Review Article

Aspects of Epidemiology, Pathology, Virology, Immunology, Transmission, Prevention, Prognosis, Diagnosis, and Treatment of COVID-19 Pandemic: A Narrative Review

Abstract

Undoubtedly, COVID-19 pandemic is one of the largest pandemics and one of the biggest international challenges for health-care system of various countries in the world. This is a narrative review study based on the studies published related with different aspects of COVID-19. The highest numbers of active cases are in the USA, Brazil, India, Russia, South Africa, as well as Colombia and the disease surveillance system must operate more quickly, timely, effectively, and sensitively in these countries. What is clear is that the SARS-CoV-2 basic reproduction number is significantly higher than one and its transmission power is extremely high. In general, it can be stated that mortality and fatality risk due to COVID-19 in men, age increase, severity of disease, systemic disease, as well as inadequate access to the sufficient health-care services will increase. There is currently no specific treatment and effective vaccine for COVID-19. The novel coronavirus pandemic is more consistent with the epidemiological triangle model, which emphasizes that the disease is the result of the interaction of three factors of host, agent, and environment. Therefore, prevention and treatment activities should focus on cutting the virus transmission chain. The main way to deal with viral epidemics is prevention. The emerging of this ruthless virus has once again reminded us that communicable diseases should never be underestimated and forgotten. Considering the rapid transmission of COVID-19, the health-care authorities and workers should consider timely detection and safeguards to prevent the transmission to healthy individuals.

Keywords: *COVID-19, epidemiology, infectious, narrative review, pandemics*

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Introduction

Several people infected with an unknown and unusual pneumonia at the beginning of new year 2020 at the seafood, poultry, and live animals' market in Wuhan City (Hubei Province, China) have led to discovery and introduction of a new type of coronavirus known as SARS-CoV 2 as a cause of an acute viral respiratory disease called COVID-19.[1,2]

After the outbreak of the disease in China and its rapid transmission to other parts of the world, there was a great deal of panic among the people of various countries and the public health authorities raised concerns that for the sixth time, on 20 January, 2020, World Health Organization (WHO) announced that the appearance of the new virus is the cause of Public Health Emergency of International Concern (PHEIC) posing

a threat not only to China but also to all countries.[3,4]

The incidence and consequently prevalence of the disease is constantly increasing, so that this zoonotic coronavirus has been able to cross continental borders very quickly and become a major pandemic.

It is the third time in the last two decades that the world has been amazed by the widespread viral pandemic of the Corona family (Severe Acute Respiratory Syndrome (SARS), 2003, Middle East Respiratory Syndrome (MERS), 2012, and Coronavirus disease 2019, COVID-19).[5,6]

One might argue that the COVID-19 epidemic is one of the largest and most challenging international benchmarks for the health system in different countries worldwide. There is currently a difficult fight between COVID-19 and health-care systems in different countries. The

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emergence of this new and ruthless virus once again reminded us that communicable diseases should never be forgotten and that every moment should be ready to meet them.[7]

Medical professionals play an important role in the prevention, monitoring, care of the disease, and eventually control and suppression of the epidemic coronavirus. Nowadays, due to the emergence of the disease, one of the most important activities is carrying out various studies and researches on different aspects of this deadly virus.[5]

The research question is what is the current situation of various aspects of epidemiology, pathology, virology, immunology, transmission, prevention, prognosis, diagnosis, and treatment of pandemic novel coronavirus (COVID-19)? What progress has been made in these aspects?

Among different studies, review studies play an important role due to their broad domain and the great information that provide for their users such as authorities, managers, supervisors, and medical professionals in a short time.[8]

Therefore, the present study could open a new insight on COVID-19 by integrating and revising various sources on epidemiological, pathological, genetic, fatality, immunogenic, recovery, preventive, virulence, as well as transmission topics.

Materials and Methods

Study design and method

This is a narrative review study based on the studies published related to COVID-19 that by compiling reliable articles published in various journals, we tried to summarize and conclude on epidemiological, pathological, virological, pathogenic, genetic, original and intermediate hosts, lethality, immunogenicity, recovery, adequacy, transmission, prevention, diagnosis, as well as treatment of COVID-19.

Data collection tools and techniques

The data collection tool was a researcher-made checklist for writing the details of the articles (author, location, time, and main results). The search process for identifying the published studies was conducted by an 8-member team in a completely independent manner.

So that each researcher completely independently using the appropriate keywords searched in the databases indexing the articles related to COVID-19 and in the next step all the articles were aggregated and duplicates were removed.

Then, after reviewing the full text and remove duplicate articles by the researchers, the articles that had the inclusion criteria were evaluated and the needed information was extracted. The inclusion criteria for the articles were: a) being about one of the specialized fields of COVID-19, b) no confounding factor and selection or measurement bias affected the results of the study, and c) articles published from December 29, 2019 to August 2, 2020.

Exclusion criteria included articles that 1) had similar evidence and results and overlapping, 2) articles that only had abstracts and their full text file was not available, and 3) short report articles and letter to the editor.

Finally, 90 articles were eligible for inclusion in the study and the study was conducted on them.

Search strategies and databases

The search was conducted using the keywords "COVID-19," "2019-nCoV," "SARS-CoV-2," and "Coronavirus 2019" for literatures until August 2, 2020. All included databases were "Web of Science," "PubMed," "Scopus," "Medline," "Cochrane," "Google Scholar," BioRxiv and Medrxiv, as well as the journals with special issues about COVID-19 in subsets of "Science Direct," "BMJ," "JAMA," "Oxford," and "The Lancet." Reliable websites such as WHO, the Centers for Disease Control and Prevention (CDC), and Worldometer were used to obtain the latest statistics and information, and all statistics related to the disease were updated on August 2, 2020.

