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An approach to the understanding of the clinical-etiopathological aspect of COVID-19 (SARS-CoV-2)

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Abstract

Currently, the world is facing a health and socioeconomic crisis caused by the novel coronavirus disease COVID-19. On 11 March 2020, the World Health Organization (WHO) has declared this disease as a pandemic. The condition (COVID-19) is an infectious disorder triggered by a newly discovered severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2. Most of the COVID-19 infected patients will experience mild to moderate respiratory symptoms and recover without any unique therapy. Assessment of the clinical and epidemiological characteristics of SARS-CoV-2 cases suggests the infected patients will not be contagious until the onset of severe symptoms and affects the other organs. Well-differentiated cells of apical airway epithelia communicating with ACE2 were promptly infected to SARS-CoV-2 virus. But the expression of ACE 2 in poorly differentiated epithelia facilitated SARS spike (S) protein-pseudo typed virus entry and it is replicated in polarized epithelia and especially exited via the apical surface. Limiting the transmission of COVID-19 infection & its prevention can be regarded as a hierarchy of controls. In this article, we briefly discuss the most recent advances in respect to aetiology, pathogenesis and clinical progression of the disease COVID-19.

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INTRODUCTION

The ongoing outbreak of novel coronavirus(COVID-19) was identified first in Wuhan, China on 1 December 2019, (Kai and Kai, 2020; Wu *et al.*, 2020) and subsequently spread to other areas of the world in early April 2020 to 190 countries (Tang *et al.*, 2020).

On 16 July 2020, data from WHO has shown that outbreak and sporadic human infections of COVID-19 have reported 13,378,853 confirmed cases with 580,045 fatalities across the world.

On 30 January 2020, the WHO officially announced that COVID-19 outbreak had become a pandemic Public Health Emergency of International Concern (PHEIC) (Li *et al.*, 2020b). WHO (World Health Organization) officially declared the COVID-19 disease on 11 February 2020 (Zu *et al.*, 2020).

Initially, WHO called the newly developed virus " novel coronavirus 2019" (2019-nCoV), (Adhikari *et al.*, 2020) but the international committee of the

Coronavirus Study Group (CSG) has renamed as "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2), (Lotfi *et al.*, 2020) (and the disease called " Coronavirus disease 2019"(COVID-19) by WHO (Zu *et al.*, 2020; Guo *et al.*, 2020).

SARS-CoV-2, related to β-coronaviridae family and subfamily Orthocoronavirus based on their serological and genomic sequences (Medhi *et al.*, 2020). This subfamily Orthocoronaviridae has been further divided into four subgroups; Alphacoronavirus (α-CoV), Betacoronavirus (β- CoV), Gammacoronavirus (γ- CoV) and Deltacoronavirus (δ-CoV) (Mona *et al.*, 2020). In which α and β- CoV are infecting the mammals while γ and δ- CoV is transmitted between birds. In which two known β- CoV, SARS Co-V and MERS CoV are the primary causative agent for severe fatal respiratory tract infections (Yan *et al.*, 2020).

SARS-CoV-2, related to β- corona viridae family have an identical genomic sequence (almost 96%) with its natural host bat β-coronavirus (Fiesco-Sepúlveda and Serrano-Bermúdez, 2020). This virus is most likely link to humans and attacks the upper and lower respiratory tract in humans. Patients with pre-existing underlying heart and respiratory diseases and aged people (>70 years) who are more susceptible to infection and prone to a severe outcome (Mona *et al.*, 2020).

Coronavirus is enveloped, non-segmented positive –sense, and single-stranded RNA viruses and highly contagious, belongs an extensive family of viruses that can cause disease in both animals and humans (Tang *et al.*, 2020; He *et al.*, 2020; Ortiz-Prado *et al.*, 2020). There no specific treatment and any vaccine yet. So, the best solution will be self-isolation (Fiesco-Sepúlveda and Serrano-Bermúdez, 2020), the adaptation of preventive measures and sensitive diagnostic approaches (Nitulescu *et al.*, 2020; Lotfi *et al.*, 2020) and implementing proper management for controlling the recent ongoing SARS-CoV infection. This pandemic infection in micro and macro environment causing more damage to the society by all means (Lotfi *et al.*, 2020) & currently available antiviral drugs are not capable of containing this deadly infection.

The outbreak of COVID-19 will have a significant global concern on the social health, cultural, and economic infrastructures at various levels because the virus is contagious, to be long-lasting and responsible for lethal respiratory infection in the human being which takes many years to recover. The genetic characterization of the viral strains will have implications related to pathogenicity, transmissibility, and response to preventive therapy of the viral makeup for global populations (Jin *et al.*, 2020). So it's tough to the understanding of this mechanism for preventive drug discovery and formation of effective vaccines.

