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ORIGINAL ARTICLE

INSIGHT TO COVID-19

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ABSTRACT

The world is experiencing a lockdown and isolation due to the pandemic caused by the corona-virus 2019 (Covid-19). Worldwide, it has up-surged the hospitalization of pneumonia patients with multiple clinical complications. The death tolls continue to increase and most of the countries have imposed social distancing. The fatality rate among the patients with Covid-19 infection varies by age groups. The major target of the virus is the respiratory system followed by the lung injury and multiple organ dysfunctions in severe cases. Several diagnostic techniques are performed to diagnose the Covid-19 infection. This article reviews the current understandings regarding enormous aspects of the Covid-19 disease and its impacts on vital organs. It has been found that some treatments are highly effective in certain regions of the world, whereas others have not improved the disease process. There is still uncertainty about the sensitivity of presently available options. The novelty of Covid-19, its global outbreak rapidity and the vaccine unavailability have contributed to the public's fear. It is concluded that the invention of effective diagnostic and treatment approaches to curb the Covid-19 is the need of the hour. Reviewed herein are, epidemiology, pathophysiology, transmission, multiple organ complications, impacts of Covid-19 infection on lungs, pancreatic and hepatobiliary system, diagnosis, in-practice treatments, recommendations for treatment, vaccine, prognosis and prophylactic measures to avert the Covid-19 infection.

Keywords: Covid-19, Pathophysiology, Transmission, Complications, Treatment

INTRODUCTION

On 30 December 2019, an emergency alert was issued by the Chinese Centers for Disease Control and Prevention (China CDC) to the local hospitals of Wuhan regarding mysterious cases of pneumonia reported in the previous week. Later, the disease turned as a pandemic, spread all over the globe and recognized as the severe acute respiratory syndrome corona-virus 2 (SARS-CoV-2) or corona-virus disease 2019 (Covid-19). It was initially considered that the Covid-19 pandemic has erupted from a market of seafood in Wuhan through a zoonotic transmission. Subsequently, human to human transmission contributed critically to the outbreak. Corona-viruses are generally enveloped RNA viruses, they are broadly disseminated among humans, different mammals and birds. Although the immediate source of Covid-19 is not bat, but the Covid-19 has 96.3% genetic resemblance with corona-virus RaTG13 which was extracted from a bat in the Yunnan city of China back then in 2013. As of 16 August, 2020, there have been 21,260,760 confirmed cases of Covid-19, including 761,018 deaths, reported to the World Health Organization (WHO). The infection caused by deadly Covid-19 can be asymptomatic or with a broad range of

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symptoms such as fever (moderate to high), myalgia, fatigue, dizziness, vomiting, diarrhea, dyspnea, pneumonia and life threatening sepsis. Current clinical management is mainly supportive and to treat symptoms with no availability of particular targeted therapy.

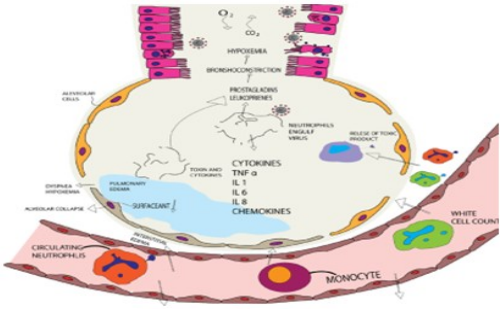

Fig. 1: The Covid-19 infected the alveolar cells of the lungs and causing the inflammatory response, which leads to the release of toxic products, the production of surfactant decreases which results into pulmonary edema and causes dyspnea and hypoxemia.

