- Under the electron microscopy, the CoV virions appear as a spherical or pleomorphic in shape with distinct club like projections formed by the spike proteins [10,23-26]. Positive sense viral genomic m-RNA, comprising a 5' terminal cap structure and a 3' poly-adenylate tail structure. This genomic m-RNA of HCoV has three crucial capabilities during the viral replication cycle: (1) act as an initial RNA of the infectious cycle; (2) acts as a template one for replication and transcription events; and (3) acting as a substrate for viral packaging into the progeny virus [27,28].

The replicase-transcriptase system act as a protein that is translated from the core region of the genome, while the rest of region of genome of all downstream open reading frames of m-RNAs contributes viral products [29]. Structurally, all the varieties of CoVs have replicase genes, which makes up approximately 5'-two-thirds region of the genome and it comprises of two overlapping open reading frames (ORFs): ORF1a and ORF1b, encoding 16 non-structural proteins [30]. And rest of the3' structural and nonessential accessory protein coding regions [31] comprises about one-third region of the CoV genomic RNA has CoV sequential set of four structural protein genes arranged in the order encoding spike (S) forming proteins, viral envelope (E), outer membrane (M) and nucleocapsid (N) layer [32]. In addition, number of several accessory ORFs are also involved and interspersed along the structural protein genes but their number and location vary among CoV species. In most, CoV m-RNAs carry an identification number of 70-90 nts leader sequences present at the 5' ends [33-35] and its upstream 3'ends of the leader sequence region have regulatory regions controlling transcription known as TRS-L regions and act as a cis-regulator of transcription [36]. Instead of this, all CoV TRS regions contain conserved 6-8 nucleotide core sequences (CS) with variable 5' and 3' flanking sequences [37]. The β form-CoVs carry a heptameric consensus sequence, 5'-UCUAAAC-3', additional contain SARS-CoV TRS a hexameric core sequences i.e. 5'-ACGAAC-3' [38,39]. Starting of replication phase, after viral entry into the host cell, uncoating of the viral particles with the incorporation of complete genetic material [15,40-42]. Virus sub-genomic region of m-RNAs through translation, form the assembly of viral proteins. The replicated RNA genome of CoV is then encapsulated and entered into the packaging phase of viral particles. A short sequence of 69-nts length is responsible for packaging signals contained in MHV-ORF1-b of approx. 20kb in length from the 5'end of the genome, also responsible for incorporation of RNA into virions [17,22,43,44]. The β form-CoVs packaging signaling sequences exhibits 74% sequence similarity index to the MHV packaging signal and localized in the same regions [45]. Similarly, the TGEV packaging signal was originally mapped to the first 649 nts at the 5' end of the RNA genome; subsequently this position was further delimited to the first 598 nts [19,46].

Mechanism of action of HCoV infection cycle- HCoVs act as an intracellular obligate parasite; take over the host cell machinery for their viral copy makeup and spread. Since, virus–host interactions actually form the basis of diseases, knowledge about their interplaying reaction mechanism become a great research interest of researchers. Here, in this study article the known contribution of the cell's during the CoV infection cycle: Completes into 4 steps: 1. Attachment; entry into the host cell; 2. translation of the replicase-transcriptase; 3. Replication of genome and transcription of mRNAs; and 4. assembly and budding of newly packaged virions [47].

Receptor Interaction, Fusion, and Entry- CoVs attach to specific cellular receptors on the host cell membrane via the club like projection formed by spike proteins (Table 1) [48,49]. The first of all identified CoV receptor was CEACAM-1, utilized by MHV (141). As the Virus is attached through spike proteins undergoes a conformational change ultimately results into the fusion of viral and host cell membranes [50]. But still no crystal structures are available for any CoV spike proteins and still it assumes that these proteins follow the similar pattern of changes as other type-1 fusion proteins of influenza virus hemagglutinin and human immunodeficiency virus (HIV)-gp120, in order to

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facilitate the process of fusion of viral and host membranous proteins. These CoV spike protein have crucial role in viral entry into the host cell, cell-to-cell attachment and spread, and determining the tissue tropism. After entering the cell cytoplasm and un-coating, the viral particles releases, its genetic material i.e. RNA genome, while CoV entry into host cells is, in general, not pH dependent, and thus, it has been believed to occur directly on the plasma membrane and not following an endosomal route [51]. However, some reports suggest that some viruses follow an endosomal route [52,53] as well. But there is some misconception about viral entry, directly attached with host cell membrane and not via an endosomal route and this can be proven by suggesting some explanation:

Entry of SARS-CoV is retracted by lysosomotropic agents to follow an endosomal route of entry (285, 349) into the host cell. Furthermore, their entry is restricted by the application of protease treatment on virus already attached to the cell. This, along with these observation, viral infection may be blocked by another inhibitors, that is, pH-sensitive endosomal protease cathepsin L, (trypsin like protease and trans-membranous protease, serine-2), suggesting that there is a requirement ofS1/S2 cleavage of the SARS-CoV spike (S-proteins)while entering through the non-endosomal entry [54,55] into host cell. Furthermore, entry at the plasma membrane following protease treatment is more efficient than entry by the endosomal pathway [53] during infection. Several precursors of RNA are also involved: heterologous nuclear ribonucleoprotein (hnRNA) family members (hnRNPA1, PTB, SYN-CRYP) have been found to be essential for efficient RNA replication [44]. Other RNA-binding proteins such as m-aconitase and poly-A-binding protein (PABP), DDX1, PCBP1/2 and zinc finger, CCHC-type and RNA-binding motif 1 (MADP1) have also been suggested to play an important role in CoV replication. After cell-cell fusion is takes place, it forms giant, multinucleated cells, or syncytia, that has been proposed as a strategy of viruses, to allow direct spreading of the virus between the cells, subverting the virus-neutralizing antibodies [47-49]. In addition to this, some other accessory proteins are also involved, N proteins its primary function to bind with CoV RNA genome and participate in the nucleocapsid events [50]. Although, N protein is majorly involved in the processes relating to the viral genome, CoV replication cycle and the host cellular response against viral attack [51]. Interestingly, boundary localization of N-proteins to the endoplasmic reticulum (ER)-Golgi region has been proposed to a function for it in assembly and budding [52,53] of virus. However, transient expression of N proteins was shown to substantially increase the production of virus-like particles (VLPs) in some CoVs, suggesting that it might not be required for viral-envelope formation, but it is necessary to complete virion formation instead [43,44,54,55].

CoV: Viral assembly formation- The viral accessible proteins such as (S, E and M proteins) are involved to make up the virions (Fig. 2). This assembly process starts with the accumulation of new genetic RNA material and structural components. During the viral infection phase, helical shaped nucleocapsid containing the RNA genome combined with other viral structural proteins.

This viral assembly of CoV starts through the budding of the helical nucleocapsid with the host cell membranes by following the secretory pathway from the endoplasmic reticulum to the Golgi intermediate compartment. The contribution of the host cells during the phase of the infection cycle doesn't find any evidence. Recent reports suggested that the known M protein orchestrates this event of the entire assembly process, by selecting and organizing the viral envelope called structural components at the assembly sites and also mediate the interactions with the nucleocapsid to initiate the process of budding of virions [48]. These membrane (M) proteins interact with other viral structural proteins, such as the Envelope (E) protein, involved in assembling of undeveloped viral state to mature state (Fig. 2). This interaction makes up the scaffold of the virion envelope and induces the budding process and ultimately release out the M protein-modified membrane and with the S protein to assemble the projection made up of spike proteins into the viral envelope [48,49]. Following the assembly and budding event, the virions are transported into vesicles and eventually released out by exocytosis mechanism. In a recent report suggest that some viral load regulatory proteins such as Valosin-containing protein (VCP/p97) is inhibited resulted in virus accumulation in early endosome phase during the infection of bronchitis virus (IBV), suggesting other investigator this VCP has an important role in the maturation of virus-loaded in endosomes [50].

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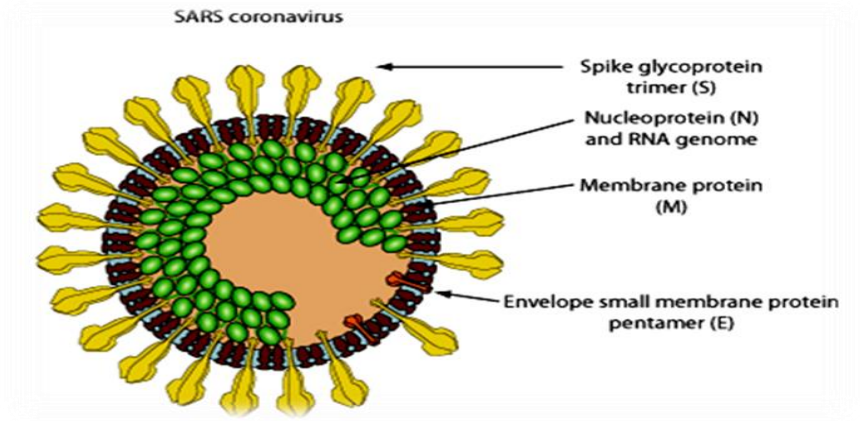

