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Review Article

COVID-19-A PANDEMIC IN NEED OF CONTROL

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ABSTRACT

The recent 'show stopper' in the world of infectious diseases is the Coronavirus Disease-2019 (COVID-19) which is caused by the severe acute respiratory syndrome corona virus-2 (SARS-CoV-2). This infection, which presents itself with a risk of morbidity and mortality, has managed to shake the medical fraternity. This can be called the sister disease to the previously known severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). The 2019-nCoV was first identified in late December 2019, in Wuhan, China and henceforth spread to multiple countries. The health care specialists were rushed in order to find a perfect diagnosis, treatment algorithm and prevention measures for such an unexpected pandemic. Monitoring the transmission trends in humans, understanding mechanism of infection, developing novel tests for detection of the virus with diagnostic guidelines, initiating clinical testing of activity of drugs to be used as potential treatment options as well as providing epidemiological isolation guidelines were some measures adopted by various nations, and are briefly addressed in this article. Apart from patients being treated, a matter of worry has been the risk the healthcare workers are facing, as they are vulnerable to becoming vectors or hosts of the viral infection. Hence, the minimal prescribed precautions those are obligatory for the professionals to be followed, alongside the general preventive measures have also been reviewed in this article.

Keywords: COVID-19, COVID corona virus, COVID detection, COVID clinical trials, COVID treatment, COVID precautions.

1. INTRODUCTION

The late December of 2019 saw an influx of patients who presented with symptoms of pneumonia with unknown origins, which is now epidemiologically associated to have spread from a seafood market in Wuhan, Hubei province, central China. As the cases seemed to grow suddenly, it caught the attention of the Chinese Center for Disease Control and Prevention (CDC) who launched an emergency response immediately. This was followed up by the response that the World Health Organization (WHO) declared viral outbreak, a "Public Health Emergency of International Concern" (PHEIC). The investigation to identify the causative agent brought forward the confirmation that the pneumonia was caused by a novel coronavirus. Further isolation and study revealed it to be distinct from both Middle East respiratory syndrome coronavirus (MERS-CoV) and severe cute respiratory syndrome coronavirus (SARS-CoV) [1, 2].

In the wake of the said pandemic, On February 13, 2020, the World Health Organization (WHO) officially named the 2019-nCoV as Corona Virus Disease-2019 (COVID-19) in Geneva, Switzerland [3].

The COVID-19 disease is believed to infect the humans via its "zoonotic" trait which caused it to spill over from its previously preferred hosts. Basically, it is contracted via close contact or any other human discharge which contains virus which might still have the potential of infectivity. This has led various nations to introduce various restrictions upon its population, thereby implementing "social distancing" as a form of "behavioral vaccine" as a primal measure against the disease spread. Various journals have emphasized the spread of important information regarding data research so that important discoveries and guidelines of treatment, emergency and supportive care may be available to physicians and other health care professionals easily. Apart from this, numerous social media platforms run

by citizens have also taken upon themselves as the self-proclaimed influencers, to make the general population aware of the preventive measures and the significance behind them.

As majority of the World's countries are yet to "flatten the curve" or completely eradicate the disease, it calls for stringent prevention measures and more proactive initiation for vaccine development as well.

1.1. History, Primary Reservoirs and Hosts

Some currently present evidences may point towards the statement that the virus spread into humans from wild animals which are sold illegally at Wuhan Seafood Wholesale Market [4].

There has been significant study regarding the identification of the source of origination and transmission of the coronaviruses. To determine these parameters in the case of SARS-CoV, scientists believed raccoon dogs and palm civets to be a key reservoir of infection. However, only the samples secured from civets at the food market showed positive results for viral RNA detection, pointing towards the possibility that the civet palm might be a secondary host [5]. Back in 2001, specimens were isolated from the healthy persons of Hong Kong and their molecular assessment revealed a 2.5% frequency rate of antibodies against SARS-coronavirus. This meant that the SARS-coronavirus must have been circulating in humans even before causing the outbreak, in 2003 [6]. Subsequent studies carried out on Rhinolophus bats have reportedly detected the anti-SARS-CoV antibodies suggesting that the bats were a source of viral replication [7]. The MERS coronavirus first spread from Saudi Arabia in 2012 [8]. The MERS-coronavirus also belongs to the beta-coronavirus and has camels to attribute as its zoonotic source or primary host [9]. A recent study, acknowledges the detection of MERS-coronavirus in Pipistrellus and Perimyotis bats, further elucidating that bats are the key host and transmitting medium of the coronaviruses. The studies conducted during the commencement of the pandemic suggested snakes would be the primary reservoir. However, it was proven later that only bats could be attributed, and not snakes (Fig 1). Anyway, to abolish the viral disease, more research can be done focusing on the aspects of the facets of identification of the intermediate zoonotic source, their characteristics, and the phenomenon that caused the transmittal of the virus to humans [10].