Results

History of Coronaviruses

The word "coronavirus" derives from the Latin word "corōna" or the Greek word "korωνη" meaning crown or aura, coronaviruses are important pathogens in humans and animals discovered in 1965.[9] Coronaviruses are a large family of viruses that are a subset of the Coronaviridae; these viruses often cause gastrointestinal diseases and a wide range of respiratory illnesses from common cold to more severe diseases such as pneumonia, SARS, and MERS.[10]

Viruses of the family Coronaviridae possess a single-strand, positive-sense RNA genome ranging from 26 to 32 kilobases in length.[11] Coronaviruses have been identified in several avian hosts, 2,3 as well as in various mammals,

including camels, bats, masked palm civets, mice, dogs, and cats.[12] High-potential coronaviruses have led to widespread epidemics in the human population, including SARS, MERS, and now COVID-19.

Geographical origin of the outbreak and the naming of the new coronavirus

On December 29, 2019, physicians in a hospital in Wuhan, China, noticed unusual cases of pneumonia. However, the first case of the disease was observed on December 12. Epidemiological evidence in China (at the time the author is writing the manuscript) indicates that COVID-19 originated from Huanan, the largest seafood, poultry, and live animal market located in Wuhan City, Hubei Province, in the center of China (30.6196° N 114.2576° E).[6] On January 1, 2020, the market was closed and disinfected by the local government. After a variety of speculation about the causative agent, the Chinese Center for Disease Control and Prevention finally confirmed the report by the Wall Street Journal and on January 9, 2020, the cause was announced as a new coronavirus named 2019-nCoV. On February 11, 2020, the International Committee on Taxonomy of Viruses (ICTV) renamed the virus to SARS-CoV-2. On the same day, WHO introduced COVID-19 as the official name for the new coronavirus disease.[6,13] Geographical origin of the previous animal coronavirus outbreaks that have been transmitted to humans and have caused a widespread pandemic over the past two decades have included Guangdong province of southern China (SARS) and Saudi Arabia (MERS).[13]

Public Health Emergency of International Concern

Following the extremely rapid transmission, increase of the incidence and prevalence of the disease in various countries, with the release of a statement, WHO on January 20, 2020, declared the outbreak of the new coronavirus as the sixth cause of PHEIC considered as a threat not only to China but also for all countries.[3] Before COVID-19, WHO has declared PHEIC for outbreaks of H1N1 influenza (2009), poliovirus or Poliomyelitis (2014), Ebolavirus in West Africa (2014), Zika virus (2016), as well as Ebolavirus in the Democratic Republic of Congo and Uganda (2019).[3,14]

Host

Phylogenetic analysis identified bats as the original host of the virus and another unknown animal in the Wuhan seafood market as the intermediate hosts, which have facilitated the transmission of the virus from bat to human.[15] Based on the findings of metagenomic-epidemiological researches and considering the presence of live animals in the seafood market as a major focus of zoonotic diseases, pangolins (Manis javanica), may play a role as an intermediate host in this transition.[3,16]

Virology and genome SARS-CoV-2

Coronaviruses (CoVs) are the largest group of viruses belonging to the Nidovirales order, which includes Coronaviridae, Arteriviridae, and Roniviridae families. The Coronavirinae comprise one of two subfamilies in the Coronaviridae family, with the other being the Torovirinae. The Coronavirinae are further subdivided into four groups, the alpha, beta, gamma, and delta coronaviruses. The viruses were initially sorted into these groups based on serology but are now divided by phylogenetic clustering.[17]

While viruses in the genera Alphacoronaviruses and Betacoronaviruses infect mostly mammals, the Gammacoronavirus infect avian species and members of the Deltacoronavirus genus have been found in both mammalian and avian hosts.[18]

In total, seven human coronaviruses, have been discovered including 229E and NL-63 from alpha-coronavirus as well as HKUL, OC43-SARS-MERS and most recently SARS-CoV-2 from beta-coronavirus.[1]

Coronavirus COVID-19 is an enveloped ribonucleic acid (RNA) genome with 29.8 kb. The genome of the virus contains 14 Open Reading Frame (ORF) that encodes 27 proteins. The new coronavirus genome in some areas is significantly different from the SARS coronavirus genome. For example, protein 8a is present in the SARS coronavirus; whereas it is not present in the new SARS-CoV-2 coronavirus. Phylogenetic analysis has shown that the new SARS-CoV-2 coronavirus is closely related to the two bat SARS-like coronaviruses called bat-SL-COVZC45 and bat-SL-COVZXC21 (88-89% similarity) but with the SARS coronoviruses (almost 79%) and MERS (about 50%) are less similar.[19,20]

In addition, coronaviruses that isolated from anteater have 99% nucleotide similarities with the new SARS-CoV-2 coronavirus. Therefore, it seems likely that the possibility of transmission to humans from anteater as the intermediate host is more than bats.[16] Surface spike (S) glycoproteins of coronaviruses play a key role in binding to the cell surface receptor and play a determining role in tissue orientation. Recent studies have also shown that the new SARS-CoV-2 coronavirus uses angiotensin-converting enzyme type 2 as a receptor for entry into the cell.[21]

Signs, symptoms, and pathophysiological characteristics of COVID-19

Infection with the new SARS-CoV-2 coronavirus is initially characterized by nonspecific and common symptoms such as feeling tired, fatigued and body ache, fever, and dry cough. Shortly before the fever, patients may have symptoms of nausea and diarrhea. A small number of the patients may also have headaches or hematemesis. SARS-CoV-2 coronavirus also tends to be located in the cells of the lower

respiratory tract and by proliferating in these areas will result in lesions in the lower respiratory tract.[20]