Aetiology

This new coronavirus origin is not known precisely. Still, at the beginning of this outbreak, many patients were diagnosed primarily with pneumonia of an unknown aetiology in the hospital in a particular area which linked epidemiologically to a Hunanan south China seafood and wet animal wholesale market in Wuhan, Hubei Province, China. These are indicative of the zoonotic origin of COVID -19 based on the wide-ranging of the infected population there and early infections animal to human transmission (Rothan and Byrareddy, 2020).

According to WHO, severe acute respiratory syndrome coronavirus -2 (SARS-CoV-2) was the primary etiological source of new developed COVID pandemic that generally attack the host respiratory system. Severe acute respiratory syndrome coronavirus 2 (SARS Co-2) is one of the most acute atypical respiratory pathogens that initially infects the human respiratory tract after which other organs involved and represents the causative factor of probably brutal death in close to 10% of cases (Rothan and Byrareddy, 2020) due to progressive respiratory failure and rapidly spreading across the world to affect thousands of populations per day (Khan *et al.*, 2020).

Coronavirus disease (COVID-19) is an acute pulmonary syndrome characterized by atypical pneumonia and represents as an etiological agent of SARS and mostly produced from bat origin. coronaviruses and affect the human populations recently (Rothan and Byrareddy, 2020). These viruses affect the animal, and some viruses attack humans in a few cases.

Pathogenesis

In the past two decades, the single-strand RNA (ssRNA) beta- coronavirus was divided into three epidemic disease- severe acute respiratory syndrome (SARS) virus, Middle East respiratory syndrome (MERS) virus and SARS-CoV-2 (Li *et al.*, 2020b). Severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) are the most causative factor for producing severe viral pneumonia (Huang *et al.*, 2020; Guo *et al.*, 2020). SARS-CoV-2 correlates with SARS CoV as 79 % identical genomic sequences (Tay *et al.*, 2020).

Inflammatory mechanism

In this process initially, SARS-CoV-2 attacks respiratory mucosal epithelial cells causing stimulated response in macrophage and lymphocyte, SARS-

CoV-2 antigen presentation on the host cell surface and activation of B cells along with this phenomena involvement of T-helper and T- cytotoxic cells also. Immunogenic structural proteins of SARS-CoV-2 virus attack the peripheral white blood cells (WBC) and immune cells of the host, particularly T lymphocytes. So in COVID -19 patients are indicated Cellular immune deficiency and lymphopenia against the pathogen (Dhama *et al.*, 2020).

Disturbance the ratio of ACE/ACE2 (↑ ACE2) by SARS CoV-2, which is responsible for the aggravation of the inflammatory process, pulmonary vasoconstriction and alveolar tissue damage, ultimately causing acute lung injury.

SARS-CoV-2 infection with aggressive up-regulation of pro-inflammatory cytokines including, interferon (IFN-γ), TNF-α, interleukin IL-6, IL-8, IL-10 responses (Henry *et al.*, 2020). In serum strongly implicated in the resulting severe destruction of lung cells and inflammation (Li *et al.*, 2020a). Excessive production of proteases enzymes and oxygen species by the inflammatory cell infiltration directly damage the lungs cells resulting from the virus (Tay *et al.*, 2020).Because Cytokine Strom syndrome correlated with progressive inflammation is playing an essential role in the immune mechanism (Li *et al.*, 2020a). Dysregulated local host immune response(adaptive T and B cell immune response) causes severity in COVID 19 infected patients (Dhama *et al.*, 2020). Activation of macrophages and monocytes that respond to the infection, release inflammatory cytokines Tay *et al.* (2020) and is also correlated with the epidemiologically of SARS-CoV and MERS-CoV. SARS-CoV-2 against T and B cells response shown in the host blood after one week of symptoms onset of COVID-19 (Tay *et al.*, 2020). Hyper inflammatory response activated by SARS-CoV-2 is a major etiological factor for disease severity and death in COVID -19 patients (Merad and Martin, 2020).

At the cellular levels, SARS Co-2 infection promotes the activation of CD-I cells and production of GM-CSF, which results of activation of CD14, CD16 with interleukin 6(IL6) and other inflammatory cytokines (Li *et al.*, 2020a). CD 8 T cells responsible for direct attach and killing the viruses (Tay *et al.*, 2020).

T cell lymphopenia and inflammatory cytokines concentrations are indicative of poor prognosis along this interleukin 6(IL6), IL10 and D-dimer continuously elevation (Helmy *et al.*, 2020) within 7-14 days after onset the symptoms marking of condition toward the severe stage of the disease (Nitulescu *et al.*, 2020).

Both cellular and humoral mediated immune mechanisms are involved in SARS-CoV-2 pathogenesis (Dhama *et al.*, 2020).