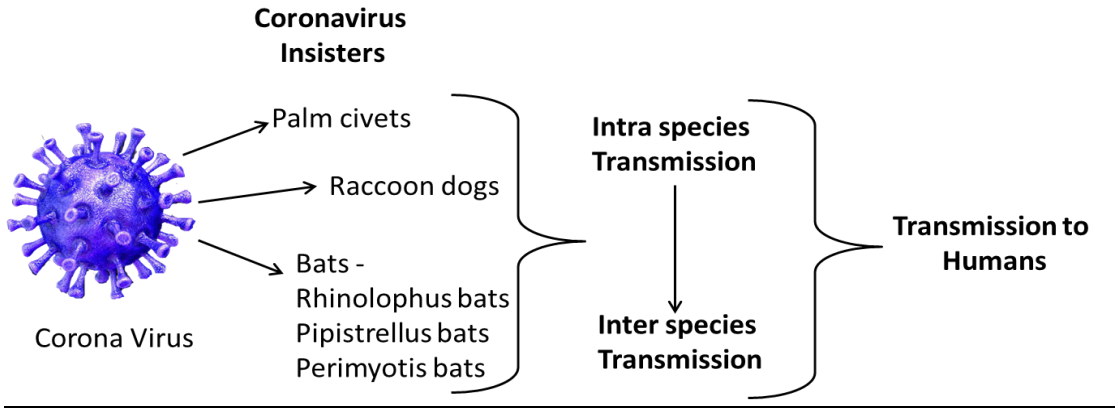

Fig. 1: Transmission of COVID-19

1.2. Structure of the Crown Like Virus

The nomenclature of Coronaviruses (CoVs) takes its origin in Latin, which means "crown-like". This is due to the spikes of the virus which protrude to the periphery. The virus measures about 60-160nm via electron microscopy. Each enveloped viral particle has genetic material with 5'-cap structure and 3'-poly A tail which interacts with nucleoprotein [12].

The novel coronavirus belongs to the "Coronaviridae" family which is home to the viruses which brought about MERS and SARS in the previous decades. It is an enveloped virus possessing non-segmented, single-stranded, positive-sense RNA genetic material (27-32 kb) (Fig.2) [13]. Because it has been found that the SARS-CoV2 genome is 96.2% identical to a bat corona-virus genome, it is suggestive of "zoonotic" potential [2]. Although it shares a high degree of similarity of genetic material with bat coronavirus RaTG13, isolated from Yunnan bats back in 2013, it has been said that bats are not the immediate source of SARS-CoV2 [4].

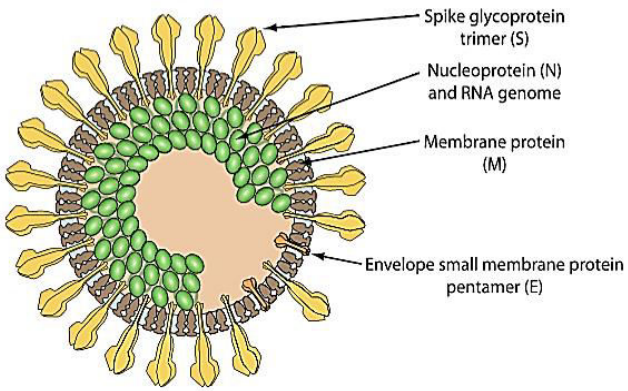

Fig. 2: Structure of Corona Virus [11]

Identification of α,β,γ and δ coronaviruses is reported, among which human coronaviruses were present in α and β coronavirus genera. The genome of SARS-CoV-2 contains at least ten open reading frames (ORFs), out of them, the ORF1a/b, and about two-thirds of the viral RNA is translated into two large polyproteins.

Two polypeptides have seen in SARS-CoV and MERS-CoV namely pp1a and pp1ab processed into 16 non-structural proteins (nsp1-nsp16), which are vital information of the viral replicase transcriptase complex. The nsps are mainly involved in the rearrangement of membranes having their origins in the rough endoplasmic reticulum (RER) into the double-membrane vesicles, the location for viral replication and transcription. The rest of the ORFs and the remaining one-third of SARS-CoV encode the structural proteins: spike (S), envelope (E), nucleocapsid (N) and membrane (M) proteins, and lots of other several accessory proteins whose functions have not been yet established and which do not tend to partake in the viral replication process. Chymotrypsin-like (3C-like protease, 3CLpro) and papain-like protease (PLP) are the non-structural proteins, vital in corona viral replication and which can inhibit the host innate immune responses [13]. The M protein helps bind nucleocapsids, enhancing the viral assembly and budding, the E protein plays a role in viral morphogenesis, its release and pathogenesis; and protein S contributes towards homotrimetric spikes which helps virus invade target host cells by recognizing cell receptors [12].

Other viruses of the same family exhibiting the zoonotic potential were the 2002-2003 SARS epidemic and MERS-CoV, having fatality rates of 9.6% and 34.4%, respectively [14]; whereas we see COVID-19 has caused the number to rise [14, 15].

A membrane-bound homologue of angiotensin converting enzyme (ACE), the ACE2 is a cellular receptor for the SARS-CoV-2. The viral entry is facilitated by the binding of its spike (S) protein to the ACE2 receptor. The ACE2 are found majorly in the lung, heart and kidneys. This possibly points towards the interactions between the virus and the renin-angiotensin system (RAS), as well as the drugs used to modify the function of the receptor. These drugs happen to belong to the class of angiotensin II receptor blockers (ARB) and ACE inhibitors (ACEI), which are widely used in ailments of the cardiovascular, renal and endocrine systems. The ACE and ACE2, the significant enzymes in the RAS pathway are responsible for the formation of the Angiotensin II (AngII), which is a vasoconstrictor and the Angiotensin-(1-7) (Ang(1-7)), a vasodilator. As expected, they exhibit the opposite effects via Angiotensin receptor 1 (ATR1) and Mas[1] receptors, respectively. The later, Ang(1-7) has been studied as it was believed to have lung-protective effects in non-SARS lung diseases. According to studies the ratio of ACE2/ACE in lungs and kidneys was found to be 1:20 and 1:1 respectively which leads us to believe that lungs are relatively less susceptible to infection. But the clinical scenario has been exactly the converse of this statement. Therefore, due to the lack of clarity of the exact manifestations of the receptor interaction, there have not been any specific guidelines issued regarding the usage of drugs used to modify ACE and AR in the treatment of COVID19 and calls for further study [16].