One of the first studies that examined the clinical features of the cases suffered from SARS-CoV-2 infection at Wuhan Hospital carried out by Huang and his colleagues. The study found that fever 98%, cough 76%, dyspnea 55%, muscle pain, and fatigue 44% were the most common symptoms, respectively[22]; these results are also found in other studies.[20] Unlike patients with typical coronavirus infections, upper respiratory tract symptoms such as sore throat and nasal congestion were less frequent in the patients with new coronavirus. Unlike coronavirus, SARS, gastrointestinal symptoms such as diarrhea are rarely seen in the patients with coronavirus SARS-CoV-2.[2,22] The results of a meta-analysis study on 50466 patients showed that fever (89.1%), cough (72.2%), muscle pain, or fatigue (42.5%) were the most common symptoms. Acute Respiratory Distress Syndrome and abnormal chest radiography was observed in 14.8 and 96.6 of COVID-19 cases, respectively. It was also noted that diarrhea, hemoptysis, headache, sore throat, shock and other symptoms occur only in a small number of cases.[23] Asymptomatic infections have also been identified, but their incidence is unknown. In COVID-19 outbreaks in Diamond princess cruise ship, about half of the 619 confirmed COVID-19 cases were asymptomatic at the time of diagnosis.[24] Unlike adults, children with COVID-19 have a milder clinical course.[25]

Lippi *et al.* have reviewed the results of 11 studies related to the tests of patients with COVID-19 and reported the most common abnormal results as lymphopenia (35–75% of cases), increased values of C-reactive protein (75–93% of cases), lactate dehydrogenase (27–92% of cases), erythrocyte sedimentation rate (up to 85% of cases), and D-dimer (36–43% of cases), as well as low concentrations of serum albumin (50–98% of cases) and hemoglobin (41–50%).[26]

Among the biomarkers associated with infection, procalcitonin (PCT) levels were normal in most individuals.[2,22] Similar to the findings of SARS coronavirus infection, plasma levels of proinflammatory cytokines in patients with SARS-CoV-2 increased and this increase has been associated with the severity of the disease.[22,27] However, elevated levels of interleukin-10, an anti-inflammatory cytokine, show a different pattern compared to SARS coronavirus infection.[22,28]

Although the respiratory and immune systems are the major targets of Coronavirus Disease 2019 (COVID-19), acute kidney injury and proteinuria have also been observed.

Acute kidney injury (AKI) and proteinuria in patients with COVID19 are resulted from the direct infection of the spiky crowned viruses to proximal tubules and podocytes, leading to acute tubular injury and collapsing focal segmental glomerulosclerosis.[29]

Collapsing glomerulopathy (CG) is increasingly being reported in patients with COVID-19 disease, especially, those African origin. Presence of high-risk alleles of APOL1 possibly increase the risk of development of CG in this ethnic group. These cases also raise the possibility of increased risk of developing kidney disease in such individuals in the setting of COVID-19 infection.[30]

Although the exact mechanism is not fully clarified, it is possible that the expression pattern of angiotensin-converting enzyme 2 (ACE2) can be associated with cellular susceptibility of SARS-CoV infection SARS-CoV-2 enters into cells using the ACE2 receptor and cellular transmembrane serine proteases (TMPRSSs) as a co-receptor. ACE2, as a membrane-bound aminopeptidase, is highly expressed in the lungs, heart, intestine, kidneys, and plays a fundamental role in the immune and cardiovascular systems and renal function.[31]

Pathogenicity, virulence, and fatality of COVID-19

In a report from CDC in China, which included 44,415 confirmed infections with an estimated severity of the disease, 81% were mild (without pneumonia or with mild pneumonia), 14% were severe (such as dyspnea, hypoxia, blood oxygen saturation less than 93%, or lung involvement above 50%), and 5% were critical (for instance, respiratory failure, septic shock, or multiorgan dysfunction). The average onset of the symptoms to improvement in mild cases was estimated to be two weeks and in severe cases ranged from three to six weeks. In addition, the duration between onsets of disease to severe symptoms such as hypoxia was reported to be one week.[32]

The Case Fatality Rate (CFR) was 2.3% in all cases.[33] The CFR is an indicator of the virulence and fatality of the disease and is calculated by dividing the number of deaths from a particular disease by the number of the confirmed cases of the disease multiple by 100. A carried out study in Beijing showed that 216 (82.4%) and 46 (17.6%) were severe and common cases, respectively.[34] According to the joint report of WHO and fact-finding mission in China, the mortality ranged from 5.8% in Wuhan to 0.7% in other parts of China.[32] In a meta-analysis study on 50,488 patients with COVID-19, 18.1% and 4.3% were severity cases and CFR, respectively.[23] In the study by Jung, the CFR estimated 5.3% and 8.4%, respectively, in two different scenarios.[35] Asymptomatic infections have also been identified, of all confirmed cases in China, 1% of the patients had no symptoms.[33] In Beijing, 5% of the cases were asymptomatic.[34]

Although SARS-CoV-2 can lead to severe respiratory illness like SARS and MERS, but the evidence shows that the virus is less pathogenic than SARS-CoV and much less than MERS-CoV.[4] The mortality rate of new coronaviruses is lower in comparison to SARS (9.6%)[36] and MERS

coronavirus (35.2%).[37] On the whole, the virulence and fatality of COVID-19 is lower than other coronaviruses, including SARS and MERS. A review study has stated that the epidemiological, clinical, and pathologic features of COVID-19 are very similar to SARS.[7]

Risk factors associated with disease and poor prognosis

According to a summary of the Chinese Center for Disease Control and Prevention (CCDC) report, among 44,672 COVID-19 patients, the CFR over the age of 80 years was 14.8%, 8% between the ages of 70 and 79, and no deaths in children under 9 years old. The CFR reported 49% in Critical Cases and no deaths in mild and severe cases. The CDCC report showed that people with systemic diseases are at greater risk for developing and morbidity and mortality of COVID-19. As the CFR for the patients with cardiovascular disease was 10.5%, diabetes 7.3%, chronic respiratory disease 6.3%, blood pressure 6%, and cancer 5.6%.[33] In Caramelo study, the Odds Ratio (OR) adjusted mortality rates in men was 1.85 times that of women, which is 1.85 times higher in men after adjusting for confounder factors. In this study, the OR adjusted mortality rate for COVID-19 patients who had simultaneously cardiac disease, diabetes, chronic respiratory disease, hypertension and cancers was estimated to be 12.83, 9.03, −7.79, −7.41, and 6.88, respectively. Also, in this study, with increasing age, the probability of mortality increased significantly, so that the OR adjusted from 0.2 in 20 to 29 years reached 86.86 at the age of over 80 years.[38] In the study by Li, the mortality rate reported 3.6% and zero in men and women, respectively.[39] Although children suffer from milder illness than adults, on the other hand, among patients under the age of 18, young children particularly infants were most at risk for severe COVID-19.[25]

