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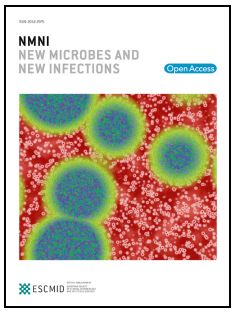

Mutated COVID-19, May Foretells Mankind in a Great Risk in the Future

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Journal Pre-proof

Mutated COVID-19, May Foretells Mankind in a Great Risk in The Future

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Abstract:

Corona virus disease 2019 SARS-CoV-2 (COVID-19) is a zoonotic virus causing a variety of severe of respiratory diseases. SARS-CoV-2 is closest to SARS-CoV and MERS-CoV in structure. The highly prevalence of COVID-19 is due to the lack onset of symptoms. Our study aimed to present an overview of the virus in terms of structure, epidemiology, symptoms, treatment, and prevention. Conduct the differences of whole genome sequence and some viral proteins to determine the gap and the change alternation of nucleotides and amino acids sequences. We evaluate 11 complete genome sequence of different coronavirus using BAST and MAFFT software. We also selected 7 types of structural proteins. We were conclude that COVID-19 might be created new mutations specifically in glycoproteins hence requires caution and complete preparation by health authorities.

Keywords: COVID-19, MERS, outbreaks, SARS, zoonotic.

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Introduction:

The first emerging of novel coronavirus disease 19 was 31th, December 2019 in Wuhan city, China. COVID-19 is classified the seventh member of the subfamily *Orthocoronavirinae* under the family *Coronaviridae*. The most members of this family are zoonotic viruses that transmitted to humans via contact with infected animals. Although the bats and snakes are the natural reservoir of wide coronaviruses, there is no evidence so far that the COVID-19 was originated and transmitted from the seafood market [1]. Previous study reported that lipid rafts of coronaviruses have made new strain COVID-19 which is identity 80% to SARS-CoV. Lipid molecules such as caveolins, clathrins and dynamin have a fundamental role in the internalization of viruses. Firstly, these molecules are involved in the entry of viruses into host cells. Second, targeting host lipids is being studied as an antiviral strategy and could have various applications [2]. COVID-19 seems to need to bind to the ACE-2 receptor on the membrane host cell to enable it to infect host cell upon coupled with a reliance of serine protease TMPRSS2. This intracellular protein seems to be a determinant of the virus ability to infect cell [3].

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Introduction:

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Prevalence and epidemiology:

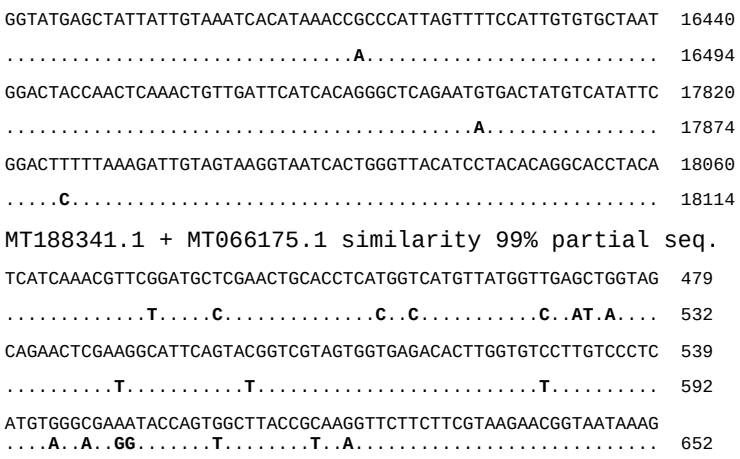
Over the past two decades, outbreaks of coronavirus have been observed, the Severe Acute Respiratory Syndrome (SARS) - COV in 2003 and Middle East Respiratory Syndrome (MERS)

– CoV previously described as a major public health threat. Nowadays, the World Health Organization considers COVID-19 is more serious and widespread epidemic disease [4]. To date, it seems that the mortality rate of COVID-19 is lower than the incidence of SARS or MERS. A significant increase number of COVID-19 cases was observed due to the absence of emerging pathological symptoms in the virus carriers. For this reason, it may foster the collapse of local health care [4]. Some countries face an outbreak crisis and try to prevent the spread of COVID-19 through preventing human gatherings, a curfew is imposed in cities, prevent travel between countries and close the land borders may reduce the outbreaks.