Epidemiology

Following the epidemic in china, Covid-19 has spread globally and become pandemic and affected more than 200 countries. The previous studies of Covid-19 revealed that at the beginning of the outbreak, the ratio of elderly people affected by Covid-19 was more as compared to the young people. Later, the cases among people aged >60 enhanced further and the cases were also detected among children. The fatality rate in Italy was 7.2% and the fatality rate in general occupied 2.3% of total cases. The fatality rate of patients aged 0-69 years was parallel in Italy and China, but the fatality rate of patients aged >70 was up-surged in Italy because the age group 65 years and above 65 comprises 23% of the total population in Italy. The China CDC disclosed the data that the number of children (<10 years-19 years) affected by Covid-19 was small within the entire number of Covid-19 patients, occupying 1% each of the overall cases. About 20% of the entire population comprises in this age group, indicating under the prevalence of Covid-19 among the pediatric population. If the less pediatric population underwent through Covid-19 tests due to asymptomatic infection, then this data might be under-estimated than the actual Covid-19 cases among the pediatric population. However, there is a possibility of less exposure of Covid-19 among the pediatric population because during the beginning of epidemic the schools were closed in china due to Chinese New Year event. The data revealed that among the 2143 reported Covid-19 pediatric patients, the ratio of asymptomatic patients was 4.4%, mild 50.9%, moderate 38.8% and severe 5.9%, respectively. The fatality rate among the age group 0-19 years was 0% in china. The ratio of patients of Covid-19 among age group 8-18 years in Italy was 1.2% and the fatality rate was 0% and 0.2% of 0-9 and 10-19 years age groups. The study of 2572 pediatric patients of Covid-19 released by US CDC showed that the pediatric Covid-19 cases occupied 1.7% of overall cases in US. The data of Chinese reports suggested that pediatric patients were less symptomatic such as 73% of total reported pediatric patients developed dyspnea, cough and fever. Initially, the ratio of male patients was slightly higher, but as the cases exalted, no major gender difference was noticed. The severity of the disease was connected with comorbidities and sequelae such as respiratory disorder, cardiovascular disorder and renal disorder. The severity and worst outcomes were more common in males and associated with alcohol drinking and smoking. The prevalence of disease was more in males than females, the immunological disparities based on sex differences might contribute critically and within the pandemic milieu the females are more likely to adopt precautionary measures such as frequently washing hands, avoiding gatherings and use of face mask compared to males. The previous study based on 85 Covid-19 patients with 65 years of average age demonstrated that most of the mortalities are due to multiple organ failure. The ratio of acute respiratory distress syndrome (ARDS), shock and respiratory failure among mortalities were 74%, 81% and 94% respectively.

Life cycle and pathophysiology of Covid-19

The name of Covid-19 is derived from characteristics crown-like appearance in electromicrograph. Corona-virus is composed of SSRNA shielded by a membrane proteins and lipid-bilayer, which also possess surface proteins recognized as Spike Glycoprotein. The major target of the Covid-19 is the respiratory system. The response is slowly triggered in the lungs by the virus during the incubation phase. The lungs are composed of sacs of alveoli; it is the place where the exchange of gases takes place, oxygen breath in and carbon dioxide breathed out. The alveolar cells form alveoli and also produce surfactants which laminate the inner-lining of alveoli and assist to retain alveoli open and allow for carbon dioxide and oxygen exchange. The Covid-19 virus mainly targets the alveolar epithelium cells. The virus binds to the ACE2 which is a receptor as well as an enzyme present on the surface of epithelium alveolar cell to gain entry into the cell. Once the virus entered inside, the particles of virus become un-coated and viral genome intrudes into the cytoplasm of cells. Since the corona-virus has +SsRNA genome, they can directly generate their protein and novel genome inside the cytoplasm via tethering to the host ribosome. The viral RNA is translated by the host ribosome to generate proteins for RNA polymerase enzyme production. In the next stage, RNA polymerase will read the +SsRNA to make the -SsRNA. Meanwhile, RNA polymerase used -SsRNA form to make +SsRNA and other small +RNA strands. The host ribosome will again read the small RNA strands in the Endoplasmic Reticulum (ER) to form viral structural constituents. The ER will relocate these proteins (accessory and structural) into the Golgi apparatus where they assembled with the +sRNA strand to create a new virus. The viral progenies emancipate from host cells via exocytosis mechanism through secretory vesicles. The viruses not only self-replicate within the alveolar cells but also cause harm and damage to it. The inflammatory response is initiated by this stimulus and injured alveolar cells start releasing interferon, cytokines and intercellular components. The primary function of interferon is to induce protection in affected and non-affected cells against viruses, while alveolar macrophages respond to damage by secreting cytokines such as TNF-α, IL1, IL6, IL8 and chemokines. The inflammatory process occurred in the lung parenchyma, stimulate nerve ending which is liable for instigating the cough reflex. The TNF-α and IL1 are proinflammatory cytokines and they enhance the vascular permeability and increase adhesion molecules expression. This allows the recruitment of more immune cells (neutrophils and monocytes) that bind with adhesion protein and enter into the site of injury. The IL8 will recruit neutrophils and chemokines will attract monocytes. The vascular permeability augmentation causes leakage of fluid into the interstitium and ultimately leading to interstitial edema. Meanwhile, enter into the alveoli causing pulmonary edema which results in dyspnea and impaired oxygenation leading to hypoxia. The Neutrophils are important in an acute setting by engulfing viruses and other debris, but they are detrimental after a while because they release chemicals as by-products damaging the surrounding tissue figure 1. All these events lead to decrease production of surfactants which ultimately leads to alveolar collapse result in hypoxemia. The WBCs and damage endothelium cells release inflammatory mediators of arachidonic acid metabolites such as leukotriene and prostaglandins. The leukotriene causes further bronchoconstriction while prostaglandins, TNF-α, IL1 and IL6 all responsible for causing fever which is a prominent feature of Covid-19.

