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An Update and Comprehensive Review on SARS-COV-2/COVID-19: Prevailing Public Health Concern

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Abstract: The emergence of SARS-CoV-2 has been marked as the third introduction of a highly pathogenic coronavirus. Even though the epicenter of infection was Wuhan, China, this pandemic has reached 67 367 046 total cases, 1 545 331 deaths, as of December 8, 2020. In response to this pandemic, we are providing detailed and up to date review which may help to offer insight on the general features of COVID-19 and countermeasures. This review identified, analyzed and discussed scientific papers published on different journals and web sites by using Google Scholar, Pubmed, bioRxiv and medRx search engine. Appropriate terms "COVID-19, 2019-NCOV, SARS-COV-2 and Coronavirus were used to screen articles for better retrieval. A review of identified articles was done by authors and finally compiled to give a complete picture of Covid-19. SARS-CoV-2 is highly contagious and has resulted in a rapid pandemic of COVID-19 affected mainland china and then distributed to all continents except Antarctica. Older peoples and patients with comorbidities like hypertension, diabetes, cardiovascular disease, chronic respiratory disease and cancer mostly require intensive care supports. At present, there is no on-hand therapeutics and but vaccine trials are promising. Tackling of this pandemic requires a long-term plan and collaborative efforts of scientists, authorities and the general public.

Key words: Covid-19 · Epidemiology · Pandemic · Pneumonia · Sars-Cov-2

INTRODUCTION

Emerging and re-emerging diseases are representing a significant threat to global health, as confirmed with several outbreaks over the past years and 75% of them are zoonotic [1]. Previously Coronavirus was not known to be pathogenic enough. Nevertheless, in 2002, *SARS-CoV* in China [2] and Ten years later, *MERS-CoV* in Saudi Arabia was emerged [3]. Again in 2019, an eruption of clusters of pneumonia that could be associated with the seafood market in Wuhan, China occurred. On 12th Jan 2020 China shared the genetic sequence of the new coronavirus which did not match any other known virus and the disease now officially called "the Corona Virus Disease 2019; COVID-19" [4].

Clinical manifestations of COVID-19 vary from asymptomatic to severe pneumonia that could lead to death. Around 80% of cases are mild respiratory infection, severe cases and deaths are more common in elder and peoples with an underline disease condition. Cytokine storm is linked with a rampant inflammatory response to SARS-CoV-2 infection is considered as the leading killer of COVID-19 patients. COVID-19 patients were reported with higher levels of many pro-inflammatory cytokines and chemokines. Blood profile of the COVID-19 patients exhibits lymphopenia, leucopenia, thrombocytopenia and RNAaemia along with increased levels of aspartate aminotransferase [5].

COVID-19 has spread globally and the numbers of cases are rising as a second wave in different regions of the world in such a way that this pandemic could bring disastrous health impacts and worldwide economic collapse. Therefore, keeping in view the importance of the disease, the current comprehensive review was done to provide updated information on epidemiological, immunological, clinical features, diagnosis, management and prevention of COVID-19 there by paving a way to adopt the control measures against this pandemic.

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MATERIALS AND METHODS

Design: We have undertaken a literature review of articles published on Covid-19 from December 30, 2019, to December 8, 2020. Even though numerous researches are undergoing and publications are available, there is a paucity of information on the overall aspects of the disease. This comprehensive review was compiled to provide the general features of the disease.

Search Method: iterature for review was identified by searching the following database; Google Scholar, PubMed, bioRxiv and Science direct. These online databases contain archives of English journals and supplemented by other papers from different institutions, international organizations and academic websites. We searched scientific publications by employing the terms "COVID-19, 2019-NCOV, SARS-COV-2 and Coronavirus. All researchers searched the literature independently and then compared and sorted out. Our exclusion and inclusion criteria were flexible by considering the scope of our review from mini-review to meta-analysis. Accordingly, our review included 34 original articles, 13 narrative reviews and 3 mini-reviews and 8 were on the preprint server.