The main transmission of COVID-19 starts with contacted human to human including relatives and friends who intimately contacted with patients or incubation carriers. Many studies reported that coughing and sneezing are the quicker way of the virus dispersion as well as droplet, and airborne precautions when encountering an infected person [5].

Virus structure:

COVID-19 relates to the betacoronavirus that infects humans and likely developed from bat origin coronaviruses. Structural analysis shows that COVID-19 probably derives from a bat SARS-like coronavirus, which has mutated in the spike glycoprotein (protein S) and nucleocapsid N protein The positive-sense RNA genomes of COVID-19 is differ from SARS-CoV and MERS-CoV approximately 29.9 kb, 27.9 kb and 30.1 kb, respectively [6]. The COVID-19 complete genome was annotated to possess 14 open reading frames ORFs encode 27 proteins. Sequence analysis revealed that COVID-19 is identity 80% more than to SARS-CoV and 50% to the MERS-CoV which originated in bat [7, 8]. In addition to that, spherical external spike protein displays a characteristic crown shape can be observed under an electron microscope [9]. Current study, we have compared between novel COVID-19 complete genome with other related corona virus to provoke the mutation and the gaps. We selected the data from NCBI and we did the FASTA and BLAST. The comparison between genomes with alignment has done using MAAFT-7 software. COVID-19 gene bank (MT188341.1), COVID-19 (MT066175.1), bat-SL-CoVZC45 (MG772933.1), SARS-CoV BJ182b (EU371561.1) are identical alignment in 99%, 89%, and 82% respectively. In figure (1) shows the differences between 4 complete genomes shows as follow:



```
MT188341.1 & MG772933.1 similarity 89% partial seq.
GAAAACTTGTTACT-TTATAT--TGACATTAATGGCAATCTTCATCCA-GATTCTGCCAC  4017
A.T..---......C..G.T.GC...T..C.....T..G...T.-...T.......-.AGA  3997
TCTTG-TT--A-GTGACATTGACATCACTTTCTTAAAGAAAGATGCTCCATATATAGTGG  4073
A.A..C..AG.G....-.--..T..GT.....C.TG....G.....A..T..C..G..A.  4054
GTGATGTTGTTCAAGAG-GGTGTTTTAACTGCTGTGGTTATACCTACTAAAAAGGCTGGT  4132
........-A...CT..T....A.A.C...TG...T..A.....CT.C............  4113
MT188341.1 & EU371561.1 similarity 82% partial seq.
```

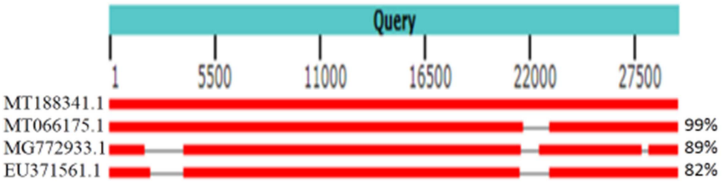


Figure (1): Final alignment between 4 complete genome

According to the alignment analysis, there is a closest similarity between 2 COVID-19 in 99% compared with other 2 Bat CoV. 7 complete genomes have been alignment for different coronavirus stains figure (2).