Transmission of Covid-19

The most prevalent ways of transmission of Covid-19 are expulsion of droplets while sneezing, coughing and talking face to face. Being in contact (15 minutes or 6 feet) with an infected person can cause transmission of Covid-19, there is a high possibility of transmission if a normal person comes in brief exposure to symptomatic (e.g., sneezing,

coughing) Covid-19 patient compared to asymptomatic patient. The other potential medium of transmission is Covid-19 contaminated surface contact. The transmission through aerosols is still controversial, because the nucleic acid of Covid-19 suspended in the air does not determine the infectious tendency of tiny airborne particles. Strikingly, the threat of vertical transmission (mother to fetus) of Covid-19 is low, most of the pregnant mothers infected with Covid-19 in third trimester, no maternal fatality and complexion in neonatal clinical courses occurred. It is hard to describe the transmission of Covid-19 via inanimate surfaces without knowing the least required viral particle quantity or dose that can instigate the infection. The Covid-19 virus seems to persist more on impermeable surface (plastic and stainless steel) rather than permeable surface (cardboards). The Covid-19 has been detected after 3 to 4 of inoculation on an impermeable surface, but the amount of Covid-19 observed on surfaces deteriorate within 2 to 3 days. At the onset of symptoms, the load of Covid-19 in the upper respiratory tract (URT) is mostly on peak but the shedding of Covid-19 starts 48-72 hours before the commencement of symptoms and the Covid-19 can be transmitted via presymptomatic and asymptomatic patients. The studies revealed that the ratio of infections transmitted via presymptomatic patient in Singapore and china is 48%-62% and the ratio of infections transmitted through asymptomatic patients fall between 4%-32%. The nucleic acid is detected via throat swabs after the 5 weeks of the beginning of illness but the viral culture of Covid-19 generally resulted in negative after the 8 days of the onset of symptoms. The epidemiological studies supported that contacts were not infected when they were exposed to the index case approximately after 5-7 days of the symptoms onset in the index case.

Multiple organ complications

The Covid-19 complications comprise of impaired nervous, cardiovascular, respiratory, hepatic, renal and coagulation system. The Covid-19 infection can cause cardiomyopathy, myocarditis, ventricular arrhythmias and instable hemodynamics. The study demonstrated that 8% of critically-ill Covid-19 patients have experienced encephalitis and acute cerebrovascular disease. Arterial and venous thromboembolism has been observed in 10%-25% of hospitalized Covid-19 patients, whereas these events occur in 31%-59% of patients admitted in ICU. Among the hospitalized Covid-19 patients, 17%-35% of them are treated in ICU due to hypoxemic respiratory dysfunction. Furthermore, 29%-91% of the patients in ICU were mechanically ventilated. Besides the respiratory dysfunction, 9% of the hospitalized patients developed renal injury and 19% of them developed hepatic dysfunction.

Impacts of Covid-19 on lungs

It is already established by previous studies that the major target of Covid-19 is the respiratory system. It has been found that severe patients of Covid-19 infection developed lung edema. The clinical phenotypes of Covid-19 patients who developed lung edema were concise by accumulating various reports of large numbers of Covid-19 patients. In chest radiographies of Covid-19 patients, the acute lung injury (ALI) and edema were obvious by several consolidations and opacities with or without air bronchogram predominantly disseminated in peripheral lesion of lungs. Patients with mild Covid-19 infection only had ground-glass opacities, demonstrating less edematous fluid which can be ameliorated with treatment and time. The dispersal and density of opacities and bilateral-lobular and sub-segmental lesions of consolidation amplified with progression of illness and escalation in severity.

