Covid-19 pandemic; pathophysiology & clinical management

Mizra Zeeshan Sikandar1, Aiman Fatima1, Syed Imran Ali Shah2
1Department of Biochemistry, Central Park Medical College, Lahore, Pakistan
2Department of Biochemistry, University of Hafr AlBatin, Saudi Arabia

Abstract
The coronavirus disease (COVID-19) pandemic has been caused by the worldwide infectious spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Its mechanism of action involves RNA virus implantation into the cell’s cytoplasm and the hijack of transcriptional machinery. The infection primarily afflicts the pulmonary system, resulting in multiple complications including, but not limited to, ground glass opacities seen on imaging. Characteristic features of COVID-19 involve pneumonia, shortness of breath, asthma, nasal congestion, sore throat, fever, fatigue, myalgia and it also encompasses a wide variety of other systemic symptoms. Multiple pharmaceutical agents have been tried as a treatment for COVID-19 but the results are inconsistent. With the intention of stopping person-to-person transmission, health measures such as quarantine and social distancing have been adopted, but the implementation was difficult. After the first wave of the pandemic, the second wave surfaced with a clear resurgence of cases followed by a third wave. The present review summarizes what is known about COVID-19 and explores the factors behind the resurgence.

Keywords
COVID-19; RNA Virus; Quarantine; Myalgia; Fever; Fatigue; Anti-inflammatory drugs; Resurgence
Introduction
The novel coronavirus disease (COVID-19) emerged as a public health emergency in China, and in a short span of only a few months, it engulfed the entire world that could not help but suffer the devastating effects of this potentially fatal disease [1]. COVID-19, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has adapted the features of a pandemic as identified by World Health Organization (WHO) [2-4].

SARS-CoV-2 is a beta coronavirus, similar in genome to the bat virus that is considered to be the natural host [5]. In December 2019, since its beginning in Wuhan, China, it spread worldwide [6]. Historically, coronaviruses have a total of 7 types, two of which are known to be the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), presented in China in 2002, and its animal- to- human transmission was traced to civets. The second severe coronavirus variant transmitted from dromedary camels, was observed in Saudi Arabia in 2012 and termed the Middle-Eastern respiratory syndrome virus (MERS-CoV) [7]. The current outbreak of SARS-CoV-2 originated in a wholesale seafood market of Wuhan city, in the Chinese province of Hubei. The outbreak was aggravated by high human- to- human transmission [8]. Coronavirus encompasses 2 major modes of transmission, including human-to-human transmission (HHT) and animal-to-human (zoonotic transmission) [9].

The virus and its nature
The virus causing COVID-19 has been labeled as SARS-CoV-2 due to its remarkable homology with SARS-CoV, which presented with Acute Respiratory Distress Syndrome (ARDS) and high mortality rates in 2002-2003 [10]. Interestingly, there is a clear similarity between the clinical presentation of COVID-19 and the disease caused by other respiratory viruses. This similarity with SARS-CoV is less than seventy percent, along with a high mutational ability of the SARS-CoV-2, which posed obstacles to the development of an effective vaccine [11]. The main proteins present in and on the surface of the virus include Membrane protein (M), Envelope protein (E), Nucleocapsid protein (N) and Spike protein (S). Mechanisms involving immune targeting of these viral protein epitopes by B and T cells have been employed to develop vaccines, which have been put through clinical trials worldwide [12]. Any stoppage in the transmission chain of COVID-19 through effective vaccinations, social measures and/ or treatment on a larger scale can help inhibit its spread [13].

Mechanism and infectivity:
COVID-19 is highly infective as the SARS-CoV-2 consists of untranslated RNA regions in the form of 5'UTR, replicase complex, S gene, M gene, E gene, N gene and several other untranslated regions that make it more virulent [14]. SARS-CoV-2 affects helper T cells and results in progressive, severe and systemic inflammation that may even lead to fulminant myocarditis or even disseminated intravascular coagulation (DIC). Inflammatory markers involved in this inflammatory cascade include interleukins like IL-6, inflammatory cytokines, membrane lipopolysaccharides, D-dimers, fibrinogen, angiotensin II release through the renin-angiotensin-aldosterone-system (RAAS), reactive oxygen species (ROS) and pro-inflammatory products released from natural killer (NK) cells (Figure 1) [15].