Data Extraction and Review: Based on the intensive literature search, a total of 130 pieces of literature that report Covid-19/SARS-COV-2 were retrieved. However, we identified and screened 58 relevant scientific publications and articles by relaying on the reliability of the data, heterogeneity of the information and reputability of that journals. Our review write-up was classified into different descriptive titles and sub-titles. All findings and statements that are mentioned regarding the outbreak in this review are based on published information as listed in the references.

RESULTS

Virological Profiles and Phylogenetic Analysis: Coronaviruses are enveloped, positive-sense, single-stranded RNA virus belonging to the Coronaviridae families that are zoonotic. Currently, there are six coronaviruses in humans. *SARS-COV* and MERS-COV have occurred as a pandemic in the previous two decades the rest were present within the different communities as a self-limiting and mild respiratory syndrome of the common cold [7].

The spike protein [S] is the major determinant of cell tropism and hence interspecies transmission of CoVs since it binds the virus to a cellular receptor and subsequently catalyzes virus entry by membrane fusion. Transmembrane protein with an N terminal cleavable signal peptide, one large and heavily N-glycosylated ectodomain, a transmembrane region and a cytoplasmic tail containing a cluster of S-acylated cysteine residues, N terminal domain [NTD] and a C terminal domain [CTD]. The NTD exhibits a structural fold as human galectins, galactose-binding lectins and hence, in most CoVs, a sugar present at the cell surface serves as an attachment factor. The CTD is responsible for binding to the host receptor angiotensin-converting enzyme 2 [ACE2] in the case of *SARS-CoV* and 2019-nCoV [8, 9].

Sequence analysis indicated that 2019-nCoV was far from *SARS-CoV* and *MERS-CoV* about 79 and 50% sequence identity from two bat-derived SARS-like coronaviruses-bat-SL-CoVZC45 and bat-SL-CoVZXC21 with 87 and 87.23% respectively [10]. Besides, other data indicated the high-level homology of the ACE2 receptor of bat origin with that of COVID-19 and the presence of a single intact open reading frame on gene 8, which is a further indicator of bat-origin CoVs [11]. Moreover, Pangolins are considered as the likely intermediate animals as a genetic sequence analysis showed a 99% identity from infected animals and humans [12].

Epidemiologic Features

Sources and Spread: In late 2019, a cluster of pneumonia of unidentified causes with people associated with the seafood market has occurred in Wuhan city, China. Soon, the spread of the disease indicated that the source of infection and transmission was to be human-to-human because there was an increase in cases on people with no history of contact with wildlife and visits among health workers [4]. As of December 8, 2020, the WHO has confirmed, COVID-19 is affecting territories around the world and has reached 67 367 046 total cases, 1 545 331 deaths [6].

Transmission, Reproduction and Fatality Rate: An early source of infection was related to the exposure of humans to animals at the seafood market in Wuhan. Genomic sequence similarity revealed 88% association with bat sourced SARS [13], with mammals being the most probable intermediate animal. The latest guidance from the Chinese health authorities identified the three main transmission routes. Transmission between human is

stated to occur when infected droplets are swallowed or inhaled by nearby individuals causing disease when inhalant reaches lung; aerosol transmission may occur when respiratory droplets get aerosolized and inhaled by the susceptible person and contact transmission occurs when surfaces are exposed to contamination and a person comes in contact and subsequently touches their mucosal exposed parts of the face [14]. Since researchers identified that GIT have ACE2 expression in their absorptive cell of the intestine, the fecal-oral transmission could be possible from a patient with gastro-intestinal manifestations [15].

Moreover, a study undertaken on 18 infected individuals showed that asymptomatic person can be infectious for the susceptible person who was evidenced by the presence of equivalent viral load in both patients [16]. Transmission from the asymptomatic individual was identified in a family of five patients hospitalized with fever and respiratory symptoms who had been in contact with symptomatic family member, a young 20-year-old woman, on her return from Wuhan [17].

In regards to the reproduction rate, the result of one meta-analysis pointed out the basic reproduction rate of SARS-COV-2 at 3.11 [2.49-3.71] persons [one person is likely to infect two to three persons in the absence of any control measures] [18]. In contrast, the reproductive rate of *SARS-CoV* and *MERS-CoV* was below 1 and 1.4-2.5. This implies the contagiousness of *SARS-COV-2* is even greater to can cause a devastating pandemic if not controlled timely and if current infection shouldn't be managed and stopped below R_o<1. The case fatality rate was 10% of 8000 total infections and 34.5% of 2465 total infection for *SARS-CoV* and *MERS-CoV* respectively. In comparison fatality rate for COVID-19 is 2.56 [2.06-3.05] percent after accounting for heterogeneity among studies, using the random-effects model, though the numbers of cases are increasing to an unpredictable percentage [19].