Table 1: Treatment recommendations for Covid-19

Clinical phase of infection	Chinese guidelines (103)	Italian guidelines (108)
Suspected and confirmed patients with mild symptoms (fever, fatigue, normal breathing).	Isolate the suspected patients, detain the confirmed patients and treat them in same room, administer TCM for symptomatic treatment, ibuprofen is recommended for fever.	Isolation of suspected and confirmed patients, treat them symptomatically and antivirals should not be administered.
Confirmed patients with mild to moderate symptoms (persistent cough, fever, ventilation support is not required).	Symptomatic treatment of cough by TCM and ibuprofen for fever.	Treat patients symptomatically and keep them hydrated. Lopinavir, ritonavir, chloroquine and hydroxychloroquine can be administered.
Confirmed patients with pneumonia and elevated respiratory rate.	Ibuprofen administration to mitigate fever, supportive care in ICU, TCM to attenuate the symptoms and administration of antivirals.	Admit in ICU for care, oral hydration, peripheral oxygenation, antibiotics to avert the opportunistic infection. First line: administer remdesivir, if unavailable then administer lopinavir or ritonavir + HCQ or CQ + tocilizumab.
Critically ill patients accompanied with ARDS.	Mechanical ventilation (invasive or non-invasive), If not responding, extra corporeal life support should be given. Administer vasoactive drugs to ameliorate the circulation, administration of empirical antibiotic therapy. Administer corticosteroids (avoid unnecessary use), Administer antivirals. In case of septic shock, crystalloids will be given via IV route.	Mechanical ventilation (invasive or non-invasive), administer broad spectrum antibiotics. Administer systemic steroids (methylprednisolone/dexamethasone). ECMO in case of refractory hypoxemia. First line: Administer remdesivir, if unavailable then administer lopinavir or ritonavir + HCQ or CQ + tocilizumab.

Table 2: Vaccines in Pipe-line

Status	Type of vaccine	Activity target	Developer entity	Country
Phase-1 accomplished NCT04313127	Recombinant Novel Covid-19 (Adenovirus type5 vector)	Protein-Spike "S"	Can Sino biologics Inc.	China (109)
Phase-2 NCT04352608	In-activated	Complete virus	Sinovac biotech	Brazil and China (110)
Phase-1/2 NCT04324606	Non-replicating Viral vaccine	Protein-Spike "S"	Oxford University	United kingdom (111)
Phase-1 NCT04336410	DNA vaccine	Protein-Spike "S"	Inovio Pharma	USA (112)

Table 3: Prophylactic measures against Covid-19

Extent	Actions
Individual extent	Personal hygiene, physical distance, utilizing protective equipment such as masks, gloves and PPEs.
Case Identification	Testing, tracing, tracking and isolation of affected people.
Government extent	Prohibition of gatherings, limits the business hours, prophylactic measures in the workplace and educational institutes, SOPs for public transport, cordoning the areas with the affected population, stay at home advisory and inter-provincial or inter-city borders closure.
International-borders extent	Imposed quarantine and borders closure.

The prognosis of Covid-19 patients is determined by ALI development and severity. The hypoxemia, dyspnea and severe lung edema were developed in 30% of Covid-19 patients warded in ICU. The ARDS developed in 17% (17/99) of Covid-19 patients (containing patients in ICU and non-ICU) and the deaths of approximately 65% of the patients with ARDS reported, indicating worse prognosis in patients with ARDS. Radiographic and autopsy findings indicated that acute lung inflammation, lung endothelial barrier failure and tissue injury in Covid-19 patients are characterized by leukocyte infiltrations, tissue edema and alveolar wall injury respectively. It is generally assumed that Covid-19 infections cause progressive hypoxemia by persuading diffuse alveolar injury, excessive generation of inflammatory agents and vascular permeability elevation. This presumption is reinforced by few findings about the pathology of the respiratory system in Covid-19 cases, indicating the desquamation of type II alveolar epithelial cells, diffuse alveolar injury, hyaline membranes and exudation of fibro myxoid. The inflammation and edema of lungs are the strategic mechanisms of the progression from ALI to ARDS as well as multiple organ dysfunctions.