The proteins that mainly function by attaching cell cytoskeleton to the extracellular matrix (ECM), and biochemically sensing the completion of adhesion, are called integrins. The integrin family is subdivided into alpha and beta subtypes, which form transmembrane heterodimers. A report suggests that the SARS-CoV-2 may also use integrins as cell receptors in the host cells, binding to them through conserved Arginine-Glycine-Aspartic (RGD) motif (a minimal binding peptide sequence), which is found to be present in all the receptor-binding domains of the spike proteins of all the SARS-CoV-2 sequences examined till date. The SARS-CoV-2 spike glycoprotein RGD is located in the receptor-binding domain (amino acids 319 to 514) at the border of the subdomain (amino acids 437 to 508), vital in binding to the human ACE2.[11] The viral

[1]Abbreviation of last name (Massey) of the person who donated the tumour from which the MAS gene was derived. MAS acts as an Angiotensin receptor

proteins possessing the RGD motifs promote infection by binding integrin heterodimers such as αVβ1, αVβ3, αVβ5, αVβ6, αVβ8, α5β1, α8β1 and αIIbβ3 [17]. They also activate transducing pathways involving phosphatidylinositol-3 kinase (PI-3K) or mitogen-activate protein kinase (MAPK), which enable virus entry into, and infection of the host cell [11].

1.3. Virulence Factors and Characteristics

The virus responsible for causing the COVID19 has been found to possess an incubation period of about 2-14 days, and its basic reproductive number falls within the range of 2.24 - 3.58; which was calculated based on intrinsic transmissibility and found to be slightly higher than that of SARS [4].

1.4. Overview of Life Cycle

The SARS-CoV-2 begins its life cycle when its S protein binds to the host ACE2 cellular receptor. Following this step, there occurs a conformational change in the S protein which facilitates viral envelope fusion with the host cell membrane utilizing the endosomal pathway. Then SARS-CoV-2 releases its genetic material, RNA into the host cell. The genome RNA is translated into viral replicasepolyproteins pp1a and 1ab, which are then cleaved into small by-products with the aid of viral proteinases. The polymerase yields a series of sub-genomic mRNAs by disjointed transcription and finally translated into relevant viral proteins. These viral proteins and genome RNA are then soon assembled into virions in the endoplasmic reticulum and golgi and then transported via vesicles and finally released out of the host cell (Fig 3) [10].

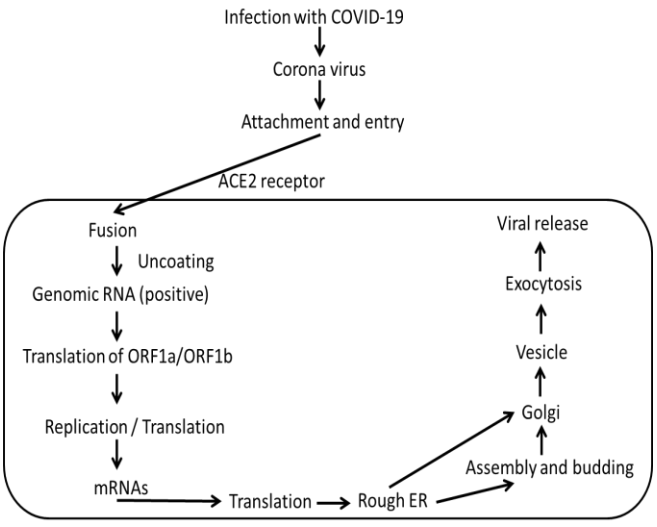

Fig 3: Life cycle of corona virus [10]

The present review article was aimed for highlighting the detail information related to all aspects of COVID-19. An extensive literature search has been carried out and around sixty research papers were collected from web sources like PubMed, Science Direct, Google Scholar, Scopus, Scifinder and some peer reviewed journals, and reviewed for the preparation of present article.

2. PATHOGENESIS AND MANIFESTATIONS OF IMMUNE SYSTEM

The S protein expressed in the coronavirus is a significant contributor towards entry into host cells. It does so by binding to the cellular ACE2 receptor for SARS-CoV and SARS-CoV-2, CD209L (a C-type lectin, also called L-SIGN) for SARS-CoV, and DPP4 for MERS-CoV. A specific critical proteolytic cleavage reaction in the S2' position at the SARS-CoV mediates the membrane fusion and facilitated viral infectivity into the host cell, alongside some clathrin-dependent and independent endocytosis mechanisms. The envelope glycoproteins now formed get inserted into the membranes of the endoplasmic reticulum or golgi and form nucleocapsid by the combination of genomic RNA and nucleocapsid proteins. After this is achieved, viral particles present themselves within the endoplasmic reticulum-golgi intermediate compartment (ERGIC). The virus is released when the virus-containing vesicles fuse with the plasma membrane, facilitating the same [13].

Antigenic peptides are normally presented by major histocompatibility complex (MHC) upon viral infection. This phenomenon in the case of SARS-CoV depends mostly on MHC I, while MHC II also contributing to the cause. Interesting research findings also have managed to divide a host's degree of susceptibility based on their HLA polymorphisms. There exist HLA polymorphisms that correlate to the susceptibility of SARS-CoV, such as HLA-B*4601, HLA-B*0703, HLA-DR B1*1202 and HLA-Cw*0801, while the HLA-DR0301, HLA-Cw1502 and HLA-A*0201 alleles are associated with the protection of host cells from SARS infection [13]. Gene polymorphisms of Mannose-binding lectin (MBL) could be also associated with an increased risk of getting infected [18].

The sequence of events that cause antigen presentation eventually stimulates the host humoral and cell-mediated immunity, mediated by B and T cells. The antibodies produced in SARS-CoV infection are IgM and IgG. The IgG, specifically S- specific and N-specific, are

believed to be more protective as it is longer lasting than IgM, which disappears by 12 weeks [13].