SARS-CoV-2 is a positively charged and single-stranded RNA virus, which infects by planting itself into the cell's cytoplasm. The hijacking of the transcriptional machinery involves an intricate initial mechanism involving the angiotensin-converting enzyme 2 (ACE-2), which allows receptors. SARS-CoV-2 interaction with the ACE-2 receptors and transmembrane serine protease 2 to gain entry into the epithelial cells of the lungs, as well as other organs such as the brain, kidneys, lungs, heart, pharynx and liver [16]. ACE-2 and RAAS counter-act each other and downregulation of one system in COVID-19 infection may trigger high immunological response leading to grave complications and organ failure [17].

Global Approaches for Pandemic Management:
Different models and approaches have been used to manage the pandemic around the world in different countries and regions. Important components involve reliable surveillance, news reports, providing detailed patient level data and construction of outbreak management. Surveillance is important as it can unmask and trace down undocumented cases, which have the highest risk of spread. Fatigued and overwhelmed healthcare systems have required encouragement and support of all kinds, which at times have not been forthcoming. [18].

Upper respiratory swab/sputum/aspirates/nasopharyngeal content tested for SARS-CoV-2 Real-time polymerase chain reaction (RT-PCR) test can allow the establishment of effective identification of COVID-19 positive patients and their timely isolation, which can reduce further transmission.

A linear correlation has been observed between the risk of contracting COVID-19 and exposure with a COVID-19 positive patient. Distance and duration of exposure also determined the transmissibility; greater the duration of exposure greater would be transmission and vice versa. The Italian catastrophe was the first major concern arising

Figure 1. Mechanism of Inflammation-induced complications of COVID-19
Figure 2. Comparison of cases and mortality (per million) between Pakistan and other countries

after the Chinese outbreak of COVID-19. It is widely perceived that the susceptibility of the Italian population to morbidity and mortality from COVID-19 was predominantly due to the large proportion of elderly individuals [19]. It has also been claimed that an earlier mass-scale influenza vaccination drive led to a hyperactive immune response, leading to elevated death rates (available at: https://emedicine.medscape.com/article/2500139-overview).

In some other parts of Europe, subjecting the susceptible population to safer lockdown arrangements suppressed their chances of getting the virus and reduced deaths. However, this approach eliminated the exposed healthy population, leading to even greater number of victims. Lockdown in developed countries has been shown to be 90 percent effective due to effective implementation, population education and awareness, but the same cannot be said about the developing world [21].

After massive endemic in USA, The Tracker of the New York Times Vaccine has listed a number of vaccines for continued clinical trials, as well as approval for full use. A process of investigating number of immunotherapies and treatment combinations is still going on in the United States of America. Following ongoing government struggle in tackling the great percentage of active cases and induced resultant deaths, two mRNA vaccines, including Pfizer and Moderna, have received FDA approval by December 2020. However, vaccines like Johnson and Johnson are nearing their final trials or phase 3 trials and can portray good prospects.

Johnson and Johnson are nearing their final trials or phase 3 trials and can portray good prospects. FDA approval by December 2020. However, vaccines like Johnson and Johnson are nearing their final trials or phase 3 trials and can portray good prospects.

Experience from Pakistan: Pakistan, as a developing country, lacked population awareness and resources for a complete lockdown. Poor socio-economic conditions and the overburdened state systems did not permit the government to provide for a large population that would have undergone unemployment as a result of lockdown. In order to avoid such chaos, only a regional and partial lockdown was observed in Pakistan [22].