Possible Risk Factors: Population categories that have been more commonly reported to have serious illness and death include elderly individuals, males and people with comorbidities like, diabetes, cardiovascular disease, hepatic disease, urinary and chronic diseases like cancer [20, 21]. Increased susceptibility to *SARS-COV-2* could be related to the high expression of ACE2 [angiotensin-converting enzyme II]. Age, tobacco use and hypertensive treatment could likely be factors for expression ACE2 in the lung tissues. This implies an older person, tobacco-user and those with hypertension are potentially susceptible to COVID-19 [22, 23].

Regarding blood group, an association study was done on 1, 775 COVID-19 patients from Wuhan Jinyintan Hospital, the proportion of blood groups A and O in COVID-19 patients were significantly higher and lower, respectively [24]. Pregnant women are showing almost similar clinical features as non-pregnant women patients and there is no proof of severe outcomes in neonates due to maternal COVID-19 pneumonia and the virus has not been found in milk [25, 26].

Immune Response and Evasion Mechanisms: During infection of coronavirus, viral RNA is recognized by the endosomal receptor and followed by nuclear translocation. Within the nuclei interferon, I and other pro-inflammatory cytokines will be expressed through the stimulation of transcriptional factors, leading the defense against viral entry [27]. Again a lesson from other betacoronavirus points out that, there was an increased influx of neutrophils and macrophages. Delayed type IFN is induced by down-regulating signaling by STAT1 phosphorylation and which compromises early phase viral control [28]. But later, active viral replication results in hyper-production type I IFN and increased influx of neutrophils and macrophages which are the major sources of pro-inflammatory cytokines. This abrupt increase in innate immune cells and cytokines leads to deleterious systemic inflammations and multi-organ failure [28].

For both *SARS-CoV* and *MERS-CoV* and even for *SARS-CoV-2*, delayed and weak humoral responses are linked with severe and poor outcomes. Some studies evidenced that, Th1-mediated response is crucial in the control of COVID-19 [29]. In a preliminary study, one patient showed peak specific IgM at day 9 after disease onset and the switching to IgG by week 2.25 interestingly, sera from 5 patients of confirmed COVID-19 shows some cross-reactivity with *SARS-CoV*, but not another coronavirus [30].

Coronaviruses are likely to have a long incubation period around 2-14, this partly explains how they are adapted to evade the human immune system [31]. Since they are a member of betacoronavirus, the mechanism of immune evasion is similar to *SARS-CoV* and *MERS-CoV*. This could relay on the overwhelming of innate immunity, particularly interferon I recognition and signaling. The viral proteins including membrane [M] or non-structural [NS] proteins are the key molecules in host immune modulation [32]. In the case of acquired immune inhibition, they down-regulate the expression of MHC class I and MHC class II whenever coronavirus infect

macrophages or dendritic cells that could inhibit T cell activation [33]. Viral persistence within the body aggravates the inflammatory process that could lead to immune exhaustion [34].

Pathogenesis and Clinical Phenotypes: Even though the pathogenesis of COVID-19 is not well investigated, a lesson from *SARS-CoV* and *MERS-CoV* can give us ample information on the pathogenesis of *SARS-CoV-2* [35]. The main pathogenic effects of COVID-19 are severe pneumonia and cardiovascular impairment [36]. A study undertaken on 41 patients indicate that there is a high amount of pro-inflammatory cytokines like IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1A and TnFa were observed in severe cases of the COVID-19. The main cause of death from Covid-19 is Cytokine storm; uncontrolled and violent systemic inflammatory attack by the immune system to the body resulting from the release of large amounts of pro-inflammatory cytokines [IFN-g, IL-1b, IL-6, IL-12, TNF-a and TGF-b] and chemokines [CCL2, CCL3, CCL5, CXCL9, CXCL10] cause Acute Respiratory Disease Syndrome and Multiple Organ Failure finally lead to Death [37-39].