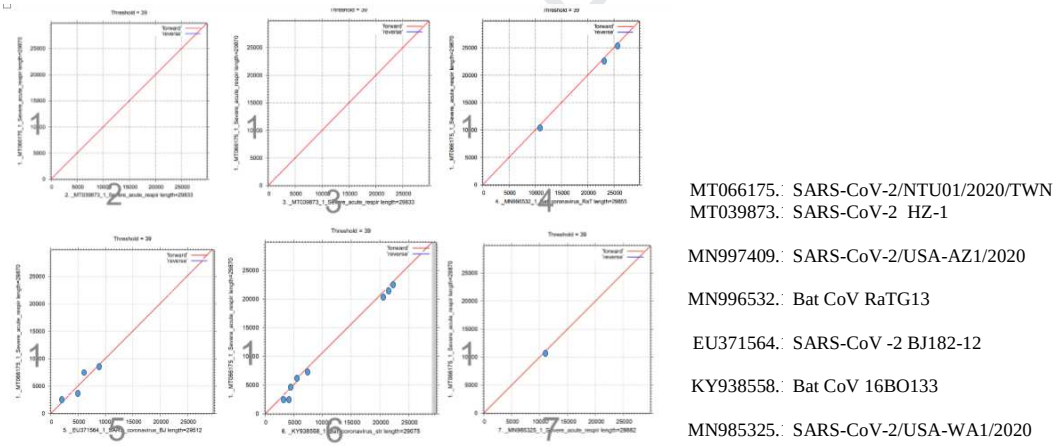


Figure (2): MAFFT considers similarities in forward strands (red) only, but ignores similarities in reverse strands (blue), Plot 1/2 alignment MT066175.1 + MT039873.1= 99.7%, plot 1/3: MT066175.1+ MN997409.1=99.7%, plot 1/4 MT066175.1+ MN996532.1= 89%, plot 1/5 MT066175.1+ EU371564.1= 82.4%, plot 1/6 MT066175.1+ KY938558.1= 68%, plot MT066175.1+ MN985325.1= 95%.

Upon to the result above, we revealed that all COVID-19 strains are closest similarity compared to other strains related to the same family. In other words, we believe that COVID-19 came from several mutations happened to other members of coronavirus relates to the same infection. Although genomic analysis does not support the belief that COVID-19 is a laboratory construct, currently it is impossible to disprove or prove the theories of its origin. To identify the COVID-19 origin, obtaining virus sequences from immediate animal sources would be the most definite method.

The first ORF (ORF1a/b) translates two polyproteins, pp1a and pp1ab, and encodes 16 non-structural proteins (NSP) which takes two-thirds of viral RNA. The remaining ORFs encode structural proteins including spike (S) glycoprotein, small envelope (E) protein, matrix (M) protein, and nucleocapsid (N) protein. COVID-19 also possesses accessory proteins that interfere with the host innate immune response [8].

We have done alignment for different strain of ORF10 COVID-19 GenBank: (QIK50446.1) with the ORF10 COVID-19 (YP_009725255.1). The result gave similarity 100% without any mutation in amino acid figure (3).

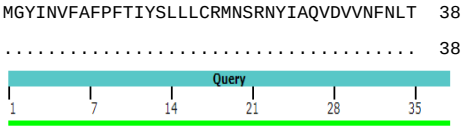


Figure (3): 100% similarity between ORF 10 (QIK50446.1) and (YP_009725255.1).

Nucleocapsid phosphoprotein COVID-19 GenBank: (QIK50445.1) has been aligned with NP COVID-19 (QIC50514.1) similarity 100%, NP SARS CoV CUHK-L2 (AAS01074.1) similarity 85%, and bat COV HKU5 (QHA24694.1) similarity 61% figure (4). Crystal structure of NP COVID-19 (6VYO) has been released in 11/3/2020 from RCSB PDB figure (5).