In acutely ill patients with SARS-CoV, a severe decrease of CD4+ T and CD8+ T cells is seen. Even in the absence of an antigen, their memory T cells may persist for four years in some of the SARS-CoV recovered patients and can induce T cell proliferation, DTH response and production of IFN-ɣ [19].

Acute respiratory distress syndrome (ARDS) is a type of respiratory failure which is characterized by rapid onset of widespread inflammatory manifestations in the lungs. ARDS has been credited to be the major cause of death in COVID-19 patients. One of the major mechanisms observed in ARDS is the "cytokine storm", a lethal uncontrolled systemic inflammatory response due to excess pro-inflammatory cytokines. These cytokines are (IFN-α, IFN-ɣ, IL-1β, IL-6, IL-12, IL-18, IL-33, TNF-α, TGFβ, etc.) and chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10) by the immune effector cells seen in COVID-19.

The survival of the SARS-CoV is vulnerable in such delirious patients. Hence to increase their chances of survival in the host, they employ multiple strategies. These viruses can avoid detection of their double stranded ribonucleic acid (ds-RNA) by inducing host production of double-membrane vesicles lacking in PRRs (pattern recognition receptors) which recognize the evolutionarily conserved microbial structures named pathogen-associated molecular patterns (PAMPs). IFN-I(IFN-α and IFN-β) have a protective effect on SARS-CoV infection, but its pathway is inhibited in infected mice. Another mechanism of Immune evasion is the down regulation of gene expression systems involved in antigen presentation [13].

2.1. Proposed Modes of Transmission

To guide the public into getting a clear picture about how the virus transmits, the People's Republic of China amended the description of COVID19 spread *as "COVID-19 is mainly transmitted by respiratory droplets and close contact",* and has also added the phrase, *"Aerosol transmission is possible when humans have prolonged exposure to high concentrations of aerosol in a relatively closed space".*[20] Highly contaminated surfaces may also cause the spread of disease [4].

A theory suggestive of aerosol transmission (Fig. 4) in a relatively closed environment in the case of long-time exposure to high concentrations of aerosol in the air also exists but lacks adequate scientific evidence. However, 2019-nCoV RNA was detected in the fecal samples of some infected patients with pneumonia, indicating that 2019-nCoV is also likely to be transmitted through feco-oral route [12].

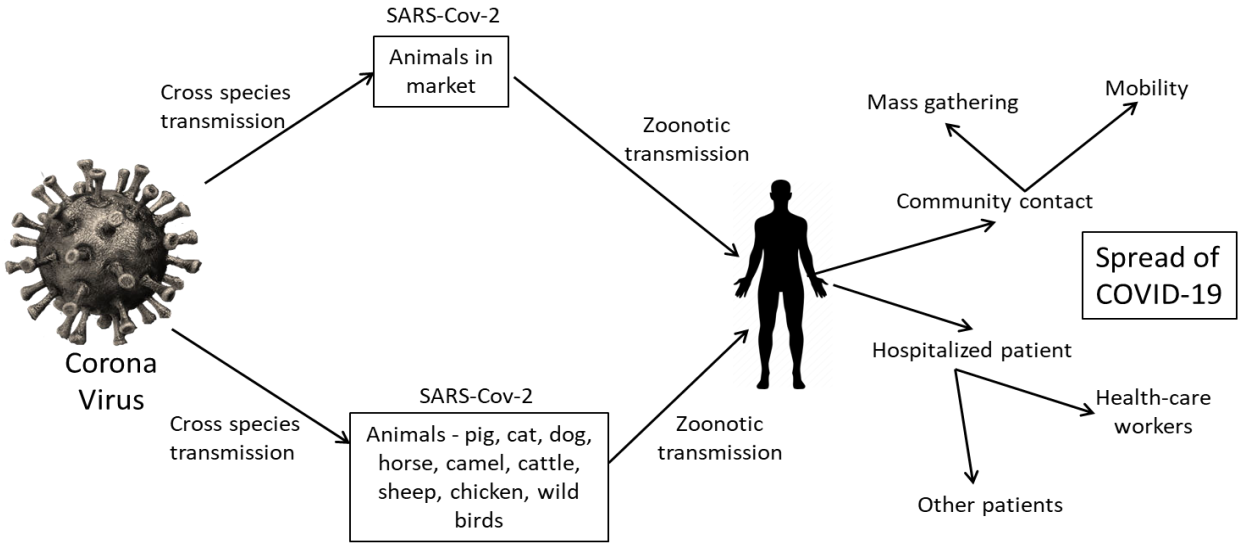

Fig. 4: Modes of transmission [21]

2.2. Symptoms/ Clinical Presentation

The mild COVID-19 infection is characteristic of symptoms commonly seen in other viral infections (i.e. fever, cough, dyspnea, myalgias, fatigue, and diarrhea) and laboratory parameters which suggest lympho-cytopenia. In severe infections, it is characteristic of pneumonia, acute respiratory distress syndrome (ARDS), maybe with or without both distributive and

cardiogenic shock, which predisposes the geriatric populations with preexisting medical co-morbid to greater risk [22].

A study conducted in the initial stages of the pandemic revealed the most common symptoms at the onset of the illness were fever [98%], cough [76%], and myalgia or fatigue [44%]; while the less common symptoms comprised of sputum production [28%], headache [8%], hemoptysis [5%], and diarrhea [3%]. It was also observed that more than half of the patients [55%] developed dyspnea. These findings were obtained from a sample size of 40 infected patients. The median duration of disease development from the onset of illness to dyspnea was 8 days. The median time from onset of symptoms to first hospital admission was 7 days, to development of symptoms of shortness of breath was 8 days, to ARDS was 9 days, to mechanical ventilation was 10.5 days, and to ICU admission was 10·5 days [23].