Severe COVID-19 infected patients have a high amount of plasma pro-inflammatory cytokines and chemokines (Dhama *et al.*, 2020), increased levels of ferritin decreased platelets count (Helmy *et al.*, 2020; Mehta *et al.*, 2020), lymphopenia, (Xu *et al.*, 2020) and abnormal respiratory findings (Rothan and Byrareddy, 2020).

Lymphopenia(infiltration of lymphocyte into the respiratory tract) in 70% cases (Mungroo *et al.*, 2020) and an increased ratio of the neutrophil-lymphocyte present in 80% patients of COVID-19. Lymphopenia is a standard clinical feature and associated with severity and mortality rate of COVID -19 patients (Merad and Martin, 2020). Corona virus-specific T cells reduce and control the disease development by eliminating the viruses and should be help of production of several vaccine formulations (Tay *et al.*, 2020).

Role of ACE 2 receptor

Dipeptidyl peptidase 4(DPP4) and angiotensin-converting enzyme 2 (ACE2) in the lower respiratory tract are two different sites for viral infection. The DPP4 are the fundamental human receptors for the surface spike (S) glycoprotein of MERS-CoV and SARS-CoV additionally recognizes its ACE2 receptor (Li *et al.*, 2020b) SARS-CoV-2 is more linked to SARS-CoV(due to similar genetic sequences) instead of MERS-CoV (Tang *et al.*, 2020).

ACE2 (mono-carboxyl peptidase) (Dariya and Nagaraju, 2020) against affinity –purified antibody is responsible for blocking of syncytial epithelium between infected host cells. So SARS-CoV-2 S protein receptor binding and membrane integration is dependent on the expression of ACE2 receptor type2 alveolar epithelial cells (Tang *et al.*, 2020) and is essential for regulating of host tropism and transmission capacity (Vallamkondu *et al.*, 2020).

SARS –CoV-2 enter into the host cell and attach to the ACE 2 (crucial cell receptor for SARS- CoV-2) (Guo *et al.*, 2020) is the first step of viral infection (Tay *et al.*, 2020). S protein of virus interacts with surface ACE2 enzyme and transmembrane protease, serine 2 (TMPRSS2) for activation of S protein which leads to the internalization of the viral substance (Ortiz-Prado *et al.*, 2020).

SARS-CoV-2, dynamic process, (Tang *et al.*, 2020) S spike protein mediates high-affinity association with ACE2 receptors 10-20 times more than the SARS-CoV spike, (Mungroo *et al.*, 2020).

It is responsible for the permission of the virus to

entering into the host cells and binds the binding domain of the ACE2 receptor resulting in spreading of SARS CoV-2 rapidly within the human body (Jin *et al.*, 2020).

During viral infection, the interaction between ACE2 and S protein which is essential for the assembly and infection of coronavirus, the structural protein S is functionally divided into S1 and S2 subunits (Tang *et al.*, 2020). The S1 subunit determines the virus-host range and containing the receptor-binding domain (RBD) is bind to the cellular receptor tropism and released during the transition to the postfusion conformation (Tang *et al.*, 2020) which is responsible for targeting to the neutralizing of antibodies (Li *et al.*, 2020a).

The membrane-anchored S2 subunit facilitates the cellular membrane integration through the two tandem HR1 (Heptad repeats) and HR2, and entrance process (Al-Qahtani, 2020).

The attachment of SARS-CoV S glycoprotein to ACE 2, can contribute to the severity of alveolar damage lung pathologies due to loss of apical airway epithelial cilia, squamous metaplasia and macrophages number elevation in the respiratory tract (Mona *et al.*, 2020).

S glycoprotein of SARS CoV bound to the ACE2 receptor on the host cell surface through the S1 subunit. It triggered due to type II transmembrane protease serine 2 (TMPRSS2) (Nitulescu *et al.*, 2020; Guo *et al.*, 2020) and cathepsins B and L to encourage the viral and host membrane fusion process through the S2 subunit within the endosome microenvironment. (Mona *et al.*, 2020). After membrane fusion, initially, the virus interacts with specific human cells that exhibit distinct receptors for the viral spike protein (Nitulescu *et al.*, 2020). Then using the host cellular machinery, it starts viral translation process after the viral genomic RNA is released into the cytoplasm and activates pathogenic responses and replicating itself, and expressing specific sequences in which translation of 2 polyproteins such as pp1a and pp1ab by uncoated RNA (Dariya and Nagaraju, 2020).

The polyproteins cleavage into 15 mature replicase proteins (processed through internal viral proteases) into the replication transcription complex (RTC) which continuously replicates and responsible for synthesis of a set a subgenomic RNAs that encode structural proteins, (Dariya and Nagaraju, 2020) endoplasmic reticulum and Golgi which facilitating the adaptation of this virus to its host (Wu *et al.*, 2020).