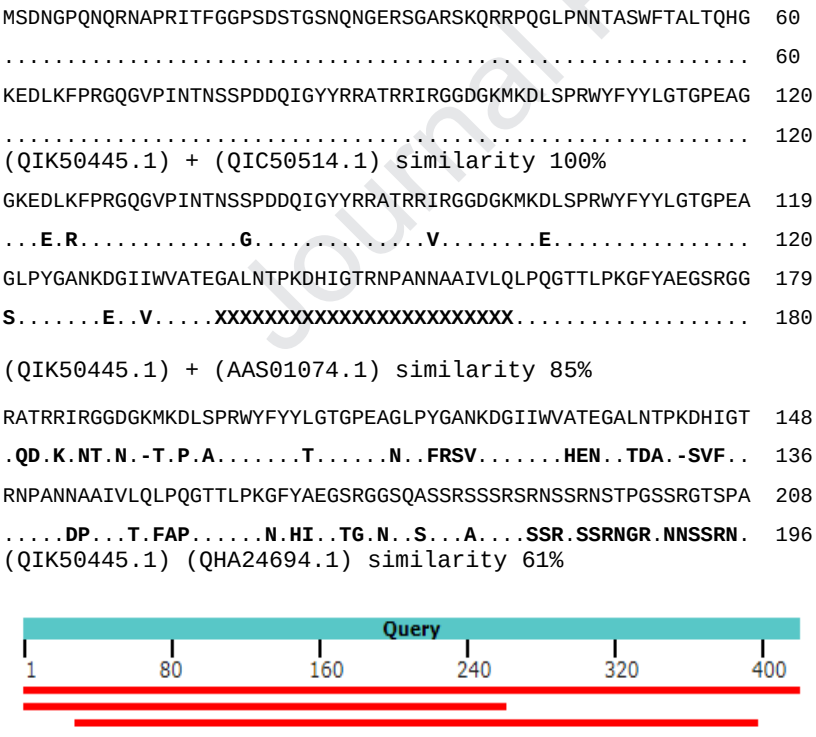


Figure (4): alignment between (QIK50445.1), (QIC50514.1), (AAS01074.1) and (QHA24694.1).

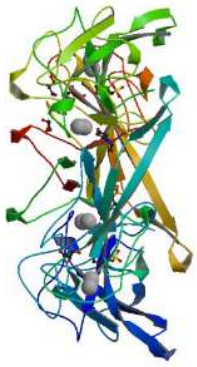


Figure (5): Crystal structure of NP COVID-19 (6VYO) from RCSB PDB.

ORF7a protein COVID-19 GenBank: (QIK50443.1) has been aligned with NS7a Bat CoV RaTG13 (QHR63305.1) similarity 99%, hypothetical protein SARS 7 CoV (AFR58706.1) similarity 89% and putative uncharacterized protein 4 SARS CoV (AAX16199.1) similarity 68% figure (6).

```
MKIILFLALITLATCELYHYQECVRGTTVLLKEPCSSGTYEGNSPFHPLADNKFALTCFS  60
.......V.V.................................................  60
TQFAFACPDGVKHVYQLRARSVSPKLFIRQEEVQELYSPIFLIVAAIVFITLCFTLKRKT  120
...............................................I.............  120
(QIK50443.1) + (QHR63305.1) similarity 99%

MKIILFLALITLATCELYHYQECVRGTTVLLKEPCSSGTYEGNSPFHPLADNKFALTCFS  60
.......T..VFTS.....................P....................T.  60
TQFAFACPDGVKHVYQLRARSVSPKLFIRQEEV-QELYSPIFLIVAAIVFITLCFTLKRK  119
.H.....A..TR.T.........X........Q......L......L..LI....I...  120
(QIK50443.1) + (AFR58706.1) similarity 89%

MKIILFLALITLATCELYHYQECVRGTTVLLKEPCSSGTYEGNSPFH-PLADNKFALTCF  59
.......T..VFTS.....................P..........AI.CFN.AYYILV.  60
STQFAFACPDGVKHVYQ  76
TRN-----.GSRRTL..  72
(QIK50443.1) + (AAX16199.1) similarity 68%
```

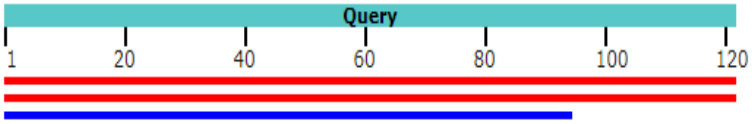


Figure (6): alignment between (QIK50443.1), (QHR63305.1), (AFR58706.1) and (AAX16199.1).