Ruan's study also showed that mortality rate rises with age increase and cardiovascular disease. In this study, the time interval between the onset of COVID-19 and death had two peaks of 14 and 22 days.[40] The study by Zhou has shown that the risk of mortality in hospital will raise with age increase, higher SOFA (Sequential Organ Failure Assessment) score, and d-dimers greater than 1 μg/L at admission.[41] In a meta-analysis study, the number of thrombocytes in more sever patients was significantly lower than in other patients. The authors pointed out that in the studies that reported thrombocytopenia, low number of thrombocytes would increase the risk of severe COVID-19 by 5 times (OR, 5.1; 95% CI, 1.8-14.6). Subgroup analysis also found that patients with lower thrombocytes had a higher risk of mortality.[26] A study in China found that more developed areas and areas with better access to health care had lower mortality rates.[42] A study found that the risk of COVID-19 was significantly higher in individuals with blood group A and significantly lower in individuals with group O than other blood groups.[43] Overall, it can

be stated that mortality and fatality risk due to COVID-19 in men, age increase, severity of disease, systemic disease, blood group A, as well as inadequate access to sufficient health-care services will increase and clinicians should pay special attention to these patients.

Incubation period

The period of incubation in epidemiology means the interval between exposure to the pathogen and the onset of clinical signs and symptoms. This period is very important in diagnosing the type of epidemics, identifying the sources of infectivity, case detection, screening, quarantine, as well as epidemic control. Researches and international health organizations have expressed various incubation period for COVID-19 disease. WHO estimates the incubation period to be between 2-10 days[44] (and US Centers for Disease Control and Prevention has reported a period between 2 and 14 days).[45] Han estimated the mean and median of incubation period between 5.84 and 5 days, respectively, using Monte Caro simulation. They also reported that patients with age $>= 40$ had a higher incubation period than age <40.[46] In the study by Stephen *et al.*, the mean and median incubation period was 5.5 days and median incubation period until the first fever was 5.7 days, respectively, using log-normal model. They also pointed out that in 97.5% of patients, symptoms appear up to 11.5 days after the infection and for every 10,000 sufferers, 101 cases develop symptoms after 14 days of active monitoring or quarantine.[47] The mean duration of COVID-19 incubation period was longer than SARS.[48] The average of incubation period among passengers traveling from Wuhan was 6.4 and its range was 2.1 to 11.1 days.[49] A study in a dedicated hospital to COVID-19 in Beijing showed that the median incubation period was 6.7 days and the interval time between the onset of the disease and the examination by the physician was 4.5 days.[34] In the study by Guan, a very wide range of 0 to 24 days was reported for the incubation period.[50] In general, it can be stated that the range of COVID-19 incubation period is variable, with a median of approximately 5-7 days and a mean greater than median.

Transmission

The rapid spread of the virus has created a major challenge in controlling the epidemic and is one of the issues that has led to the fear of the society and the concern of the health authorities. The virus has grown exponentially in less than two months from a Wuhan outbreak to a major pandemic worldwide. Initial ways of transmitting the virus include close person-to-person transmission, transmission via droplets during cough and sneeze, transmission via aerosols, touch-contamination, and contact with contaminated objects and fomites.[4,51] At the outset of the outbreak, some patients reported having a presence on the Huanan market (as a major focus of zoonotic infections) and contact with animals; and this draw the attention to the transmission of the disease from animals to humans.[52,53] Subsequently,

human-to-human transmission through respiratory droplets and contaminated objects was confirmed by observing clusters of the virus in family members, health-care workers and people who had no previous travel in Wuhan province.[50,54] Contaminated respiratory droplets can enter the oral mucosa, eyes, nose of healthy individuals up to 3 feet directly through sneezing or coughing[51,55] or land indirectly on the objects and surfaces and enter the body through exposure to the contaminated hands and then to the mouth, nose, and eyes with the contaminated hands.[22] Newer studies have reported the possibility of virus transmission via aerosol and fomite.[56] Other ways of spreading the virus include shaking hands with infected people, constant touching of the nose, mouth, and eyes as well as hidden transmission which asymptomatic infected individuals or carriers unknowingly transmit the virus to unsuspecting contacts.[54] To date, there has been no credible evidence of vertical transmission from mother to fetus, such as MERS and SARS.[8,57] However, in some cases, the existence of the virus in the patient's feces has also been identified,[58] but whether it can be transmitted through the fecal-oral way is unclear and may be confirmed in the future. Like MERS and SARS, nosocomial transmission plays a very important role in the transmission of the disease presumed to be responsible for infection of 29% of affected health professionals and 12% of hospitalized patients in a recent study.[59] Among all confirmed cases in China, 3.8% of the patients were health personnel.[33] Most viruses are transmitted when the person has clinical symptoms, however some patients are able to transmit the infection to others before the onset of clinical symptoms and at the incubation stage.[54,60] Therefore, the exposure time to the virus to infectiousness (latent period) may be shorter than the incubation period, which is very important for transmission dynamics.[47] It was recently announced that the new Corona virus test has been repeatedly positive in a domestic dog in Hong Kong. Therefore, it is necessary to consider the possibility of transferring COVID-19 from pet to human.[61] The reported transmission rate of a person with symptomatic infection varies depending on the location and interventions of infection control in the area. Considering the speedy transmission of COVID-19, the health-care worker should consider timely detection and safeguards to prevent the transmission of the virus to healthy individuals.