The clinical exhibition of COVID-19 ranges of asymptomatic to multiorgan failure [11]. Studies indicated that the average incubation period of COVID-19, which vary from 2-14 days. Chinas CDC showed that 80.9% of cases were mild. Severe illness and critical cases were 13.8 and 4.7% respectively [40]. Mild illnesses are manifested by dry cough, mild fever, sore throat, mild headache and malaise. Moderate cases are presented by productive cough, high fever, shortness of breath and tachypnea. Severe cases are cases with severe pneumonia, acute respiratory distress syndrome [ARDS], sepsis, or septic shock. However small percent, 5% of patients are critical cases with respiratory failure, RNAaemia, cardiac injury, septic shock, or multiple organ dysfunctions [11].

Patients with preexisting comorbidities have a higher case fatality rate. These comorbidities include diabetes [7.3%], respiratory disease [6.5%], cardiovascular disease [10.5%], hypertension [6%] and oncological complications [5.6%]. The development of ARDS indicates a new-onset or worsening respiratory failure. PaO2/FiO2 $\leq$ 100 mm Hg is indicative of severe ARDS. Higher levels of AST [aspartate transaminase] and ALT [alanine transaminase] at admission result in rapid clinical deterioration to ARDS. The most frequent finding on CT scan includes ground-glass opacity [86%], consolidation [29%], crazy paving [19%], bilateral disease distribution [76%] and peripheral disease distribution [33%] [41]. A person with septic shock and sepsis is indicated by Signs of organ dysfunction include severe dyspnea, low oxygen saturation, reduced urine output, tachycardia, hypotension, cold extremities, skin mottling and altered mentation [11].

Who Case Definitions: *Suspected case* A] A patient with acute respiratory illness [fever and at least one sign/symptom of respiratory disease e.g., cough, shortness of breath] and with no other etiology that fully explains the clinical presentation and a history of travel to or residence in a country/area or territory reporting local transmission of COVID-19 disease during the 14 days before symptom onset; B] a patient with an acute respiratory illness and has been in contact with a confirmed or probable COVID-19 case in the last 14 days before the onset of symptoms; or C] a patient with a severe acute respiratory infection [fever and at least one sign/symptom of respiratory disease [e.g., cough, shortness breath] and requiring hospitalization and with no other etiology that fully explains the clinical presentation. *Probable case* A suspect case for whom testing for COVID-19 is inconclusive. Inconclusive being the result of the test reported by the laboratory *Confirmed Case* A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms [42].

Diagnostic Approaches: Currently, confirmatory diagnostic method is molecular methods as RT-PCR [reverse transcription] or real-time PCR, which is done by using RNA from respiratory samples such as oropharyngeal swabs, sputum, nasopharyngeal aspirate, deep tracheal aspirate, or bronchoalveolar lavage. In particular, lower respiratory tract samples can offer significantly higher viral load and genome fraction than upper respiratory tract samples. These techniques are beneficial in terms of evaluating the results quickly, showing the genome structure and viral load [43].

FDA proved non-PCR test kits, a new COVID-19 testing kit from Abbott Laboratories that uses isothermic nucleic acid amplification instead of PCR [44]. Detection of antibodies can also be used both for clinical purposes and population surveillance. These can be used to detect infection in individuals starting from 7 days or after the onsets of symptoms to determine immunity. NBGS'novel coronavirus [2019-Nov] antibody rapid test kits recently approved by the FDA can give results in 15 minutes, with

91% clinical specificity rate and 99% clinical sensitivity rate [45]. In late march 2020 Euroimmun Medical Laboratory Diagnostic also received European approval for their test kits, which can detect IgG and IgA antibodies against the virus in blood samples [46].