Impacts of Covid-19 on pancreas

The recent study consists of 52 Covid-19 patients disclosed that pancreatic injury occurred in 17% of patients among them, recognized by fluctuations in amylase and lipase expressions. Although the severe pancreatitis symptoms as of yet have not been observed, but the expression of ACE2 receptors in islet cells of the pancreas is escalated, therefore theoretically the Covid-19 infection can damage islets and leading to acute diabetes. The six out of the nine patients with the injured pancreas experienced blood glucose level abnormality. The pancreatic injury may occur via direct cytopathic effect of the Covid-19 infection, or indirect cellular immune mediated or systemic inflammatory responses, causing the single or multiple organ injury or abnormalities of enzymes. The drug associated pancreatic injury could also occur because the majority of the patients included in this study took antipyretic medications prior to admission. Further research is required to determine the broad spectrum impacts of the Covid-19 on the regulation and function of the pancreas.

Impacts of Covid-19 on hepatobiliary system

The recent studies showed that a large number of patients of Covid-19 have experienced mild to severe hepatic injury as a sequelae. The abnormalities have been detected in the specific laboratory tests of these patients which supported the occurrence of hepatic injury. Considering the pathophysiology of Covid-19 infection, the injury may occur due to the course of infection. The ratio of 20%-30% confirmed Covid-19 patients have experienced liver enzymes abnormality. In China, 148 confirmed Covid-19 patients have been examined at admission and liver function abnormality has been found in 50.7 % of these patients. Additional studies have supported these findings with malfunction in total

bilirubin and liver enzymes. It has been found that the Covid-19 patients with liver function elevation were more prone to experience a fever (moderate to high) and the prevalence of these finding were more in male Covid-19 patients (68.67% vs. 38.36%). Consequently, the significant down-regulation of CD4+ and CD8+T cells has been observed in these patients. The leukocyte counts were reduced and white blood cell count was considerably exalted, indicating the poor prognosis. The majority of liver injuries examined were mild and transient. The patients with severe Covid-19 infections developed severe liver injuries and that patients received administration of hepato-protective drugs. The organized mechanism of lung injury manifestation of Covid-19 is yet to be cleared but viral infection pathophysiology can indicate this phenomenon. The Covid-19 virus enters cells via ACE2 receptors and this receptor is found abundantly in epithelial cells of the gastrointestinal tract. The Covid-19 may cause liver function disorder through infecting cholangiocytes by ACE2 receptors. The liver can be injured because ACE2 receptors are highly expressed in hepatic tissues for the bile duct (epithelial cells) derived hepatocytes compensatory proliferation.

The liver biopsy acquired from the deceased patient of Covid-19, histological examination indicated mild lobular activity and micro-vesicular steatosis but did not show viral intrusion, this finding supported that the Covid-19 can diminish liver functions by directly binding to cholangiocytes of ACE2 receptors. Moreover, liver dysfunction or hepatocellular injuries occurs secondary to immune mediated inflammation and hypotension in critically-ill patient of Covid-19. Lastly, liver enzymes can be enhanced due to hepatotoxicity induced by drugs and the administration of hydroxychloroquine and remdesivir to the Covid-19 patient may play a critical role in this regard.

Diagnosis

The Swift and accurate espial of Covid-19 is important to manage the epidemic in population and hospitals. Currently available tests that are performed to diagnose the virus include nucleic acid detection based tests, CT scans, immunological assays and blood culture to check virus growth. According to protocols established by China CDC, nasopharyngeal and oropharyngeal swab tests have become a standard assessment for the detection Covid-19. The WHO guidelines suggest real time reverse transcription polymerase chain reaction (RT-PCR) is the forthright and most efficient tool to detect the Covid-19 infection. RT-PCR is performed by taking genomic material (RNA) of the virus from the upper and lower respiratory tract such as nasopharyngeal sample, sputum and bronchoalveolar lavage, etc. It has been reported in the literature that for the detection of virus conventional RT-PCR is not reliable sometimes, because it is associated with false-negative results, if it is performed in the early stage of infection. To overcome this problem Next generation sequencing (NGS) performed, virus detection along with mutation of a pathogen can be analyzed by NGS. A study conducted in Huazhong University of science and technology, Wuhan, China reported sensitivity of the RT-PCR test was 59%. Whereas, a research group of Fred Hutchinson Cancer Research Center reported the sensitivity of the RT-PCR test was 84.6%. Recently few research groups have reported that lower respiratory tract contains more viral and genomic content as compared to the upper respiratory tract infection. The most efficient detection technique for Covid-19 is virus blood culture and high throughput screening method of the entire genome, but due to high cost and dependence on equipment use of this technology is limited. The virus culture method is more beneficial in the early stage of outbreaks when there are no other diagnostic approaches available. As compared to all diagnostic techniques the viral culture is more time-consuming procedure. To compensate the false-negative result limitation of RT-PCR, physicians proposed to use RT-PCR along with the chest CT scan. The chest radiography is very helpful for the diagnosis and evaluation of the disease condition of Covid-19 patients.