The epidemic curve of COVID-19 has been categorized into two distinct waves with an intervening plateau phase after the first wave, followed by an exponential resurgence of cases upon the arrival of the second wave [23]. Immunological responses have been greatly emphasized for the double peak epidemic curve, and both innate and adaptive immunity play a crucial role in responses generated against viral exposure [24]. Innate immunity, if active and efficient, including natural killer cells (NK) cells, interferon, and complement systems of protein and IgA immunoglobulin secreted in body fluids, can inhibit the virus in initial phases. However, the mode of action of adaptive immunity requires the initial viral load and viral replication for presenting its viral particles to CD8+T along with MHC antigens class1 developing memory cells [25].

Clinical Features and Diagnostic Approaches

The incubation period of the SARS-CoV-2 has been averaged as 6.4 days with a range from 0 to 24 days. Symptoms typically appear 5-7 days after initial exposure to the virus [26]. SARS-CoV-2 mainly affects the pulmonary system [27] and eventually leads to ground glass opacities and patches in the lungs [28]. but every infected person does not develop symptoms [29]. A number of affected individuals developing complications were found to have chronic comorbidities [30] like hypertension, diabetes, coronary heart disease, cerebral infarction, chronic bronchitis, asthma and others [31]. Among adults across all age groups, males are more affected than females. The clinical manifestations observed in patients suffering from COVID-19 include a spectrum of different combinations and intensities of various signs and symptoms, including some major indications like fever and cough in up to 80% of cases with fever of 101°F or above. Shortness of breath has been observed in 31% of clinical cases with the coarseness of breathing sounds upon auscultation.

Table 1. Clinical signs and symptoms of COVID-19 infection

| Features          | Values in COVID | Reference Range | Clinical |
|-------------------|-----------------|-----------------|----------|
| Respiratory Rate  | >30 breaths/min | 12-16/min       | Raised   |
| Oxygen Saturation | < 93%           | > 95%           | Decreased|
| Temperature       | > 100 F         | 98F – 99F       | Raised   |
| Sensations        | Loss of smell and taste | Presence of sense of Smell and Taste | Absent |

Physicians experience diagnostic traps in treating COVID-19 patients. One good example is the pneumonia-like appearance on the X-ray that can mask the virus and perplex the physician. In 50 percent of the cases, CT remains normal for 0 to 2 days after the onset of flu-like symptoms [32]. COVID-19 RT-PCR sensitivity is low (60-70 percent). X-ray may show peripheral or multi-focal opacities, but PCR may still be negative [33]. The virus attacks the respiratory system, resulting in severe acute respiratory syndrome characterized by pneumonia, shortness of breath, asthma, nasal congestion, sore throat, fever, fatigue and myalgia [34]. Apart from respiratory involvement, the virus has also been shown to enter and disrupt the gastrointestinal, hepatic and neurological domains [35]. The worst CT findings appear 9-13 days after contracting SARS-CoV-2, after which CT scan begins to clear and shows a decrease in the ground glass opacities provided no further complications develop [36, 37].

As the world is progressing to the era of molecular mechanics, thus COVID-19 is ideally detected using RT-PCR [38]. As the infection persists, immunoglobulins of IgG and IgM types are produced as a response to control the infection [39]. COVID-19 RT-PCR has a low sensitivity of 60 to 70 percent and mostly
Covid-19 pandemic; pathophysiology & clinical management
depends on the degree of shedding of the virus by the individual in the oropharynx secretions [40]. Complete blood counts giving a viral picture, including leucopenia or decreased lymphocyte count, are also suggestive of COVID-19 in patients with a history of possible exposure. Serum Ferritin, C-reactive protein and D-dimer levels also are useful in the diagnostic and prognostic management of COVID-19 as they reflect inflammatory and immunological responses to the viral invasion [41]. The SARS-CoV2 antibody test is efficient after 1 to 3 weeks following the appearance of symptoms [42].

Radiological aspects such as observance of a pneumonia pattern [43] are important in assessing disease severity, and they are assessed better and earlier on CT-scan rather than on chest X-ray [44]. In 57% of cases, these are referred to as ground- glass opacities or consolidations, or cavitation, depicting airspace disease [45].