Infectivity

Basic reproduction number or R0 in epidemiology means the average number of at-risk and susceptible (unsafe) people who can be infected by a contagious person. This indicator indicates the virulence and viral transmissibility, which is influenced by the duration of infectivity, the transmissibility of the pathogen, and the number of susceptible contact; if R0 (pronounced "R naught") is smaller than one, it means that each patient will be less likely to be ill than another; in this situation, the epidemic

goes into extinction. Second, if R0 is equal to one, each patient will develop a new case; in these conditions, the disease is moving toward stability; in the third and worst case, if R0 is higher than one, each person will have one person affected. In this case, the prevalence will increase exponentially; and the disease will turn from a low-level outbreak in a small geographic area to an epidemic of over-expectations in a wider area, and eventually a pandemic with many occurrences throughout the world.

Different R0 values are currently reported for SARS-CoV-2. WHO reported it between 1.4 and 2.5; Zhao *et al.* between 3.5 and 5.5; J. Read *et al.* between 3.6, and 4 and M. Shen *et al.* between 4.5 and 4.9.[62-64]

Chen presents the range of these estimates (1.4 to 5.5), along with estimates of the CFR and R0 values of several other known emerging viruses.[4] WHO and CDC have clearly indicated that airborne viruses tend to have a higher R0 than contact spread. Viruses or subgroups of a particular virus that have higher pathogenicity are also less transmissible. A good example of this is the influenza virus, while pandemic H1N1 virus binds to upper respiratory receptors and is transmitted rapidly but they cause mild illness; while the H7N9 virus binds to the lower respiratory tract receptors, they are less transmitted but have higher fatality.[4]

Different R0 values are currently reported for SARS-CoV-2. WHO reported it between 1.4 and 2.5; Zhao *et al.* between 3.5 and 5.5; J. Read *et al.* between 3.6 and 4, and M. Shen *et al.* between 4.5 and 4.9.[62-64] Liu *et al.* reviewed the results of 12 studies on R0 in a review study and the results showed that it ranged from 1.4 to 6.49, with a mean of 3.28, a median of 2.79 and IQR of 1.16. They conclude that R0 COVID-19 is higher than SARS.[65] So, what is clear is that the SARS-CoV-2 basic reproduction number is significantly higher than one and its transmission power is extremely high.

Aerosol and surface stability of SARS-CoV-2

Survival of the virus in the environment is one of the key criteria for making health interventions such as disinfection, wearing masks and gloves, observing the minimum distance between people and other interventions to cut the virus transmission chain. In this regard, Neeltje *et al.* designed a study in which the half-life of the virus was evaluated by Bayesian regression model analysis in five different environmental conditions. Median and 95% confidence interval half-life of SARS-CoV-2 in aerosols equal to 1.9 hours (CI 95% 0.64-2.64), on copper 0.774 hours (CI 95% 0.427-1.19), on cardboard 3.46 hours (CI 95% 2.3-5.5), on steel 5.63 hours (CI 95% 4.59-6.86), and on plastic 6.81 hours (CI 95% 5.62-8.17). Therefore, the highest virus viability is seen on the plastic and the lowest in the copper. The results also showed that median lifetime in SARS-CoV-2 and SARS-CoV-1 viruses were almost

identical in plastic, copper, and aerosol environments, but SARS-CoV-2 survives 2.85 and 1.46 hours longer in the cardboard and steel environments, respectively.[56]

Therefore, the epidemiological differences between these two diseases are probably due to other factors, such as high load of virus in the upper respiratory tract and the potential ability of asymptomatic patients to spread the virus in COVID-19. There is still no evidence of the presence of COVID-19 in surface and groundwater resources, sewage or their transmission through contaminated drinking water. Thus, the results of recent studies suggest that the COVID-19 coronavirus may survive on the surfaces for several hours to several days and be transmitted to humans. Survival time of the virus varies on the surfaces and depends on various factors such as surface type, temperature or environmental humidity, and other factors.

Age and sex distribution of the patients

Age and sex distribution are very important in planning and performing preventive and therapeutic interventions such as quarantine, isolation, hospital beds, school and university closures, risk factor research, and epidemic resource factors. The age distribution of novel coronavirus cases is relatively different from that of influenza. In all studies, very few cases, especially serious or fatal child cases, have been reported in children. In Japan, 55% were men. The highest frequency was reported in the age group of 20-59 years old and the lowest was in the age group of less than 19 years old. In this study, the lowest attack rate (AR) was found in the 0-19 age group with 7.2% in men and 3.8% in women; on the other hand, the highest AR in the age group of 50-59 years was 22.2% and 21.9% for men and women, respectively.[66] According to the CDCC, 44762 cases were found to have the lowest number of cases, with 38680 (87%) between the ages of 30 and 79 years and the least under 10 years with 416 (1%).[33] In the study by Shi, 52% of men had a mean age of 49.5 years old (SD = 0.11).[67] In a study in Beijing, the median age of the patients was 47.5 years old.[33] In the study carried out by Sun, 55% of the patients were men, median age was 46 years old (IQR 35-60), and only 3% were younger than 15 years old. In this study, the relative risk (RR) of COVID-19 was found to be 0.5 (Low risk) in children under 15 years old and higher than 1 (High risk) after age 30 years old.[68]

Undoubtedly, gender-related behavioral factors, such as higher amounts of smoking, alcohol consumption, and biological differences in immune systems could make males more vulnerable. The role of androgen-responsive elements (AREs) of transmembrane serine proteases type II (TMPRSS2) gene as one of the major players of male dominancy in severe COVID-19 infection has been under appreciated and needs to be clarified.[69]

Morbidity, mortality and recovery of patients

The latest statistics on the incidence, mortality, and recovery of COVID-19 worldwide updated on the Worldometer website on August 2, 2020 show the total number of cases is 18,026,721 out of which 6,002,752 are active cases that 5,937,000 (99%) and 65,752 (1%) of whom were mild and serious or critical, respectively. On the other hand, 12,023,969 of the total cases are Closed cases, of which 11,334,985 (94%) have recovered and have been discharged and 688,984 (6%) have died.