The other more reliable diagnostic tools are Chest X-ray and Computed tomography both presenting bilateral infiltrates and chest ground-glass opacities characteristics [40]. In comparison, the CT scan had a higher sensitivity as compared with an initial reverse-transcription polymerase chain reaction. With RT-PCR as a reference, the sensitivity of chest CT imaging for COVID-19 was 97% [580/601]. In patients with negative RT-PCR results but positive chest CT scans [n = 308 patients], 48% [147/308] of patients were re-considered as highly likely cases, with 33% [103/308] as probable cases by a comprehensive evaluation [47]. Promising serology based ELISA kits have been developed and have shown higher detection rates, however, there is no peer-reviewed published article stating the product [48].

Clinical Management of Cases: Like other pathogenic coronaviruses, for now, there is no clinically effective antiviral drug for COVID-19 as well. Hence, clinical management of cases should focus on supportive therapy like maintenance of body fluid, use of broad-spectrum antibiotics for secondary infection and artificial oxygenation [36]. Following the COVID-19 outbreak, several clinical trials have been registered for evaluating antiviral drugs, vaccines, glucocorticoids, antimalarial drugs and plasma therapy, while Traditional Chinese Medicine [TCM] accounted for half of the studies [49]. Currently, broad-spectrum anti-retroviral such as Nucleoside, HIV protease inhibitors could attenuate viral replication [50].

There is another report shown the in-vitro efficacy of broad-spectrum antiviral like remdesevir and antimalarial chloroquine [51]. Another clinical candidate EIDD-2801 compound that has shown high therapeutic potential against seasonal and pandemic influenza virus infections and this represents another potential drug to be considered for the treatment of COVID-19 infection [51]. Newer therapies like brilacidin, leronlimab [PRO 140], a CCR5 antagonist and neutralizing monoclonal antibodies are being tested along with trials of different other antivirals like ritonavir, lopinavir, oseltamivir [52].

Public Health Response

Personal Protective Behaviors: To date, there is no drug with proven clinical efficacy even though there are several international studies of a potential treatment for COVID-19. So, Preventive action is the only option we need to stop the spread of this pandemic disease. Measures must concentrate on personal protective, self and patient isolation; identification and follow up of contacts and environmental disinfection. Routine hand-washing protocol by water with soap for at least 20 seconds or alcohol-based solutions is very imperative. Cough and sneeze protective measures like the use of tissues alcohol and flexed elbow. The surgical masks may decrease the transmission of disease from infected persons to uninfected [53].

Undeniably, Physical distancing, avoiding mass gathering, avoiding crowded transports, non-essential meetings and avoiding hand-shaking should be practiced and also have paramount importance [54]. Direct physical contact with wet objects should be considered vital in dealing with the virus because body secretion and excretion could be a potential source of infection [55]. Travel restriction is best to avoid the distribution of the virus within the country and to the abroad [14].

Vaccines: To date, there are several vaccines company currently started production with different level of vaccine efficacy and safety and in phase 3 trials and the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use has initiated the rolling review procedure for four vaccines (AstraZeneca/Oxford, Janssen-Cilag International NV, Pfizer/BioNTech and Moderna) Sinovac, Sinopharma an Novavax. Two of these vaccine developers (Pfizer/BioNTech and Moderna) have now applied for Conditional Marketing Authorisation to the EMA. On 2 December 2020, the UK's Medicines and Healthcare Products Regulatory Agency approved the Pfizer/BioNTech vaccine for use in the UK. Moreover, report from WHO indicates that, 52 candidate vaccines are in different clinical evaluation [56, 57].

Future Perspectives: Even though the fatality rate is low in comparison with *SARS* and *MERS*, there has been a surge in the COVID-19 pandemic case number at an alarming rate on the globe in terms of mortality and morbidity. Due to the high adaptive mutation ability of the virus and great similarity in ACE2 of animals and humans, coronavirus will probably cause a widespread outbreak of the mutant strain; hence we should have coordinated efforts via one health approach to prevent future outbreaks. Undoubtedly, further investigation is required to define the exact epidemiological and immune-pathological aspects of the COVID-19 to develop a safe, accurate and reliable vaccine, diagnostic technologies and therapeutic against COVID-19. As there

was no approved drug, vaccine given against *SARS-COV-2* so far, utmost care should be given for patients receiving vaccine and to avoid unwanted side effects. Moreover, government agencies must quickly integrate up to date scientific results into public health care to reduce further health impacts of the disease and to lessen economic collapse and social crisis.

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