**Treatment Choices**
The search for an absolute treatment of COVID-19 has been going on for the last year, but a single magical therapeutic agent has remained elusive. The combination of anti-influenza agent Oseltamivir and anti-HIV agent Lopinavir/Ritonavir has been used together, but no definitive comment can be made on their efficacy [46]. Chloroquine/hydroxyl-chloroquine administration in some studies were shown to interfere with the replication cycle, but larger clinical studies have not shown much therapeutic benefit [47]. Immunity boosters such as multivitamins and the use of vitamin D may potentially interfere with the intensity of the disease as well as quicker recovery due to their suggested role against aggravated allergic and anti-inflammatory response [48-51]. Antibiotics like azithromycin for bacterial complications has also been used. Anti-inflammatory drugs have been employed to reduce elevated inflammatory and immune responses and extend protection against cytokine strike complications and risks [52]. Nucleoside analog trials such as Remdesvir proved to be useful against a wide range of RNA viruses, but their use in COVID-19 has not yet been established [53-57]. Table 2 lists the various pharmacologict agents that have been tried in the treatment of COVID-19.

**Preventive Measures**
With the intention of stopping person- to -person transmission, health measures such as Isolation, Quarantine, Social distancing, and Community containment were taken into consideration [77]. The elimination of viruses from the surfaces by chemical means, especially in places with a high risk of contamination, has further reduced their spread. Furthermore, measures at an individual level that include frequent hand washing, use of sanitizer, and wearing of masks have been proven to be beneficial [78-80]. Timely dissemination of information in the media is crucial to effective administration of personal protection, limiting imports, public gatherings and anything aggravating chances of contact and spread. Proper Screening and travel restrictions can potentially withhold the spread of the virus to a great degree. Training of Medical and non-medical teams should avoid reducing the burden on health care professionals [81].

**Vaccination**
Collaborative initiatives between public and private sectors and facilitated by the World Health Organization (WHO) have allowed for rapid vaccine development programs, which have led to successful production and development of many different vaccines against SARS-CoV-2 involving various mechanisms of action. Pfizer-BioNTech was the first one to gain recognized approval. It has been shown to confer 95% protection against COVID-19 in people older than 16 years of age through a two-shot regimen with the second dose given two weeks after

**Table 2. Impact of several drugs and their consequences in COVID-19 patients**

| Treatment options | Proposed Mechanism | Contraindications | Side effects/toxicities |
|--------------------|--------------------|--------------------|------------------------|
| Hydroxy-Chloroquine (HCQ)/Chloroquine (CQ) [58,59] | Inhibition of viral protein synthesis | Any case of known hypersensitivity | Prolonged QT interval resulting in arrhythmia |
| Azithromycin [60,61] | Inhibition of bacterial protein synthesis and potential anti-viral role | Contraindicated in hypomagnesemia and hypokalemia as well as myasthenia gravis | - Prolonged QT interval |
| Remdesivir [62,63] | Analog to adenosine; Quick termination of viral RNA | | Kidney complication |
| Ritonavir/Lopinavir [64,65] | HIV-1 protease inhibitor stopping viral maturation and infection, same mode of action for SARS-CoV-2 | Nausea and GIT-related complications are common | Interference with transaminases levels |
| Favipiravir [66,67] | Chain termination due to inhibition in the action of RNA dependent type of RNA polymerase | Neutropenia and diarrhea | |
| Ribavirin [68,69] | Guanosine analog and causes inhibition of RNA polymerase | Pregnant female or men with a pregnant partner or hemoglobinopathy | Teratogenic effects and induced cases of hemolytic anemia |
| Ivermectin [69,71] | Reduction of viral RNA and anti-parasitic effect | May induce rashes on the skin and related muscle and joint pain | |
| Immunoglobulin [72,73] | Neutralization of virus due to injection of antibodies collected from Covid-19 recovered patients | Induced headache, fever, malaise, flushing, thrombosis, renal impairment and cardiac arrhythmias | |
| Corticosteroids [74,75] | Anti-inflammatory role against cytokines (IL-6, IL-1, IL-12, IL-8, TNFα) and decreased pathological damage | Patients with diabetes, hypertension and other chronic ongoing infections | Short term does not cause complications but long-term use can cause weight gain, osteoporosis, hypertension and diabetes. |
| Interferon [76,77] | Proteins produced by the immune system, immunity boosters | Fever, chills, flu-like symptoms, fatigue, headache and weakness | |
| Tocilizumab [78,76] | Affinity for IL-6 receptors; recombinant monoclonal antibody (Human IL-6) | Any previous allergy established to tocilizumab and patients with thrombocytopenia and neutropenia | Respiratory tract infection including tuberculosis, nasopharyngitis and other complications like headache, hoarse voice, allergic reactions and GIT perforations |