ORF8 protein COVID-19 GenBank: (QIK50444.1) has been alignment with ORF8 protein COVID-19 (QHN73801.1) similarity 99%, hypothetical protein Bat SARS CoV Rs806/2006 (ACU31050.1) similarity 76% and hypothetical protein Bat SARS CoV HKU3-8 (ADE34775.1) similarity 84% figure (7).

```
MKFLVFLGIITTVAAFHQECSLQSCTQHQPYVVDDPCPIHFYSKWYIRVGARKSAPLIEL  60
............................................................  60
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```
CVDEAGSKSPIQYIDIGNYTVSCLPFTINCQEPKLGSLVVRCSFYEDFLEYHDVRVVLDF  120
.....................S.................................  120
(QIK50444.1) + (QHN73801.1) similarity 99%

MKFLVFLGIITTVAAFHQECSLQSCTQHQPYVVDDPCPIHFYSKWYIRVGARKSAPLIEL  60
..L.IVF.LL.P.YCI.K...I.E.CEN...QIE......Y..D.F.KI.S....R.VQ.  60
CVDEAGSKSPIQYIDIGNYTVSCLPFTINCQEPKLGSLVVRCSFYEDFLEYHDVRVVLDF  120
.EGDY.KRI..H.EMF....I..E.LE....A.PV...I....YDY..V.H.........  120
(QIK50444.1) + (ACU31050.1) similarity 76%

GNYTVSCLPFTINCQEPKLGSLVVRCSFYEDFLEYHDVRVVLDFI  121
....I..E.LE....A.PV...I....YDY..V.H..........  47
(QIK50444.1) + (ADE34775.1) similarity 84%
```

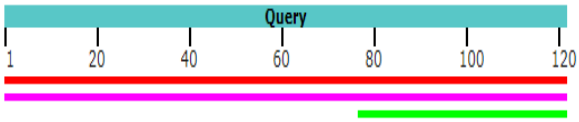

Figure (7): alignment between (QIK50444.1), (QHN73801.1), (ACU31050.1) and (ADE34775.1).

ORF6 protein COVID-19 GenBank: (QIK50442.1) has been aligned with ORF6 protein COVID-19 (QIG55989.1) similarity 98%, protein 7 Rhinolophus affinis CoV (AHX37562.1) similarity 88% and NSP 6 SARS CoV ExoN1 (AGT21083.1) similarity 86% figure (8).

```
MFHLVDFQVTIAEILLIIMRTFKVSIWNLDYIINLIIKNLSKSLTENKYSQLDEEQPMEI  60
..............................................V.............  60
(QIK50442.1) + (QIG55989.1) similarity 98%

MFHLVDFQVTIAEILLIIMRTFKVSIWNLDYIINLIIKNLSKSLTENKYSQLDEEQPMEI  60
..............I.......IA.....V..SS.VRQ.F.P..KKN..E..D.E....  60
(QIK50442.1) + (AHX37562.1) similarity 88%

MFHLVDFQVTIAEILLIIMRTFKVSIWNLDYIINLIIKNLSKSLTENKYSQLDEEQPMEI  60
..............SI......RIA.....V..SS.VRQ.L.P..KKN..E..D.E...L  60
(QIK50442.1) (AGT21083.1) similarity 86%
```

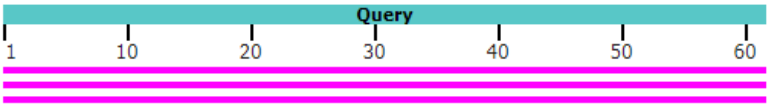

Figure (8): alignment between (QIK50442.1), (QIG55989.1), (AHX37562.1) and (AGT21083.1).