Fig. 2: Structural view of the Coronaviruses

The 2/3rd of viral genome constitutes replicase gene encoding ORFs regions: ORF-1a and ORF-1b, and theses ORFs region translated by frame shift mechanism (Fig. 3). Translated ORFs regions generates the polyproteins, further processed into complex system of replication-transcription component by the viral protease. and rest of 1/3rd region of genome form the structural proteins known as S, E, M, and N, as well as the genus specific proteins, which is the characteristics of several CoV viruses expressed from bunch set of 3' co-terminal sub genomic m-RNA [25,56,57].

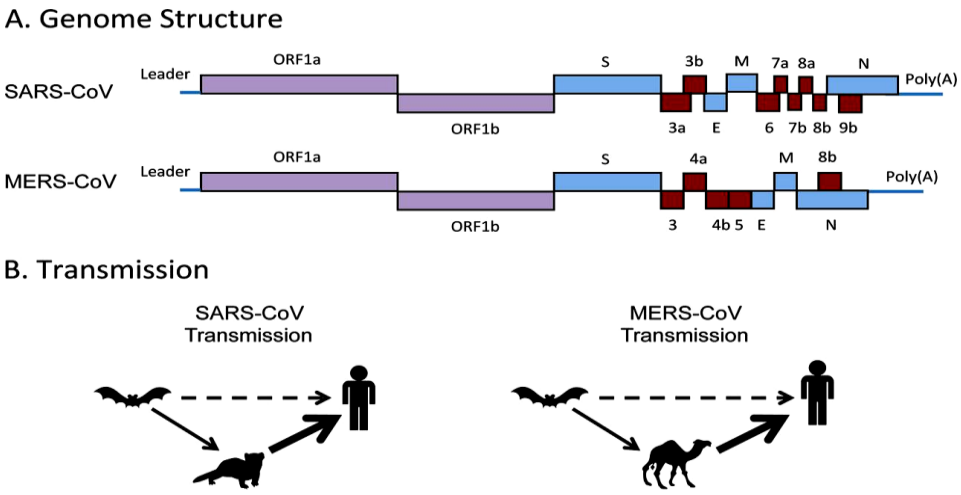

Fig. 3: Genomic structure and transmission of Coronavirus

The first ORFs sequences of DNA make up the 67% of the entire genome encodes 16 non-structural proteins (nsps), while the remaining ORFs sequences encode only accessory proteins and structural proteins [58]. Some reports found some differences between SARS-CoV and MERS-CoV, SARS-CoV have angiotensin-converting enzyme 2 (ACE2), act as one of the main receptors reported by Kawai and Akira [59] also known as CD-209L as a substitute receptor [59], while MERS-CoV utilized dipeptidyl peptidase 4 (DPP4), also known as CD-26 act as the primary receptor. Phylogenetic analysis study of 2019-nCoV had found a close evolutionary relationship with the SARS-like bat coronaviruses. Here in this report, three of the newly identified genomes of (2019-nCoV) with accession no. was represented, first one was Wuhan/IVDC-HB-01/2019 (GISAID accession ID: EPI_ISL_402119) (HB01), second one was Wuhan/IVDCHB-04/2019 (EPI_ISL_402120) (HB04), and third one was Wuhan/IVDC-HB-05/2019 (EPI_ISL_402121) (HB05) [1,11,60]. More in-depth genome annotation, analysis of coronavirus was performed with a comparison to related families of coronaviruses, including the count of 1,008 human SARS-CoV, 338 bat SARS-like CoV, and 3,131 human MERS-CoV, whose genomes were already published in journal before January 12, 2020 (release date: September 12, 2019) and source of data generated from the Virus Pathogen

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Database and Analysis Resource (ViPR) and NCBI database.

CoV Virus Symptoms- Cold or flu-like symptoms appear within two to fourteen days after exposure. Common signs include respiratory symptoms, fever, and cough, shortness of breath and breathing difficulties. In more severe cases; infection can cause pneumonia, severe acute respiratory syndrome, kidney failure and death [61].