Not all patients start with out of control presentations, but some have mild disease. The geriatric patients (aged >60 years) are relatively more at risk to progress into severe acute respiratory distress syndrome, and this presents a need for intubation and intensive care [24].

A report has also concluded that pregnant women were also susceptible to SARS-CoV-2 infection, upon contraction of which it may increase health risks to both mothers and infants during the pregnancy. Hence, efforts should be taken to reduce the infection rate in the perinatal period with more intensive attention being given to pregnant patients [25].

2.3. Sample Collection SOPs From ICMR

The guidelines enlist different types of patient samples that can be collected. The main being Nasopharyngeal and oropharyngeal swab, serum (2 samples-acute, during the first week of illness and convalescent, taken 2 to 3 weeks later) and whole blood sample in EDTA vial. The other tests listed amidst the list include bronchoalveolar lavage, tracheal aspirate, nasopharyngeal aspirate or nasal wash, sputum, tissue biopsy or autopsy including from lungs. These samples are collected in sterile containers. Samples must be accurately collected with protective equipment in check and labeled appropriately with complete standard details recorded [26].

3. DIAGNOSIS

With having the task of controlling a pandemic in our hands, accurate, rapid and reliable detection is very important to do so [27]. The current practices in place include reverse-transcription polymerase chain reaction (RT-PCR), real-time reverse-transcription PCR (rRT-PCR), and reverse transcription loop-mediated isothermal amplification (RT-LAMP).[28] The samples used are obtained from nasopharyngeal and oropharyngeal swab tests. These tests along with other lab tests and diagnostic criteria by the China National Health Commission have been treated as the standard assessments for diagnosis of the infection [4].

There has also been three novel RT-PCR assays under analysis that target the RNA dependent RNA polymerase (RdRp)/helicase (Hel), spike (S), and nucleocapsid (N) genes of SARS-CoV-2.Out of these the COVID-19-RdRp/Hel assay displayed the lowest limit of in vitro detection, of which highly specific specializations may help in the improvement of the diagnostic procedures [29]. The SARS-CoV E gene essay was proposed to be sufficient for rolling out a positive test as it is also more sensitive than the RdRp gene assay coupled with the one-step RT-PCR system, but the RdRp protocol was deemed the appropriate recommendation for confirmation of infection results [4].

Quantitative reverse transcription PCR (RT-qPCR), applied in diagnosis has some shortcomings, which are certain biological safety hazards brought on by the collection, retention and operation of patient's samples, the cumbersome nature of nucleic acid detection procedures, and long waiting time for the results [13].

The typical radiological findings via CT scans of COVID19 patients possess similarities to those seen in MERS and SARS [30]. Typical radiological findings included bilateral pulmonary parenchymal ground-glass opacities and consolidative pulmonary opacities which sometimes manifested with rounded morphology and peripheral lung distribution [31]. These abnormalities in CT scans were the most severe about 10 days from the detection of initial COVID symptoms [32]. It is to be taken into account that events like lung cavitation, pleural effusions, discrete pulmonary nodules and lymphadenopathy were not observed [33].

The SHERLOCK technique, which stands for Specific High Sensitivity Enzymatic Reporter unLOCKing technique, is highly sensitive to RNA or DNA from patient samples and is portable. The assays when setting up with recombinase-mediated polymerase pre-amplification of DNA or RNA and subsequent Cas12- or Cas13- mediated detection carried out by colorimetry or by fluorescence, should be able to provide results in

less than one hour, excluding about fifteen minutes required for setup. Two guide RNAs are used, one recognizes the S gene of the new coronavirus and the other recognizes the Orflab gene. When these RNAs encounter the virus in the sample, it recognizes it and activates the Cas13a which inturn cuts any other RNA material it comes across. Hence by confirming whether or not any molecules have been cut, we can confirm test results [12].

To assess a "suspected" case, the patient's epidemiological history is first acquired and checked if he/she has returned from places that have been hit hard by the infection. They are assessed to find out whether or not they exhibit any respiratory symptoms or fever. Whether or not features of pneumonia have been presented upon imagery or a decrease in WBC or lymphocyte is checked. Patients who present themselves with these symptoms but have not extensively traveled are also treated as suspected cases. It is important to have a positive pathogen test obtained to deem a case as "confirmed". This is done by real time fluorescence reverse transcription-polymerase chain reaction (RT-PCR). The cases are classified as mild, moderate and severe. Hence, the patients with lesions progressed to over 50% within a span of 24-48 hours seen upon pulmonary imaging should be classified as a severe case [26].

When preliminary reports were examined by the experts, around 51% of acutely ill patients were found to have been presented with hyperglycemia, which is due to other factors and also endogenous stress induced glucocorticoid hypersecretion. Similar cases of hyperglycemia were found to be present in the cases with the SARS and MERS as well, out of which SARS virus was found to lead to transient pancreatic islet cell impairment. This may be because of the anchoring of the human coronavirus-EMC being anchored to the host cells via the dipeptidyl peptidase 4 (DPP4). This enzyme is responsible for regulation of Insulin action and glucose metabolism. It also degrades incretins such as glucagon like peptide - 1 (GLP-1). As hyperglycemia may lead to further immunological suppressions and complications, we should not let it go unchecked [34].

A prospective measure suggested by another study was to test for soluble CD-163 (sCD-163), which represents the activation of macrophages, whose parameter was found to increase in Macrophage activation syndrome (MAS) and to parallel the ferritin level. This is correlated with increased levels of ferritin seen during the acute stage of the inflammation. Another interesting discovery which supports measurement of these parameters is the involvement of the H-chain of the ferritin in activating macrophages to increase the secretion of inflammatory cytokines. This helps in better understanding of the pathogenesis of the hyperferritinemic syndrome seen in inflammatory diseases, including the infection with Covid-19 [35].