Membrane glycoprotein COVID-19 GenBank: (QIK50441.1) has been aligned with MG COVID-19 (QIG55988.1) similarity 99%, M protein COVID-19 (APO40582.1) similarity 93% and membrane glycoprotein Rousettus Bat CoV HKU9 (YP_001039974.1) similarity 61% figure (9).

```
MADSNGTITVEELKKLLEQWNLVIGFLFLTWICLLQFAYANRNRFLYIIKLIFLWLLWPV  60
.....................................................V...  60
TLACFVLAAVYRINWITGGIAIAMACLVGLMWLSYFIASFRLFARTRSMWSFNPETNILL  120
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```
.............................R.............................  120
(QIK50441.1) + (QIG55988.1) similarity 99%

SNGTITVEELKKLLEQWNLVIGFLFLTWICLLQFAYANRNRFLYIIKLIFLWLLWPVTLA  63
E.D....DQ..H.............FA..L......S...........V.......I...  62
CFVLAAVYRINWITGGIAIAMACLVGLMWLSYFIASFRLFARTRSMWSFNPETNILLNVP  123
............A.....................V...........W.............  122
(QIK50441.1) + (APO40582.1) similarity 93%

DSNGTITVEELKKLLEQWNLVIGFLFLTWICLLQFAYANRNRFLYIIKLIFLWLLWPVTL  62
NCTN.VPRP.VIAA.KD..FAVSVIL.FITV...WG.PS.CKPIWV..MFI......LSI  63
ACFVLAAVYRINWITGGIAIAMACLVGLMWLSYFIASFRLFARTRSMWSFNPETNILLNV  122
.AA.F..IHP..SVAF.F...F..IS.I.......S....LC..G.A...M...DM.I.I  123

(QIK50441.1) + (YP_001039974.1) similarity 61%
```

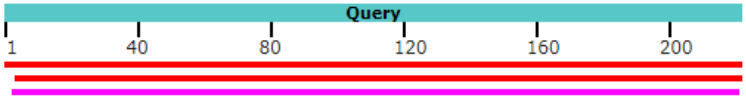

Figure (9): alignment between (QIK50441.1), (QIG55988.1), (APO40582.1) and (YP_001039974.1).

Envelope protein COVID-19 GenBank: (QIK50440.1) has been aligned with EP COVID-19 (QHZ00381.1) similarity 98%, Chain A, Envelope small membrane protein SARS CoV (5X29_A) similarity 90% and envelope protein Hypsugo Bat CoV HKU25 (ASL68947.1) similarity 56% figure (10).

```
MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPSFYVYS  60
.....................................H.....................  60
 (QIK50440.1) + (QHZ00381.1) similarity 98%

FVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPSFYVYSRVK  63
.Q.M.................................A..AA..........TV.......  79
 (QIK50440.1) + (5X29_A) similarity 90%

MYSFVSEETGTLIVNSVLLFLAFVVFLLVTLAILTALRLCAYCCNIVNVSLVKPSFYVYS  60
.LP..Q.QI.SF...FFIFTV.CAIT...CM.F...T...MQ.AIG..TL..Q.AI...N  60
(QIK50440.1 (ASL68947.1) similarity 56%
```

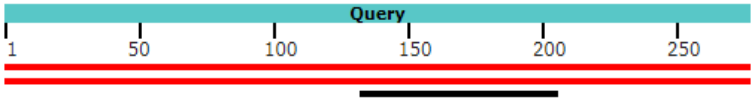

Figure (10): alignment between (QIK50440.1), (QHZ00381.1), (5X29_A) and (ASL68947.1).

By analyzing the series compatibility of the proteins sequences under study, we can confirm that there is a match between strains of COVID-19. There are obvious differences with respect compared to other species of coronavirus family. This may indicate that COVID-19 originated from mutations happened in coronavirus family. In clearer terms, new mutations may be created as there in a high probability, specifically in glycoproteins.

We are unable to give reasonable explanations for the significant number of amino acid substitutions between the COVID-19 and SARS-CoV or MERS-CoV due to very limited knowledge of this novel virus.

Clinical manifestation and symptoms:

The incubation period of the virus may dissimilar accordingly to the age and immune status. As a general, it has been assumed that incubation period sites between 2-14 days while some cases observed till 23 days after exposure. The main symptoms can easily seem with elderly aged above 70 and immunocompromised and diabetic patients. The symptom starts with fever, dry cough, dyspnea, as well as sore throat, nasal congestion, malaise and bilateral infiltrates may be seen on chest X-ray, however some cases are detected absence of fever. Clinical features of COVID-19 include the targeting of the lower airway as evident by upper respiratory tract symptoms like rhinorrhoea, sneezing, and sore throat which is developed to gastrointestinal symptoms like diarrhea [10]. Severe cases may present with sepsis, heart attack or even shock. Conversely, some cases may show mildly ill or asymptomatic altogether.