About 97.2% sensitivity of CT scan is reported in the diagnosis of Covid-19 cases. The typical findings of CT show bilateral, peripheral and subpleural ground-glass opacities, air space alliance, thickening of bronchovascular part and traction bronchiectasis. The atypical findings consist of mediastinal lymphadenopathy, tree in bud appearance, pneumothorax, pleural effusion and multiple tiny pulmonary nodules. The researchers of Zhongnan Hospital Wuhan University recommended the use of CT imaging for the diagnosis and evaluation of Covid-19 patients. The hematological examinations, pathological findings obtained from biopsies and autopsies and additional laboratory tests such as blood gas analysis, hepatic and renal function tests, erythrocytes sedimentation rate, C-reactive protein, lactate dehydrogenase, inflammatory markers and anti-acid staining can also commonly used to make diagnosis stronger and monitoring the condition of the patient.

Treatment

Supportive management

In case of Covid-19, the protocols of supportive care of ARDS and hypoxemic respiratory failure should be implemented. The oxygen therapy or mechanical ventilation is required usually in >75% of the hospitalized Covid-19 patients and the heated high flow oxygen via nasal cannula should be administered if the patient is not responding to conventional therapy of oxygen. The lungs protective ventilation system with less than 30 mg Hg plateau pressure and small tidal volume such as 4-8ml/kg is recommended in the Covid-19 patients who required mechanical ventilation support. In addition, neuromuscular blocking for short term with cisatracuruim, escalated positive-end-expiratory pressure technique and prone positioning can assist in oxygenation. The large number of Covid-19 patients can breathe normally but experience severe hypoxemia, therefore intubation is so far controversial in Covid-19 patients with respiratory failure. The early intubation facilitates to attain a better controlled process of intubation, but the hypoxemia without respiratory distress is not only tolerable for patients but also early intubation can cause supplementary complications and gratuitously providing ventilation support to the patients. There is a lack of significant evidence to recommend early or late intubation and is yet to be studied further. As per observational studies, the co-existing fungal or bacterial infections were developed in up to 8% of the hospitalized Covid-19 patients, but approximately 72% of them were cured by administering broad spectrum antibiotics.

Antiviral drugs

Currently, the anti Covid-19 efficacy of numerous antiviral drugs have been assessed via in-vitro trials. The protease inhibitors hold substantial inhibitory activity against the RNA viruses, therefore an open-label and random control trial (ChiCTR2000029539) of lopinavir-ritonavir against Covid-19 was carried out in China. The standard treatment protocols were followed to treat one group and the second group was treated with lopinavir-ritonavir, but results showed no significant difference. The nucleoside-structural-analogs such as ribavirin, favipiravir, remdesivir also possess anti Covid-19 in-vitro activities. The five antiviral drugs are undergone through in-vitro trials to evaluate their anti Covid-19 properties such as inhibiting incorporation as well as multiplication of virus inside the cells (Vero E6). It was found that remdesivir among them holds a notable anti Covid-19 properties in combination with chloroquine (antimalarial), half maximal effective concentration values of remdesivir and chloroquine against Covid-19 were EC_{50} 0.77μM and EC_{50} 1.13μM respectively. Remdesivir is a broad spectrum antiviral drug which was developed by US-based firm against Ebola virus and recently being used to treat Covid-19 patients in many countries. Strikingly, it is the single antiviral drug that is recommended to treat patients with the lowest saturation of oxygen i.e. <94% and those on mechanical ventilation. However, remdesivir is prohibited in patients with mild symptoms. The administration of remdesivir to in Covid-19 patients has diminished the mortality rate from 7% to 11% in hospitalized Covid-19