3.1. Differential Diagnosis

Mild symptoms of disease should be studied properly in order to rule out the possibility of viral pneumonia caused by influenza virus, adenovirus or RSV, and mycoplasma pneumonia [26].

4. PREVENTIVE MEASURES TO BE FOLLOWED BY MEDICAL PERSONNEL

Having close contact with suspected or confirmed patients puts the medical personnel at a greater risk of attaining infection, given the nature of their jobs as well. Hence they must adhere to strict medical protection, as given in Fig 5.

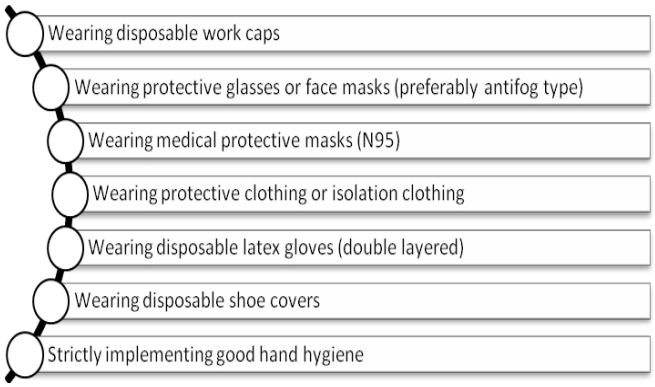

Fig. 5: Preventive Measures to Be Followed By Medical Personnel

Hence, PPE is recommended to avoid any occupational risks [3].

The use of a properly fitted respirator is recommended, in the absence of which masks should be used. Their extended overuse should be avoided as it may lead to self-contamination phenomena. The protective equipment must not be removed between patient consultations or encounters [36].

The coronavirus is seen to persist on inanimate surfaces at typical room temperatures and humidity for up to 9 days but can be inactivated efficiently by surface disinfection procedures using 62-71% ethanol, 0.5% hydrogen peroxide or 0.1% sodium hypochlorite within 1 minute [37].

4.1. Exploring Treatment Options

The reason why there is frenzy regarding the treatment approach to this new pandemic is because there seems to be less available options that actually show very good and fast recovery rates with minimal side effects, and also the lack of time and resources available for the fraternity as well. So, different options have been put up for testing and trials in the hope of developing an accepted algorithm.

Chloroquine, a popular anti-malarial, was found to have potential broad-spectrum antiviral spectrum [4]. The mechanism it is known to act is by inhibiting virus infection by increasing the endosomal pH which facilitates virus/cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV [38]. A study in China has observed chloroquine to be superior to the control group in decreasing the duration of symptoms, pneumonia exacerbations seen via radiological improvement and faster virus-negative seroconversion, keeping severe side effects at bay. This trial is among the first human trials to be conducted using chloroquine against COVID-19, which lead to China including it in treatment of COVID19 pneumonia. The same study also suggests the synergistic activity of Azithromycin, which has in vivo activity against Zika and Ebola as well [39]. Chloroquine phosphate at the dose of 500mg for adults every 12 hours has been added to the guidelines as a trial drug as well [26].

A Central Clinical Task Force from Korea having treated 27 COVID-19 patients have recommended using lopinavir 400mg/Ritonavir 100mg BID or Chloroquine 500mg orally per day or Hydroxy-chloroquine 400mg orally per day for 7-10 days, in moderate to severe case of COVID-19 [39].

Lopinavir (LPV), an agent which acts by inhibiting the protease enzyme has shown to reduce death (2.3% vs. 11.0%) when added as an initial therapy alongside ritonavir. This is also supported as a treatment for COVID as it has been seen to show effectiveness in managing SARS and MERS symptoms [4].

A guanosine analogue, Ribavirin, is an antiviral drug has been implicated in treatment of RSV, hepatitis C virus and some viral hemorrhagic fevers. After recognizing the targeting of SARS-CoV-2 RNA-dependent RNA polymerase (RdRp) model by this drug after sequence modeling and docking processes, the potential against SARS-CoV-2 has been believed to have been increased [40]. While trying to understand on a molecular level in cell-based assays, we see that the triphosphate form of Remdesivir gets incorporated at position i, the RNA chain termination was subsequently delayed, which explains the high potency of remdesivir against the RNA virus [41].

Remdesivir, an adenosine analogue, which targets RdRp is an antiviral which has been specifically intended against Ebola virus disease [42], and also shows a broad spectrum activity against many RNA viruses, competing for RdRp to inhibit replication [43]. Both IFNb and Remdesivir have been found to be superior in comparison to Lopinavir and Ritonavir in vitro studies [44]. Multiple clinical trials have been started involving Remdesivir against COVID-19, the main being NIH sponsored, in which patients receive an initial dose of 200mg of IV remdesivir on day 1, followed by maintenance doses of 100mg per day upto maximum 10 total treatment days [45].

The researchers tried using Umifenovir (arbidol) in conjugation with Lopinavir/Ritonavir so as to control early stages of the disease, decrease peak viral loads, hence reducing immunopathological damage. Controlling early stages of disease is hopeful in reducing the need for immunosuppressants, in turn reducing the risk of nosocomial infections. In this approach, Arbidol was given at a dose of 200 mg every 8 h and lopinavir (400 mg)/ritonavir (100 mg) orally every 12 hours. Therapy was continued until the patient was negative, confirmed by RT-PCR for three times. The therapy duration ranged from 5-21 days. These ideas were applied as Arbidol and arbidolmesylate were believed to have a direct antiviral advantage (in vitro for SARS-CoV) when applied in early stages. Therefore, Arbidol with LPV/r hopes to delay development of severe lung lesions, decrease gastrointestinal and respiratory transmission rates, and decrease in the count/load of the virus [46].