A review of the daily trend of new cases showed an increasing trend from January 22 to February 13, followed by a decreasing trend from February 13 to February 23 and then to May 13 due to the involvement of most countries around the world it has undergone a significant upward trend. On February 2, the recovery rate was 58.2% and the death rate was 41.8%, but on August 2, they reached 94.27% and 5.73%, respectively. By examining the values of these indicators and considering the increase in recovery and reduction of mortality, it can be said that over time, our knowledge has gradually increased from various dimensions of COVID-19 disease, which has led to promoting the health-care system in different countries.

According to data taken from the Worldometer website (which uses updated WHO data), 10 countries with the highest numbers of confirmed cases are USA, Brazil, India, Russia, South Africa, Mexico, Peru, Chili, Spain and Iran, respectively. However, the number of the cases per 1 million is seen in Qatar (39501), French Guiana (26,253), Bahrain (20,597), San Marino (20,950), Chile (18,836), and Kuwait (15,221), respectively.

These results show that after Southeast Asia, Europe, and North America have become the second and third major hotspot (High Risk Clusters) for the disease, respectively.

The highest recoveries were seen in USA, Brazil, India, Russia, South Africa, Chili, Peru, Mexico, and Iran, respectively. But the results of percentages recovered that obtained by dividing the number of recovered cases by the number of confirmed cases showed the highest percentages recovered in Qatar (97%), China (94%), Turkey (93%), Chile (92%), Germany (91%), Switzerland (88%), South Korea (87%), Pakistan (89%), Iran (86%), Turkey (80%), and Denmark (79%). It indicates the provision of appropriate health care to patients and their ability to detect and treat patients early. The highest number of active cases are in the USA, Brazil, India, Russia, South Africa, Colombia and the disease surveillance system must operate more quickly, timely, effectively, and sensitively in these countries.

Diagnosis

In the event of an emergency, the number of cases is rapidly increasing. Therefore, accurate detection of all suspected

cases as soon as possible and their rapid removal are crucial for discontinuing the source of infection. The diagnosis of COVID-19 relies on a narrative review of radiological, laboratory, clinical, and epidemiological findings. Reverse transcription polymerase chain reaction (RT-PCR) tests are used as standard gold, but their false negative numbers are considerable.[70] The US CDC notes that screening and case finding should primarily be based on the most common clinical symptoms (fever, dry cough, shortness of breath) and epidemiological evidence such as travel in the last 14 days to high-risk locations, contact with patients with COVID-19, and attendance at crowded health-care services centers, thereafter, if a person is suspected of having the disease, he or she is referred for confirmatory diagnostic tests such as pathological and radiographic examinations.

Conventional experimental methods such as assaying antiviral antibodies or viral antigens as well as new diagnostic techniques such as real-time RT-PCR and CT-SCAN can be used to detect SARS-CoV-2. Nucleic acids of novel coronavirus-2019 are detectable in samples including nasopharyngeal and oropharyngeal swabs, sputum, lower respiratory tract secretions, blood, and feces. Nasopharyngeal swabs are the most common type.[71] Diagnostic confirmatory testing is based on RNA detection using Reverse Transcribed Real-Time PCR (RT-PCR) that identifies the ribonucleic acid genome of the virus. Typically, the region identified by this technique comprises the RNA dependent RNA polymerase (RdRP) region along with other regions such as the E or N genomic regions.[71,72]

Currently, the detection method for SARS-CoV-2 is based on viral RNA detection using Reverse Transcribed Real-Time PCR (RT-PCR). WHO initially distributed the guideline for confirming COVID-19, based on RNA dependent RNA polymerase (RdRP) viral RNA gene detecting RT-PCR method. 3 Accordingly, Korea Centers for Disease Control & Prevention (KCDC) has used confirmatory RT-PCR based on RdRP gene. On the other hand, US CDC recommended to use SARS-CoV-2 nucleocapsid protein (N) genes instead of RdRP gene as a confirmatory test.[73]

A positive RT-PCR test confirms the detection of COVID-19. If the initial test is negative but suspicion of COVID-19 persists, WHO recommends that the test be repeated from multiple respiratory tract sections and re-tested.[74] Negative RT-PCR tests on oral-pharyngeal swabs have been reported in some patients despite CT findings of viral pneumonia that finally, they tested positive for SARS-CoV-2.[75] The collection of respiratory specimens should be subject to the necessary precautions for the risk of airborne transmission. For safety reasons, suspected or documented COVID-19 patient samples should not be sent for viral culture.

A prominent feature of radiological imaging in patients with severe coronavirus pneumonia (ground glass opacity) includes opaque vitreous with or without consolidation that can affect both lungs.[76] Chest involvement is most likely bilateral, with peripheral distribution and involving the lower lobes. Less common findings include pleural thickening, pleural effusion, and lymphadenopathy.[77]

Since negative testing in the incubation period is not ruled out and the influx of people to the hospital for testing may even increase the prevalence of the disease, testing in asymptomatic or mildly ill patients is not recommended.

Prevention

The main way to deal with viral epidemics is prevention. Now, the slogan of prevention is better than cure more must be done than ever. Due to the lack of standard treatment and effective vaccines for the new coronavirus, the best way in the current situation is to prevent the disease, eliminate the major sources of infection and carry out the principles and rules of public health. In this regard, one of the most important things to do is to reverse quarantine by keeping healthy people in their homes until the virus transmission chain is cut off. In general, the following actions are recommended to reduce or prevent transmission of COVID-19 to others[5,20]

Rinse hands thoroughly with soap and water for at least 20 seconds, especially after direct contact with patients or their traffic environment, after going to the public toilet, before consuming foods and drinks, after sneezing and coughing, after leaving a crowded place like hospitals or health centers, alcohol-based hand sanitizers (contains at least 70% alcohol) can be used before entering home in the absence of soap and water. Unwashed hands should not contact the eyes, nose, or mouth.