patients. Umifenovir (Arbidol) is a monocular agent, it has antiviral properties against numerous viruses such as influenza virus, rhinovirus, adenovirus and recently its anti Covid-19 activity has been determined and it is undergoing through clinical trials (Phase IV) so far. Moreover, a randomized control trial was executed in China regarding the comparison of cure ratio and the recovery ratio disparities of Covid-19 patients placed randomly in two different groups (favipiravir and umifenovir). The results of that study disclosed that the recovery ratio of patients treated by favipiravir is 61.21% while umifenovir group has 51.67% recovery ratio. It has been found that N-hydroxycytidine possesses an antiviral caliber against SARS-COV, MERS-COV and Covid-19. Therefore it is being considered for human-based trials. Table 2 explains vaccines which are in pipeline.

Antibiotic drugs

The study conducted in China has compared the post treatment viral load in different groups of patients treated by standard care, monotherapy of hydroxychloroquine and combined therapy of azithromycin with hydroxychloroquine. The results revealed the supremacy of combined therapy of azithromycin with hydroxychloroquine (100%) over standard care and monotherapy of hydroxychloroquine (57.1%). Besides, the study conducted in the USA unveiled that the combined therapy of azithromycin and hydroxychloroquine can effectively decrease the viral load and alleviates the rate of mortality. Contrarily, this therapy is not in-practice treatment due to several confines of this study and recent recommendations by NIH negate the administration of this therapy to the Covid-19 patients. It has been reported that another macrolide “carrimycin" is under a clinical trials (phase IV) at a Chinese hospital named Beijing You An hospital under the supervision of Ronghua Jin.

Antimalarial drugs

Among numerous antimalarial drugs, Chloroquine has been exhibited remarkable activity against the Covid-19. In China, 10 hospitals have been reported to conduct human-based trials of chloroquine against Covid-19 because it possesses a high value of cytotoxic concentration (CC_{50}) as well as a low value of EC_{50}. The promising results were found in that study because chloroquine had effectively prevented the Covid-19 pneumonia exacerbation and not only alleviated the duration of illness but also shrunk the viral load(84). Most probably, the activities of chloroquine against the Covid-19 virus are due to its caliber of prohibiting viral entry into the cells of the host and restrain viral fusion. On the contrary, NIH has not executed human-based clinical trials of chloroquine due to its toxicity related margins. Currently, Hydroxychloroqunie is undergoing through random controlled clinical trial (phase III) because it has emerged as a better alternative of chloroquine with less toxicity i.e. 40% and considerable activity against Covid-19. The underlying activities through which hydroxychloroquine act as an anti Covid-19 are inhibiting the viral entry into the cells and enhancing the pH level of endosomes. Thus far, no substantial results have been attained from clinical trials to recommend antimalarials (chloroquine and hydroxychloroquine) for the treatment of Covid-19 patients.

Anti Covid-19 novel small molecular drugs

The development of novel small molecular drugs with potent efficacy against Covid-19 is the need of the hour. The effective protease inhibitor "camostat mesylate” typically used in flu and pancreatitis cases, can prohibit the viral entry inside the host cells by activating the TMPRSS2 (serine protease) lysis, which correlate with the spike “S” protein of the Covid-19 virus. Unfortunately, this potential drug is not enlisted for its therapy in Covid-19 patients due to the lack of enough clinical trials and studies on it. The parenteral administration therapy of soluble ACE2 can cause cellular endocytosis blockade and lead to the amelioration of cellular level injury of lungs. The human recombinant ACE2 recognized as APN01 was developed and upon trial, it has not only diminished the expression

levels of IL6 but also improved the AN-II-associated injury of lungs. The clinical trials regarding the APN01safety and effectiveness have entered into the phase II and are being sponsored by Apeiron Biologics.