From WHO records, the period from the symptoms onset and to death of COVID-19 ranged from 6 - 41 days with a median of 14 days. This period depends on the age and the status of immune system. It has been shorter with age under 70 years [11].

Preventions:

To prevent spreading virus, managed care of patients with entails early identification. Rapid isolation, timely establishment of infection prevention and control measures, together with symptomatic care for patients with mild disease. Supportive treatment for those with severe COVID-19. Specific attention and spend more efforts to reduce transmission should be presented to susceptible populations including health care providers, immunocompromised patients, children, and elderly people [5]. Health care systems around the world must operate with more than one maximum capacity. It is necessary to cooperate between HCS and WHO to reduce infection. The use of international media, social media and societal culture by maintaining personal cleaning, minimizing risk of exposure, avoiding gatherings and preventing all phenomena that lead to contact between persons [12]. COVID-19 vaccines is under accelerated development.

The global public health community have to consider the effects of mass gathering cancellations on the future wellbeing of communities through economic recession as well as through the spread, or otherwise, of COVID-19 [13].

Diagnosis:

Quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) is the most specific and sensitive assay approved and straightforwardly used by many reference laboratories worldwide. Other laboratory tests may help assessing disease severity and predicting the risk of evolution such as cute respiratory distress syndrome (ARDS) disseminated intravascular coagulation (DIC) and multiorgan failure (MOF). Moreover, C reactive protein (CRP), lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR) and D-dimer, along with diminished concentration

of serum albumin, increased values of LDH, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, creatinine, cardiac troponins, are used to enhanced and helpful tests for organs function. Notably, a combined IgM-IgG rapid immunoassay has also been recently developed as well as elevation of pro-inflammatory cytokines detection kits such as IL1-β, IL1RA, IL7, IL8, IL9, IL10, basic GCSF, IFNγ, TNFα,and IP10 [14]. A study revealed that gastrointestinal symptoms with COVID-19 was not associated with viral RNA in the fecal sample or extended duration of the viral RNA positivity in the feces.

COVID-19 RNA has been isolated from human saliva, nasopharynx and lower respiratory tract. CT findings and lung abnormalities increased quickly after the onset of symptoms, and followed by persistence of high levels in extent for a long duration. CT manifestations are important inspected pattern over time [15]. A study was conducted that there is no evidence that TNF-α inhibition will increase the risk of COVID-19 outbreaks, specifically [16].

Treatment:

At a moment, there is not yet any approved antiviral treatment for COVID-19. The implementation of antiviral treatment and prophylaxis has several requirements to dip their risk. Drugs can be administered shortly after symptom onset to reduce infectiousness and plummeting viral shedding in the respiratory secretions. Some studied have approved hydroxychloroquine as antiviral activity in vitro against coronaviruses, and specifically, COVID-19. Remarkably, this drug was licensed for the chemoprophylaxis and treatment of malaria. Furthermore, drug testing suggest that prophylaxis with hydroxychloroquine at approved doses may prevent COVID-19 infection and amend viral shedding [17]. Clinical trials of hydroxychloroquine treatment for COVID-19 pneumonia have showed positive preliminary outcomes in China.

Unfortunately, corticosteroid treatment is commonly used in clinical practice for influenza virus such as acyclovir, ganciclovir, ribavirin, and methylprednisolone as well as neuraminidase inhibitors including (peramivir, oseltamivir, and zanamivir,) are invalid for COVID-19 and not recommended [18].

Conclusions:

Currently, the scientists have made progress in characterizing the new coronavirus, and there are still many questions that need to be answered. COVID-19 is the greatest biological hazard to assume the relevance of insidious worldwide threat today. COVID-19 is a highly contagious during the latency period. It is necessary may adopt and invest more modern technologies both to facilitate notification, to allow speedier data dissemination and analysis in keeping with the principles of precision epidemiology.