Preventive measures- Middle-East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) are type of coronavirus. Coronavirus transmitted human to human through droplets, contact and fomites, similar pattern of transmission follows by 2019-nCov [62]. To diminish the wide-ranging jeopardy of spreadof acute respiratory infections, Standard recommendations to prevent infection spread include regular hand washing, covering mouth when coughing and sneezing, thorough cooking of meat, avoiding vulnerable interaction with animals along with improving the healthcare services in emerging sectors. No specific guidelines given by WHO for explorers. If any symptoms of respiratory illness appeared during or after the travel, traveler pursues the consultation from the medical experts [63].

Vaccine development- Emerging and reemerging of infectious viral diseases appears fatal for global health, economic stability and national security. Vaccines development are key strategies for reducing the load of coronaviral disease [64,65]. However, the utility of live-attenuated vaccines is limited in this sense because of the risks of reversion or repair. Because of their history of emergence events due to their prevalence in zoonotic pools, designing live-attenuated coronavirus vaccines is an attractive and fruitful option for human welfare that can be rapidly and broadly implemented is essential for outbreak preparedness. Here in this report discuss about the coronaviruses with more complex transcription regulatory networks (TRNs) acting as an effective vaccine against the SARS-CoV [23,66,67]. By nature, TRN-complex containing viruses are attenuated and protective against the lethal action of SARS-CoV. Hence, the TRN complex utilization for vaccine development appears as a feasible strategy for limiting reversion in an effective live-attenuated coronavirus vaccine candidate and potential vaccine for all Nidovirales orders [68,69]. MERS is a deadly viral respiratory syndrome resulted due to MERS-CoV infections. Unfortunately, still no treatment is available till date against the MERS-coronavirus infection. In addition, no protective vaccine has been developed to prevent MERS-CoV infection thus far [70]. Basis of effective MERS vaccine development against MERS infection depends on the viral spike (S) protein, has a significant role in the viral infectivity, although, other studies intensively focused on other viral proteins such as the nucleocapsid (N) protein, envelope (E) protein, and non-structural protein 16 (NSP16) has also been discussed [34,71,72].

Impact of CoV on Socioeconomics status- China's economic growth expected to slow to 4.5% in the first quarter of 2020 year during the SARS-CoV outbreak, which is the slowest pace since the financial crisis, according to a Reuter's poll of economists. In present scenario, the coronavirus and resulting measure adversely reduces the global GDP rate by 0.4% in 2020 year [71,73]. On the other hand, if confinement measures against this virus begin to lift up to Feb-10, the impact on the global GDP rate would be more limited resulting in a 0.1% of reduction in global GDP rate [74,75]. Global oil demand has been hit hard by the novel coronavirus, 2019-nCoV according to the International Energy Agency (IEA) [76]. So, much impact on factory shut downs are slowing, the flow of products and parts from China, affecting the companies around the world, including Apple and Nissan. As the world captured with the coronavirus attack, their economic impact is mounting with the OECD warning the virus presents the biggest danger to the global economy since the financial crisis [77]. There are now more than 85,000 confirmed cases of COVID-19 globally arises today, the new coronavirus that emerged in Wuhan, China in December 2019 and was spreading around the world. Many businesses are adversely affected with lost revenue and disrupted the supply chains due to almost China's factories were totally shutdowns, tens of millions of people were already lockdown in dozens of cities and other countries extending travel restrictions across the world [78].

CONCLUSIONS

The study concluded about the prevalence and genome organization of HCoV. For this purpose, study relevant to the RNA structures, occasionally in the cis-acting region

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containing the MHV5' untranslated region (5'UTR) and this region is extending up to the N-terminal (nsp1) coding sequence of trans-regulatory sequences (TRS), 3'UTR and poly(A) tail is necessary to viral replication. A detailed understanding of the RNA structures within the cis-acting sequences of 5'UTR and 3'UTR region of m-RNAs. Understanding of these genetic material interactions, helpful to define pathogenic coronaviruses, such as SARS-CoV and MERS-CoV. The potential risk to public health posed by SARS-CoV and other CoVs, and the lack of prevention agents, because of these two crucial matters a global effort is needed to study about the molecular level of viruses in order to develop effective strategies against the Coronavirus infections.

Corona viruses like MERS-CoV have a property of emergence and reemergence from Zoonotic sources: Bats and other small mammals and continue to transmit into human population. Before emergence of novel species of coronaviruses, viral surveillance studies of animal species including bats, rodents, and livestock, are essential to understand the potential human pathogens exist in the environment before they can spread in human populations.

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Research design- Dr. Keertana Rao
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