Cough etiquette by covering the cough; it means that during sneezing and coughing, the mouth and nose should be covered with arms or paper towels. If you are using a napkin or cloth, they should be discarded immediately and hands washed. If you do not have access to the napkin at the moment of sneezing, turn your head over your arms to prevent the virus from spreading to the environment. According to WHO, healthy people will only need a mask when they are caring for a sick or suspected person. But people with symptoms such as cough and sneezing are advised to use appropriate masks such as N95. Masks are only effective when the individuals do not forget to wash hands with soap and water or alcohol-containing hand sanitizers. Healthy people who do not have respiratory symptoms such as cough do not need to wear medical masks. The hands should be rinsed well with the mentioned cleaners before covering masks. The mask should then be worn over the mouth and nose so that there is no gap between the face and the mask. Touching should be avoided when using the masks. If the mask gets wet and damp, it should be replaced. To remove the mask, act from behind and there should be no contact with the front of

the mask at all. The applied mask should then be placed in a waste bin with door and hands should be immediately washed with soap and water.

For drying hands, personal towels, paper towels or an automatic dryer should be used to prevent the virus from spreading to others. The automatic dryer is not capable of removing viruses alone. Cleaning with soap and water or other detergents should be a priority before disinfecting with alcohol. The cleaning person needs to justify to disinfect all parts including office, toilets, and public places used by the patient, especially surfaces that are often touched (dining table, doorbell, lighting switches, handles, the chair apron, desk, toilet, sanitary taps).

UV lamps should not be used to sterilize hands or other areas of the skin. If you use UV lamps, serious damage to the skin will occur.

Quarantine and traffic control of cities that are candidates for quarantine, such as cities that new cases have recently diagnosed there, and act as the major hubs for viruses and hotspots but there are fewer cases in other cities and regions of the country. Appropriate disinfectants can be used to eliminate the virus at various levels.

Travel history is important for early detection and isolation of cases of coronavirus pneumonia. One of the first steps in this situation is not to travel to epidemic areas. People who have traveled to an epidemic area during the last 14 days should be followed up for 14 days and if the symptoms were observed, they should be isolated and the diagnosis and treatment actions should be implemented as soon as possible.

Patients who have tested positive should be isolated (preferably an isolated negative pressure room or otherwise a separate ventilated one). If the symptoms improve after 24 hours and the result of two consecutive tests is negative, the individual can leave the isolated room.

Coronavirus-infected corpses should be buried in deeper parts of the earth in full compliance with environmental health principles. The body should be worn to carry the body and it is essential that people use all personal protective equipment. The outer surface of the deceased bag should be disinfected.

Due to the transmission of different coronaviruses from animals to humans and to prevent this transmission, direct contact with the animals on the market and the surfaces in contact with these animals should be avoided. Raw or semi-cooked animal products should also be avoided. Reducing the stress and anxiety of the patients to improve their immune system can be effective in controlling COVID-19 infections.

Avoiding close and direct contact with people with acute respiratory infections and avoiding unprotected contact with pets and wild animals is important. To prevent infection, healthy people should be at least 1-2 meters away from the person with respiratory symptoms. In addition to the preventive and control actions mentioned above, more precautionary actions are needed in relation to high-risk occupations such as health workers, treatment personnel, and coronavirus diagnosis laboratory centers. Especially, health and screening, emergency, infectious and laboratory staff should wear all personal protective equipment during providing health care. In case of exposure to blood or body fluids of the patients should wash the exposed part with soap and water. Necessary trainings should be done to select the appropriate equipment, its proper use as well as correct removal. Using the model of Traffic Control Bundling (TCB) is suggested to reduce the risk of personnel in health centers.[74] Long hours of work, inappropriate hand cleanliness after contact with the patients, and activity in high-risk wards (intensive care unit, surgical and infectious wards, and respiratory diseases) are associated with the risk of COVID-19.

Treatment and immunogenicity

Under normal conditions, doing various stages of clinical trials and eventually producing new drugs is a very long process; however, in epidemic conditions, scientists have less time because of the rapid growth of diseases and should treat patients as quickly as possible. Therefore, a systematic and extensive screening of available drugs for efficacy in the treatment of COVID-19 can be used. Due to severe pulmonary damage of SARS and MERS coronavirus infection, mortality rate in infected patients and requiring mechanical ventilation (artificial respiration) was very high.[78] There is no specific antiviral drug for the treatment of coronavirus at the time of writing this manuscript and the main strategy is supportive care, such as maintaining vital signs, regulating oxygen and blood pressure, and reducing complications such as secondary infections or organ failure. The previous studies have shown that a combination of protease inhibitors and lopinavir and ritonavir drugs significantly improve the status of patients with SARS. In addition, the results of *in vitro* and *in vivo* laboratory studies indicate that a combination of lopinavir, ritonavir, and interferon beta may be effective against MERS coronavirus.[79,80]

To this end, recent drug screening has shown that nelfinavir has potential antiviral activity against the new coronavirus. In addition, perampanel, pitavastatin, and praziquantel also have moderate efficacy against modern coronavirus.[81] According to previous studies, an anti-HIV drug called Kaletra, which has had therapeutic effects on SARS and MERS, has recently been recommended by the National Health Commission of the People's Republic of China for the treatment of COVID-19 pneumonia. Other drugs, including ribavirin, interferon, and corticosteroids, used for patients with SARS and MERS, have also been suggested for COVID-19; however, the efficacy of these drugs has

not yet been fully proven and is being evaluated more closely.[79,82,83]