We suggest that close contact with an infected person is the major factor in disease transmission. Healthcare workers also have to follow the CDC guidelines and should not attempt to perform any virus isolation or characterization. The effect of mass gathering cancellations on reducing the spread of COVID-19 needs to be determined. Current study conducted that any mutation occurred in the former protein is especially important. There is no evidence that part of COVID-19 is synthetic.

Declaration of competing interest:

The authors declare no conflicts of interest.

Acknowledgement:

At the end of this study, we would like to inform that all research budgets were self-supporting without any institute donation.

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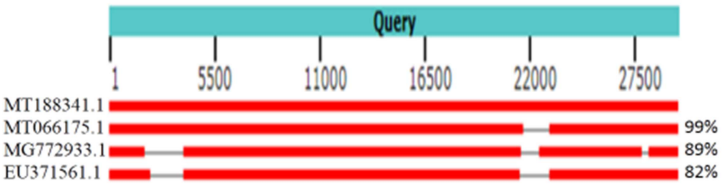
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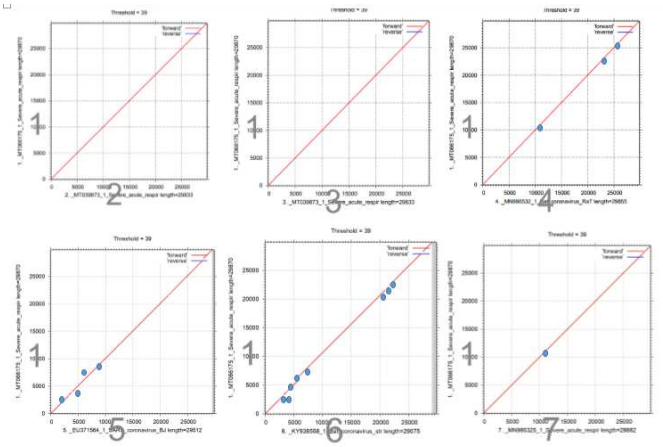

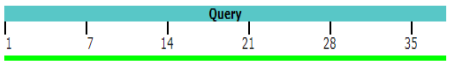
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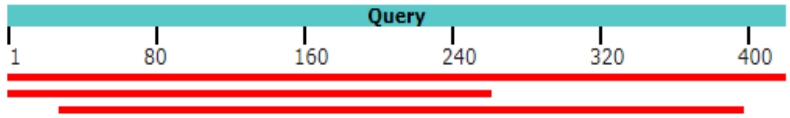
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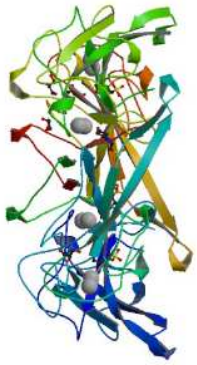

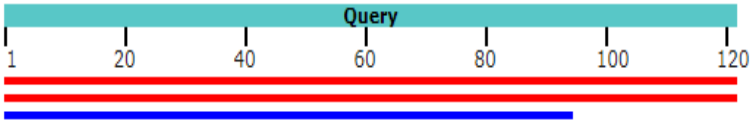
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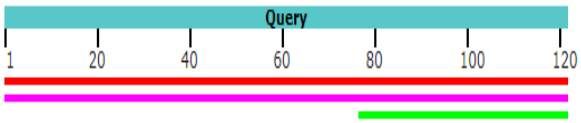

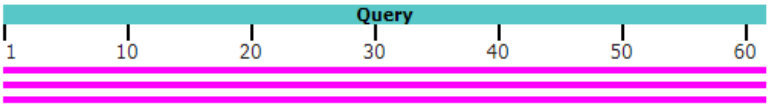

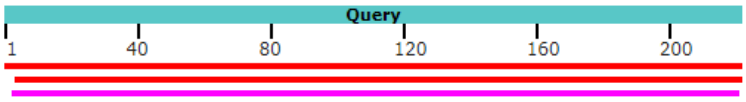

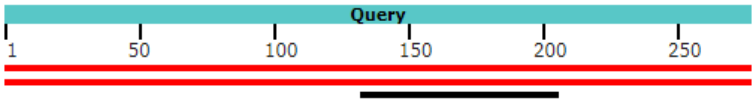

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