[825] Annals of Clinical and Analytical Medicine
the first. Safety over a median of 2 months has also been demonstrated to be similar to that of other viral vaccines (available at: https://www.biospace.com/article/comparing-covid-19-vaccines-pfizer-biontech-moderna-astazeneca-oxford-j-and-j-russia-s-sputnik-v/).

Table 3 provides a list of some of the vaccines that are currently being used in the world and their mechanisms of action [84]. Vaccine-induced immunity is considerably different from naturally induced immunity, as the majority of the population (up to 74 percent) who are asymptomatic or have mild symptoms may develop very few antibodies and this may not last long. This seriously changes the dynamics of the possible chances of herd immunity. Keeping tracks of subjects after vaccination is a key feature of any vaccine trial. Making comprehensive data of T-cell and antibody presentation will allow a record of the vaccine-induced protection and its effects later on [83].

Conclusion:
The importance of a well-coordinated approach cannot be denied, and the management of the second wave could be a deciding point in a successfully combating the COVID-19 pandemic. A structured approach is essential for the management of this global crisis. The development of a reliable and effective treatment and fast vaccine deployment are crucial factors. Economic management is required, as well as special attention to patients with other underlying conditions like cancer, renal failure, diabetes and pregnant women [84]. Vaccines are our greatest hope, and transmission prevention should remain a priority to allow for the flattening of the epidemic curve and halt COVID-19 intensity. A better understanding of the disease spread, the initiation of vaccination drives, and adequately equipped healthcare facilities are cause of optimism, but slackness at the government or public levels may lay waste the gains obtained so far.

Scientific Responsibility Statement
The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Funding: None