A study conducted in South Korea on a patient with COVID-19 showed that taking lopinavir and ritonavir reduced the titre of the virus and improved the patient's condition.[84] Adenosine nucleoside analogue Remdesivir with extensive antiviral activity against multiple RNA viruses may also be effective in patients with novel coronavirus.[85] The trial drug is a nucleotide analog made by the pharmaceutical company of "Gilead Sciences." This drug, not yet approved by the Food and Drug Administration (FDA), was a multiple antiviral drug made against Ebola and SARS viruses. The efficacy of this drug on the new SARS-CoV-2 coronavirus is currently under investigation.[20] For example, the use of this drug in a patient with COVID-19 coronavirus in the United States has reduced the viral load in nasopharyngeal and oropharyngeal specimens and improved the clinical status of this patient. However, different clinical trials are needed to determine the safety and efficacy of this drug for the treatment of patients with COVID-19 infection.[58] Plasma therapy can be referred to as another treatment strategy. In this method, the plasma of individuals recovered from COVID-19 disease is extracted and used for passive immunization.[20] The Fifth Edition of Infectious Diseases Prevention and Control (IPC) stated that patients with severe and critical illnesses can be treated with recovery plasma.[58]

Recent studies have shown that viral polymerase may be a suitable template for the design of new antiviral drugs to prevent SARS coronavirus replication.[86] Because of the similarity of the nucleotide sequence of the new coronavirus to that of the SARS coronavirus, this information could be very useful in the development of new drugs against the new coronavirus.[20] Chloroquine phosphate is another drug that has shown good results against new coronavirus pneumonia in clinical trials in China. It is used to prevent and treat malaria and is used as an anti-inflammatory agent to treat rheumatoid arthritis and lupus erythematosus.[87] According to recent reports, more than 85% of patients have received antiviral medications, including oseltamivir (75 mg every 12 hours orally), Ganciclovir (0.25 g every 12 hours intravenously), and lopinavir/ritonavir (400/100 mg twice daily orally).[2,88,89] An angiotensin-converting enzyme 2 (ACE2)-based peptide based on the 3CLpro-1 inhibitor and a new vinyl sulfone proteinase inhibitor, in theory, appear to have potential for antiviral activity against novel coronavirus-19.[90] Lu has proposed that in addition to antiviral and antibiotic interactions, neuraminidase inhibitors, RNA synthesis inhibitors, and traditional Chinese medicine can also be used in the treatment of COVID-19. However, clinical trials are still needed to confirm the efficacy of these drugs.[91] Recently, the combination of hydroxychloroquine and azithromycin has been recognized as an effective treatment for the patients with COVID-19.[92]

A study in China reported 25 positive cases of RT-PCR of COVID-19 with quarantine after discharge from the hospital with a negative test. According to the study, patients were tested positive for COVID-19 mRNA again 3 days after discharge and 6 days after the last negative test. All patients (100%) were asymptomatic, 12 patients with improved CT scan findings, and 13 patients with no change in CT scan findings were reported. The findings of this study suggest permanent no immunogenicity and the possibility of recurrence of the disease.[93]

Although no antiviral therapy for COVID-19 has been approved, however many trials are processing to introduce the best effective treatment. Now, for the patient, some supportive cares like oxygen therapy and inhibition of septic shock are critical actions to manage the disease; nevertheless, there are several studies proposing the combination of chloroquine (500 mg), lopinavir/ritonavir (400/100 mg), and hydroxychloroquine (200 mg) as the most effective treatment.[94,95] Also, inhibition of severe immune response, e.g., tocilizumab, a monoclonal antibody against interleukin-6 and mesenchymal stem cells or their derived extracellular vesicles are reported for reduction of severe manifestations.[94,96,97] Convalescent plasma containing anti coronavirus antibodies can improve the clinical features of severe patients and should be considered as the promising treatment of COVID-19.[98-100]

Conclusion

Undoubtedly, COVID-19 pandemic is one of the largest pandemics and one of the most international challenges for the health-care system of various countries in the world. The emerging of this ruthless virus has once again reminded us that communicable diseases should never be underestimated and forgotten. China's experience shows that COVID-19 can be restricted if general health strategies and tactics are implemented in response to the outbreak in the early stages. To combat the spread of coronavirus, WHO Secretary-General has asked that anyone with a suspicion of coronavirus be tested to identify those infected with the virus as soon as possible. There is currently no specific treatment and effective vaccine for this disease and the best action is to emphasize different aspects of prevention as a way to get rid of these conditions. Now, the slogan of prevention is better than cure more must be done than ever. The coronavirus pandemic is more consistent with the epidemiological triangle model, which emphasizes that the disease is the result of the interaction of three factors of host, agent, and environment. Therefore, prevention and treatment activities should focus on cutting the virus transmission chain. Some actions such as health education and using mass media influence, observing all individual, public and environmental health principles, adequate planning and management of health-care services, proper nutrition, promoting of mental health and reducing fear and anxiety of the people, decreasing social gatherings

and communication, government financial support to encourage individuals to stay home, closure and continuous disinfection of public and high traffic places like subways, cinemas, stadiums, universities, etc., traffic control and screening at city entrances, patient detection and early diagnosis, suitable reporting system, quarantine and timely isolation, treatment support for epidemic control and silence, is recommended.

Ethics statement

This article is based on the results of Research project in Shahid Beheshti University of Medical Sciences (IR. SBMU.PHNS.REC.1399.027).

Authors' contribution

SRP, SS, AHD: Substantial contributions to the conception, design of the work, acquisition, analysis, and interpretation of data for the work; SRP, AHD, SS, MHV,HA, ZKh, EG, EM, DB, MR, HN: Drafting the work and revising it critically for important intellectual content; and all of the authors: Final approval of the version to be published; and all of the authors: Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflicts of interest

There are no conflicts of interest.

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