The use of antibodies has not been extensively done, but considering the relative high identity of the Receptor binding domain (RBD) in SARS-CoV-2 and SARS-CoV, a cross reactivity study of the anti-SARS-CoV antibodies and COVID19 spike protein was done. The spike protein induces neutralizing antibodies. Upon study it has been found that the SARS-CoV-specific human monoclonal antibody CR3022 was successful in binding with the COVID-19 RBD [47].

A part of the coronavirus, the S2 subunit is important in entry and fusion into the host cell. Heptapeptide repeat 1 (HR1) and heptapeptide repeat 2 (HR2) interact to form six helix bundles (6Hb), which tightly binds the virus and host cell membrane. A range of potentially

effective fusion inhibitors against SARS and MERS were developed by using S-HR1 and S-HR2, such as HR2P peptide. It has also been observed that the HR1 and HR2 regions of the 2019-ncov could interact to form 6hbs, and scientists have designed a pan-coronavirus fusion inhibitor denoted as EK1, which is believed to be significantly capable in inhibiting the 2019-nCoV pseudo virus infection when administered dose-dependently [12].

Patients with COVID-19 with CVD present as co-morbidity have increased risk of morbidity and mortality. The risk of developing complications like myocarditis, acute myocardial injury, arrhythmias and venous thromboembolism, also puts them in danger. Hence the antiviral therapy given must be carefully regulated so that it doesn't produce CVS side effects. Even though drugs like Ribavirin has no evident CV side effect, Lopinavir/ritonavir may prolong QT and PR intervals, especially in patients with baseline risk. When heart transplant patients were considered, a couple of patients who presented with the COVID symptoms were managed by withholding the baseline immunosuppressants and initiating high dose steroids IV Ig, and antibiotics. The doctors were able to avert any graft rejections [22].

Keeping Venous thromboembolic disease, to which chronically bedridden patients are also predisposed at risk to, it has been suggested that since direct anticoagulants and some antivirals may have an interaction, low molecular weight heparins or unfractionated heparin maybe with or without prophylaxis be preferred in acutely ill patients [48]. This is supported by the observation that Ribavirin has variable interactions with warfarin and Lopinavir /Ritonavir may require adjustments of CYP3A4 receptor mediated drugs as in Rivaroxaban and Apixaban [22, 49, 50].

Lopinavir/Ritonavir have also been observed to decrease the efficacy of clopidogrel and prasugrel (P2Y12 inhibitors) whereas increase in ticagrelor is seen. Hence care must be taken to avoid excessive bleeding episodes [51]. Finally, the use of IV Cangrelor which is also a P2Y12 receptor inhibitor independent of major hepatic biotransformation has not brought forward any major drug interactions as of yet [52].

Statins, anti- hyperlipidemics which inhibit HMGCoA may also react with the Lopinavir/Ritonavir combination and cause the patient to be at an increased risk of rhabdomyolysis, which is characterized by breakdown of damaged skeletal muscles. Hence, consider switching Lovastatin and simvastatin with low dose Atorvastatin and Rosuvastatin, if needed [52].

In severe and critical case presentations, "Convalescent plasma therapy" is recommended depending upon patient's condition. Extracorporeal methods of blood purification may also be necessary, which includes plasma change, perfusion, adsorption, plasma filtering etc. if deemed necessary in the treatment of patients with severe inflammatory reactions [4, 26].

Since the virus possesses Chymotrypsin like proteases, 3CLpro inhibitors like cinanserin and flavonoids, and PLP inhibitors such as diarylheptanoids maybe other attractive alternatives to be considered against SARS-CoV-2 [13]. Another strategy of ACE2 blockage could also be of some significance as targets for further research [53].

Patients presented with comorbidities may require rehabilitation treatments while still in quarantine. The most practical approach would be home exercises with ramped up infection control. Tele-rehabilitation is a concept which demonstrates improvements in the motor, higher cortical, and mood disorders post stroke when compared with the conventional therapy. One advantage is being able to remotely supervise patients without increasing risk of viral exposure. Diabetes being an immunocompromising disease could increase the risks of severe COVID presentation and hence, mortality of the patient. Apart from Diabetes, Chronic respiratory disease, cancer, stroke and cardiovascular diseases also increase the risk of death. Hence, more attention must be given to their therapy and rehabilitation approaches [37].

Various other potential agents which may confer anti-viral effects are currently being evaluated against the disease. These include Interferons, Nafamostat, Nitazoxanide, Ribavirin, Penciclovir, Favipiravir, Ritonavir, AAK1 and Baricitinib [10].

Interferon alfacon-1 is a recombinant synthetic type-1 interferon. Findings suggest that interferon alfacon-1 may not directly block viral replication in infected cells, but may be effective in suppressing viral spread to uninfected cells by turning the cells refractory to viral infection. This is believed to be a part of the normal cellular response when treated with to type 1 interferons. This further suggests that SARS-CoV may contain a viral gene product that functions as an interferon antagonist like other RNA viruses. Therefore, as this agent has exhibited inhibitory effects against SARS-CoV in cell based models (in vitro), more research is needed to fully exploit its risks

and benefits upon application in the treatment of the disease [54].

Since there have been suggestions of Integrins being used as cellular receptors, which when bound to the virus leads to infection as well, the testing of agents that antagonize or inhibit integrin binding may provide an encouraging target of research. Recognized integrin blockers consist of agents such as the antibody natalizumab (a $\alpha4\beta1/\beta7$ integrin antagonist) used in the treatment of multiple sclerosis and Crohn's disease, Tirofiban n (an $\alpha IIb\beta3$ inhibitor) applied in acute coronary syndrome, as well as inhibitors of αV RGD-binding integrin. New agents can be developed, and existing molecules can be tried or tested in order to explore new horizons of research [11].