Conflict of interest
None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

References
1. Baloch S, Baloch MA, Zheng T, Pei X. The Coronavirus Disease 2019 (COVID-19) Pandemic. Tohoku J Exp Med. 2020;250(4):271-8. DOI: 10.1620/tjem.250.271.
2. Luo H, Teng QL, Shang YX, Liang SB, Yang M, Robinson N, et al. Can Chinese Medicine Be Used for Prevention of Coronavirus Disease 2019 (COVID-19)? A Review of Historical Classics, Research Evidence and Current Prevention Programs. Chin J Integr Med. 2020;26(4):243-50.
3. Bwire GM, Paolo LS. Coronavirus disease-2019: is fever an adequate screening for the returning travelers? Trop Med Health. 2020;48:14. DOI: 10.1186/s41182-020-02021-2.
4. Centini C, Di Nuzzo M, Barg N, Bonazza A, Di Giorgio R, Tognon M, et al. The novel zoonotic COVID-19 pandemic: An expected global health concern. J Infect Dev Ctries. 2020;14(3):254-64.
5. Dong XC, Li JM, Bai JY, Liu ZQ, Zhou PH, Gao L, et al. [Epidemiological characteristics of confirmed COVID-19 cases in Tianjin]. Zhonghua Liu Xing Bao Xue Za Zhi. 2020;41(5):638-41. (in Chinese). DOI: 10.3760/ cmj.j.cn112338-20200221-00146
6. She J, Liu L, Liu W. COVID-19 epidemic: Disease characteristics in children. J Med Virol. 2020;92(7):747-54.
7. Shenemerdine SC, Lovrenski J, Caro-Dominguez P, Toso S. Collaborators of the European Society of Paediatric Radiology Cardiothoracic Imaging Taskforce. Coronavirus disease 2019 (COVID-19) in children: a systematic review of imaging findings. Pediatr Radiol. 2020;50(9):1217-30. DOI: 10.1007/s00247-020-05475-6.
8. Luo H, Teng QL, Shang YX, Liang SB, Yang M, Robinson N, et al. Can Chinese Medicine Be Used for Prevention of Coronavirus Disease 2019 (COVID-19)? A Review of Historical Classics, Research Evidence and Current Prevention Programs. Chin J Integr Med. 2020;26(4):243-50. DOI: 10.3760/cma.j.cn112338-20200221-00146
9. Lun ZR, Qu LH. Animal-to-human SARS-associated coronavirus transmission? Emerg Infect Dis. 2004;10(5):959. DOI: 10.3201/eid1005.040022.
10. Wang Y, Wang Y, Chen Y, Qin Q. Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicates special control measures. J Med Virol. 2020;92(6):568-76. DOI: 10.1002/jmv.25748.
11. Lipsitch M, Sverdlov DL, Finelli L. Defining the Epidemiology of Covid-19 - Studies Needed. N Engl J Med. 2020;382(3):1194-6. DOI: 10.1056/NEJMc201225.
12. Chang Y, Tung Y, Lee K, Chen T, Hsiao Y, Chang, H, et al. Potential Therapeutic Agents for COVID-19 Based on the Analysis of Protease and RNA Polymerase Docking. Preprints. 2020; DOI: 10.20944/preprints202002.0242.v2.
13. Lipsitch M, Sverdlov DL, Finelli L. Defining the Epidemiology of Covid-19 - Studies Needed. N Engl J Med. 2020;382(3):1194-6.
14. Annnal Ud Din M, Boppana LKT. An update on the 2019-nCoV outbreak. Am J Infect Control. 2020; 48(6):713. DOI: 10.1016/j.ajic.2020.01.023.
15. Conti P, Ronconi G, Caraffa A, Galienga CE, Ross R, Fridyas I, et al. Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus disease 2019 (COVID-19) or SARS-CoV-2). anti-inflammatory strategies. J Bio Regul Homeost Agents. 2020;34(2):327-331. DOI: 10.23812/CONTI-E.
16. Saracci, R, Pagotto, A, Longo, B. Prevention in COVID-19 time: from failure to failure. J Epidemiol Community Health. 2020;74(9):689-91.
17. Ni W, Yang X, Yang D, Bao Li R, Xiao Y, et al. Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. Crit Care. 2020;24(1):422. DOI: 10.1186/s13054-020-03120-0.
18. Ibrahim, N, Tian, M, Gu, Q. Epidemiological surveillance for controlling Covid-19 pandemic types, challenges and implications. J Infect Public Health. 2020;13(11):1630-8.
19. Rudan I. A cascade of causes that led to the COVID-19 tragedy in Italy and in other European Union countries. J Glob Health. 2020;10(1):010335. DOI: 10.17188/jogh.10-010335.
20. Nacciotti M, Ciocco A, Giapponi P, Brambillasca P, Lussana F, Pisano M, et al. A Review of Historical Classics, Research Evidence and Current Prevention Programs. Chin J Integr Med. 2020;10(1):3016-9. DOI: 10.1002/hpm.3016.
21. Sahin, A, Erdogan, A. 2019 Novel Coronavirus (COVID-19) Outbreak: A Review of Historical Classics, Research Evidence and Current Prevention Programs. Chin J Integr Med. 2020;10(1):3016-9. DOI: 10.1002/hpm.3016.
22. Atef, M, Malik, T, Younas, M, Javed, S, Imran, A. Why is Pakistan vulnerable to COVID-19 associated morbidity and mortality? A scoping review. Int J Health Plan Manage. 2020;10(102):3016-9. DOI: 10.1002/hpm.3016.
23. Abid, K, Bari, Y, Younas, M, Javed, S, Imran, A. Progress of COVID-19 Epidemic in Pakistan. Asia Pac J Public Health. 2020;32(4):154-6.
24. Xu S, Li Y. Beware of the second wave of COVID-19. Lancet. 2020;395(10233):1321-2.
25. Zielecki F, Weber M, Eickmann M, Spiegelberg L, Zaki AM, Matrosovich M. Human cell tropism and innate immune system interactions of human respiratory coronavirus EMC compared to those of severe acute respiratory syndrome coronavirus. J Virol. 2013;87(9):5300-4.
26. Nishimura H, Mizumoto K, Ejima K, Zhong Y, Cowling B, Omori R. Incubation...
period as part of the case definition of severe respiratory illness caused by a novel coronavirus. Euro Surveill. 2021;127(4):20296.