Anti Covid-19 immunomodulatory agents

The immunomodulatory agents might be proved as potent drugs to curb the Covid-19 infection and mitigate the illness and reduce the mortality rate among the Covid-19 patients. The recombinant humanized monoclonal anti-body "Tocilizumab" was previously approved for several immune-associated disorders. Recently, the study comprising on 21 patients of Covid-19 with hypoxia, worst CT results and persistent fever, was recommended tocilizumab therapy with antiviral drugs. The reported results of that study demonstrated the mitigation of fever, down-regulation of inflammatory markers, improved CT results and ultimately improved the respiratory system without any major tragedy. Therefore, numerous randomized trials are being conducted in the USA and China regarding the role of tocilizumab in Covid-19. Sarilumab, another monoclonal anti-body (human IgG1) is being assessed by a collaboration of pharmaceutical giants (Sanofi Aventis and Regeneron pharmaceuticals) in hospitalized patients of Covid-19. Similarly, anakinra is clinically used to curb the hyper-inflammatory, sepsis and auto-inflammatory disorders. Intravenous and subcutaneous both routes are feasible to administer anakinra and due to its safety and efficacy, the trials are being executed to evaluate its anti Covid-19 activities. The small molecular agents such as Janus-kinases inhibitors (ruxolitinib and baricitinib) are reported to possess a potential of attenuating the viral passage into the cells and suppressing the generation of cytokines. The trials are carried out to assess their pharmacological potential against Covid-19 infection.

Corticosteroids and interferon-α against Covid-19

The experiments and studies executed in the USA and Greece have supported the impacts of corticosteroids therapy in severe Covid-19 patients with cytokines storm (hyperactive immunity). NIH (National Institute of health) has provisioned the recommendations regarding the doses of and administration of corticosteroids in Covid-19 patients. The scientists consider that the innate immunity of Covid-19 patients can be boosted by INF-α because Covid-19 has structural similarity with SARS-CoV-1. Therefore, the clinical trials are launched in China to reveal the impacts of combined therapy of ribavirin with INF-α on Covid-19 infection. The clinical trial (Phase I) is being sponsored by the Tongji hospital to verify the INF-α2β safety in Covid-19 patients.

Traditional chinese medicines

The Chinese studies indicated that Traditional Chinese medicines (TCM) are being administered to mitigate the Covid-19 infection. The TCM against Covid-19 includes Shu Feng Jie Du and Lianhuaqingwen capsules. The Chinese tea such as perilla leaf (6g), stewedamomumtsaoko (6g) and agastache leaf (6g) are also being used against Covid-19 infection. Huoxiang Zhengqi Shui or Huoxiang Zhengqi capsules are used prophylactically to avert the Covid-19 infection.

Convalescent plasma treatment

The Covid-19 patients can be treated with the immunoglobulins present in the plasma of already recovered patients. The NIH had carried out trials in 2014 to determine the viability of plasma therapy against ARDS induced by MERS-CoV, but that project was halted due to unsatisfactory results. The impacts of this treatment have also been assessed on the Ebola virus. In the context of the Covid-19 pandemic, several clinical and experimental trials were launched for the recuperation of severe Covid-19 patients by convalescent plasma treatment, but the results were disappointing with no attenuation in the duration of illness and negligible recovery among patients. FDA suggested the administration of plasma treatment in only life threatening patients of Covid-19 due to risks associated with immunoglobulins.

Prognosis

About 40% of the hospitalized Covid-19 patients required admission in ICU, but the rate of hospital mortality among Covid-19 patients is 15%-20%. However, the rates of mortality vary in different age groups. The rate of hospital mortality is <5% among Covid-19 patients aged younger than 40 years and the Covid-19 patients aged 70-79 years have 35% hospital mortality among them. The reported figure of mortality rate due to Covid-19 is far less than actual deaths due to this virus; because Covid-19 test was not conducted of all the people who decease throughout the pandemic table III explain prophylactic measures. Currently, the long term outcome from Covid-19 infection is unknown but the critically ill patients might experience substantial sequelae. The prone to recurrent disease, cognitive damage, the physical disability is likely to be observed in people who undergone through severe infection of Covid-19.

CONCLUSION

While the Covid-19 origin is yet to be revealed, its features and characteristics are similar to the corona-viridae family, therefore classified in the 2b lineage of β-corona-virus. It can be transmitted from human to human via respiratory droplets. The respiratory system is the most vulnerable to get devastating impacts by Covid-19 infection. The mechanism through which other vital organs affected during Covid-19 infection is yet to be cleared. To eradicate this Covid-19 pandemic the early diagnosis and the timely treatment is necessary. The existing diagnostic procedures still have some confines due to slow and prolonged mechanisms. The development of effective treatment and vaccines to curb this deadly virus is urgently required. The prophylactic measures including contact tracing, quarantine, isolation and tracking can diminish the outbreak of the virus, with the effect of travel restrictions, personal hygiene, wearing masks and gloves as well as sanitizing surfaces contribute to tumble the danger of infection.

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