4.2. Treatment Inspirations Drawn From Nature

When we consider the ancient belief of applying sesame seed oil, we see that because of low intermolecular attraction between the oil molecules, pure oil extract may have great wettability. Although how and when to use, and the exact underlying mechanism in prevention in the context of COVID19 is uncertain. Another instance presents glycyrrhizin, in Chinese medicine, which was suggested in SARS treatment. It was low in toxicity and was considered effective as well, hence could be used as a strategy for the same [12].

Another approach brought forward the efforts at molecular docking being used to find natural compounds, for which they proposed the five candidates including Scutellarin, baicalin, Hesperetin, Nicotianamine and glycyrrhizin. These are believed to be potential compounds targeting the ACE2 receptor and exert anti-viral effects to prevent 2019-nCoV infection [55].

4.3. Emotional Impact

Although common mental health disturbances are found among patients and some health workers in stressful conditions, it is seen that many health care professionals who work in isolation did not receive any prior training or guidance specifically [56]. This isolation which in turn led them to practice confinement gradually caused them to develop a sense of collective hysteria [57]. And during this COVID19 pandemic, a rise in the levels of anxiety, depression and stress has been noted [58], which can also lead to further implications and affect other health care measures which are applied [59].

4.4. Attempts At Creating Vaccines

There is no commercially available vaccine against COVID-19. Hence the race for launching one into the market immediately has been intensified. When the recombinant protein from the Urbani (AY278741) strain of SARS-CoV was administered to animals, mice and hamsters, neutralizing antibodies were produced and protection against SARS-CoV was conferred [60, 61].

The DNA fragment had inactivated whole virus or live-vectored strain of SARS-CoV (AY278741), which resulted in remarkable reduced viral infection in different animal models. Other strains of SARS-CoV have also been used to produce inactivated or live-vectored vaccines which efficiently reduced the viral load in animal models. These strains include, Tor2 (AY274119), Utah (AY714217), FRA (AY310120), HKU-39849 (AY278491), BJ01 (AY278488), NS1 (AY508724), ZJ01 (AY297028), GD01 (AY278489) and GZ50 (AY304495) [10].

Nevertheless, there are few vaccines in that can be streamlined against SARS-CoV-2. The mRNA based vaccine prepared by the US National Institute of Allergy and Infectious Diseases against SARS-CoV-2 is has entered phase 1 trial [62] The INO-4800- DNA based vaccine will be soon embark on its next step and be available for human testing b [63] The Chinese Centre for Disease Control and Prevention (CDC) has been working on the development of an inactivated virus vaccine [64, 65]. Moreover, the mRNA based vaccine's sample (prepared by Stermirna Therapeutics) will be available soon for the same too [66]. GeoVax-BravoVax, a biotechnology company is working to develop a Modified Vaccina Ankara (MVA) based vaccine [67], while Clover Biopharmaceuticals is developing a recombinant 2019-nCoV S - protein subunit-trimer based vaccine as well [68]. We therefore might just have an effective vaccine in the market soon.

One factor that must not be overlooked during vaccine development would be the occurrence of cross-resistance for SARS-CoV in people immunized against diseases like rubella and measles. This is because children who were immunized for the same were hypothesized to be less vulnerable to the COVID19 [10].

5. CONCLUSION

The novel coronavirus which has managed to unfortunately carve a name for itself in history, is a virus that is believed to have originated from Wuhan, China

and has cumulated about 70 million cases and has been responsible for more than 2 million deaths as of mid-December 2020, worldwide [69].

Although a lot of theories have been brought forward by scientists, the most convincing one has been that suggesting the "spill-over" from bats to the humans. The phenomenon of DNA recombination at virus spike glycoprotein which assorted SARS-CoV (CoVZXC21 or CoVZC45) with the RBD of another Beta CoV, was hypothesized to be behind the for cross-species transmission and rapid viral infection [10].

As of today, no specific treatment algorithm has been developed targeting the COVID-19 nor has there has been any immunization strategy launched, due to the absence of the availability of any effective vaccines. Hence this infection which is mainly seen to present with pulmonary clinical features has been attempted to be treated with drugs like Hydroxyhloroquine, Lopinavir, Remdesivir, Umifenovir and other drugs being brought forward after clinical trials. Extra-pharmacological approaches are slowly being brought forward as potential treatments for this disease, along with a number of suggestions that aim to help physicians manage pre-existing comorbidities. Specific detection and diagnosis guidelines have been put in place to assess the grade and degree of infections. This being said, apart from allopathy a lot of scientists familiar with phamacognosy are also exploiting natural resources in their search for a potent molecule in nature as well.

The basic prevention guidelines have been publicized by majority of the governments of the world, mainly emphasizing the importance of "social distancing" as the "behavioral vaccine" in their shot at reducing the drastically increasing numbers of the infected patients and hence, flattening the curve to bringing the infections to a minimal and hopefully to nil soon. Keeping in mind the different occupational risks that entail, the healthcare professionals are fully committed towards providing infection control services and gradually eradicating this deadly pandemic.

There must be strict vigilance of the ongoing prevention measures as well as implementations of a uniform code or policy which entitles the professionals involved proper access to personal protective equipment. Apart from the much needed participation in the search of a specific drug treatment, the research and development sector is in direct need of more biotechnological laboratories to come up with novel vaccine approaches in order to render the human population immune to the viral infection.

Conflict of interest

Authors declare that there is no Conflict of interest

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