27. Lai CC, Liu YH, Wang CY, Wang YH, Hsueh SC, Chen MY, et al. Asymptomatic carrier state, acute respiratory disease, and pneumonia due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): Facts and myths. J Microbiol Immunol Infect. 2020;53(3):404-12. DOI: 10.1016/j.jmii.2020.02.012.

28. Broga B, Bignardi E, Broga C, Alberigi M, Grappone M, Megliola A, et al. Typical CT findings of COVID-19 pneumonia in patients presenting with repetitive negative RT-PCR test. Radiology. 2020;2020:870-6. DOI: 10.1148/rt.2020200870.

29. Bhattachar R, Sindhujha T, Bhattachar D, Dev T, Gupta A, Bajpai M, et al. Intragenic dermatitis in times of COVID-19: a pandemic within a pandemic. J Eur Acad Dermatol Venereol. 2020;34(10):e563-6. DOI: 11.1111/jdv.17610.

30. Giaroli CA, Coro GM, Treatment of patients with risk factors contributing to the management of COVID-19 pandemic. J Glob Health. 2020;10(1):010377. DOI: 10.1091/jogh.010377.

31. Rajgor DD, Lee MH, Archuleta S, Badgasion S, Querk SC. The many estimates of the COVID-19 case fatality rate. Lancet Infect Dis. 2020;20(7):776-7. DOI: 10.1016/s1473-3099(20)30449-9.

32. Su, S. Wong G, Shi W, Liu L, Lai A, Zhou J, et al. Epidemiology, Genetic variation, and Pathogenesis of Coronavirus. Trends Microbiol. 2021;1.4:460-502. DOI: 10.1016/j.tim.2020.10.009.

33. AY-M, Lee EY, Yang J, Yang F, Li X, Wang H, et al. Imaging profile of the COVID-19 infection: radiologic findings and literature review. Radiol Cardiothoracic Imaging. 2020;2(1):e200034.

34. Jin YH, Cai L, Cheng ZS, Cheng H, Deng T, Fan YP, et al. A rapid advisory guidance of treatment and 2019 novel coronavirus infection pneumonia (standard version). Mil Med Res. 2020;7(1):4. DOI: 10.1186/s40779-020-0233-6.

35. Daiwei W, Bo H, Chang H, Fangfang Z, Xing, L, Jing Z, et al. Clinical characteristics of 183 Hospitalized Patients With 2019 Novel Coronavirus Infection Pneumonia in Wuhan, China. JAMA. 2020;323(11):1061. DOI: 10.1001/jama.2020.1585.

36. Ding X, Xu J, Zou J, Long Q. Chest CT findings of COVID-19 pneumonia by duration of symptoms. Eur J Radiol. 2020;127:109009. DOI: 10.1016/j.ejrad.2020.109009.

37. Ng MY, Lee EY, Yang J, Yang F, Li X, Wang H, et al. Imaging profile of the COVID-19 infection: radiologic findings and literature review. Radiol Cardiothoracic Imaging. 2020;2(1):e200034.

38. Wieder-Smith A, Freeman DO. Isolation, quarantine, social distancing and community containment: pivotal role for old-style public health measures in the management of COVID-19 infection: radiologic findings and literature review. Radiol Cardiothoracic Imaging. 2020;2(1):e200034.

39. Gao J, Tian Z, Yang X. Breakthrough: chloroquine phosphate has shown effective in treatment of 2019 novel coronavirus pneumonia (standard version). J Int Med Res. 2020;48(2):573-9. DOI: 10.1177/030146472004800202.

40. Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W, et al. Correlation of Chest CT and RT-PCR Testing for Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. Radiology. 2020;296(3):E20-E30. DOI: 10.1148/radiol.2020206642.

41. Konrad R, Eberle U, Dangel A, Treis B, Berger A, Bergs K, et al. Rapid establishment of laboratory diagnostics for the novel coronavirus SARS-CoV-2 in Bavaria, Germany. February 2020. Euro Surveill. 2020;25(9):2000173. DOI: 10.2807/1560-7917.ES.2020.25.9.2000173.

42. LIZ Y, Yi, Luo X, Xiong N, Liu Y, Li S, et al. Development and clinical application of a rapid IgM/IgG combined antibody test for SARS-CoV-2 infection diagnosis. J Med Virol. 2020;Sep 29(9):S18-5. 10.1002/jmv.25727.

43. Shi Q, Wang Q, Gao Y, Alwattar M, Alzahrani A, Alzahrani U, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet Infect Dis. 2020;20(4):245-34. DOI: 10.1016/s1473-3099(20)30086-4.

44. Chua F, Armstrong-James D, Desai SR, Barnett J, Kouranos V, Kon OM, et al. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infection. Lancet Respir Med. 2020;8:493-7. DOI: 19.1016/s2213-2600(20)30212-6.

45. Jin YH, Cai L, Cheng ZS, Cheng H, Deng T, Fan YP, et al. Clinical and CT features in pediatric patients infected with pneumonia (standard version). Mil Med Res. 2020;7(1):4. DOI: 10.1186/s40779-020-0233-6.

46. Meini S, Pagotto A, Longo B, Vendramin I, Pecori D, Tascini C. Role of vitamin D and parathyroid hormone as risk factors of myocardial infarction and their correlation with lipid profile. Medical Science. 2021;1.5:179-84.

47. Shah SIA, Sikandar MZ, Qazi UY, Haq I. Comparative assessment of vitamin D and parathyroid hormone as risk factors of myocardial infarction and their correlation with lipid profile. Medical Science. 2021;1.5:179-85.

48. So LK, Lau AC, Yom LY, Cheung TMT, Poon E, Yung RWH, et al. Development of a standard treatment protocol for severe acute respiratory syndrome. Lancet. 2003;361:1615-7. DOI: 10.1016/s0140-6736(03)13265-5.

49. Kim Ui, Won EJ, Kee SJ, Jung SJ, Jung HC. Combination therapy with lopinavir/ritonavir, ribavirin and interferon-alpha for severe acute respiratory syndrome. Antiviral Ther. 2016; 21(5):455-9.

50. Alsawalmy FK, Sikandar MZ, Shah SIA, Parey MuR, Jelani S. Serum Vitamin D, sun exposure and clinical attributes of local patients with respiratory allergies. Medical Science. 2021;1.5:179-84.

51. Shah SIA, Sikandar MZ, Qazi UY, Haq I. Comparative assessment of vitamin D and parathyroid hormone as risk factors of myocardial infarction and their correlation with lipid profile. Medical Science. 2021;1.5:179-85.

52. So LK, Lau AC, Yom LY, Cheung TMT, Poon E, Yung RWH, et al. Development of a standard treatment protocol for severe acute respiratory syndrome. Lancet. 2003;361:1615-7. DOI: 10.1016/s0140-6736(03)13265-5.

53. Kim Ui, Won EJ, Kee SJ, Jung SJ, Jung HC. Combination therapy with lopinavir/ritonavir, ribavirin and interferon-alpha for severe acute respiratory syndrome. Antiviral Ther. 2016; 21(5):455-9.

54. Alsawalmy FK, Sikandar MZ, Shah SIA, Parey MuR, Jelani S. Serum Vitamin D, sun exposure and clinical attributes of local patients with respiratory allergies. Medical Science. 2021;1.5:179-85.
How to cite this article:
Mirza Zeeshan Sikandar, Aiman Fatima, Syed Imran Ali Shah. Past, present and future of Covid-19 pandemic; review of the pathophysiology and clinical management. Ann Clin Anal Med 2021;12(7):822-828.