After this process, new multiple subgenomic negative-strand RNAs and structural protein genes are produced and eventually released into the host cytoplasm through exocytosis (Tang *et al.*, 2020).This virion- containing vesicles fuse in the cytoplasm and release a million copies of the new viruses (Guo *et al.*, 2020) and newly formed virus attack the other healthy host cells (Vallamkondu *et al.*, 2020).

Knowledge of this virus pathogenesis may be helpful for the improvement of new therapeutics to invent new antiviral strategies against SARS-CoV-2 infections by the breakdown of the SARS-CoV-2 life cycle through the blockage of the host target ACE2 receptor (Tay *et al.*, 2020).

At a molecular level

The pathogenesis of COVID-19 virus and SARS CoV are differentiated at the molecular basis due to ACE expression on different levels which help to understand the disease and its preventive measures.

COVID -19 patient's respiratory and serum specimen contains SARS –CoV RNA which easily detected by RT-PCR mechanism (major confirmatory test) (Khan *et al.*, 2020) and specific antibodies react with SARS antigen (Medhi *et al.*, 2020) . This process contributes to inflammatory responses and cell-mediated responses which are responsible for disease severity, as well as alveolar tissue destruction. The adaptive protective immunity formed antigen-specific antibody, which binds to the S spike protein of SARS-CoV-2 and decreases the ability of the virus to attach the respiratory tissues.

Genetic alteration changes of coronavirus are lesser than to other RNA viruses, but homologous recombination may be rapidly occurred and primarily acting on the antiviral drug activity (Nitulescu *et al.*, 2020) due to the proofreading activity of RNA dependent RNA polymerase (RdRp) enzyme of these viruses (Mona *et al.*, 2020).

In the intra, alveolar spaces contain large nuclei amphophilic granular cytoplasm with atypical enlarged pneumocytes and Multinucleated syncytial cells, prominent nucleoli (showing viral cytopathic like changes) (He *et al.*, 2020).

Mostly laboratory testing focused on Virus-specific nucleotide –positive and viral protein seroconversion of known respiratory pathogens of these viruses, which specifically attacks the lower respiratory tract through the progression of disease and correlation between disease and viruses.

Human tissues PCR analysis has observed efficient expression of ACE2 on 293 T cells by an anti-ACE2 antibody and messenger RNA in the pulmonary parenchyma as well as in the tissues of heart, kid-

ney and gastrointestinal tract. The primary sites of expression of murine ACE2 are lung and kidney cells, which is consistent with the pathology of acute viral infection of SARS (Vallamkondu *et al.*, 2020).

In SARS-CoV infection Lungs, histopathology images show the destruction of bronchial epithelium, loss of alveolar cilia and giant cell infiltrate with a marked high levels macrophages in the alveoli and lung interstitium (Merad and Martin, 2020).

Recently some evidence has revealed that SARS CoV is a newly emerged virus from a zoonotic source, (Mona *et al.*, 2020) because the amino acid and genomic sequences of the receptor-binding domain (RBD) of human SARS-CoV are homologous to animal genetic phenomena, that's indicative of identical receptor for those viruses (Wu *et al.*, 2020). It is originated from animals as per earlier outbreaks in humans.

In SARS CoV-2 infection, an adaptive immune response required to control of disease progression by the production of antigen-antibody complex and destroy the virus. In the early stage, if the host has strong endogenous immune, better personal health and specific genetic environment which has antiviral activity, then immunity booster strategies help protect from the virus individuals. The innate immunity of the host is the first line of defence mechanism against the viral infection (Naqvi *et al.*, 2020; Shi *et al.*, 2020).

Clinical features

SARS–CoV and MERS–CoV infection features are approximately similar experienced but progression rate to respiratory failure is high due to MERS-CoV infection.

COVID-19 infection represents sign and symptoms after almost 5.2 days. Incubation period starts from the onset of COVID-19 symptoms to ranging between 2 days to 14 days with a median of 7 days. The incubation period and the severity and outcome of the disease depend upon the patient age (>55 years old) and immune system status (Rothan and Byrareddy, 2020). Therefore COVID-19 spreading rate reduced by self –isolation and social distancing, especially in more susceptible people as adults or patients with comorbidities.

COVID-19 clinical features are classified into a stage-I(Asymptomatic or non-specific symptoms), stage –II(symptoms with a virus) with severe dyspnoea and associated pneumonia, Stage III(severe respiratory symptoms with excessive virus presence) (Shi *et al.*, 2020) with inflammatory responses related to multiple organ damage pathology (Nitulescu *et al.*, 2020) and critically based on clinically aggravated symptoms and their imaging reports and some severe cases leading to death (Shi *et al.*, 2020).

SARS-CoV-2 patients may respond initially with loss of smell (anosmia), loss of taste (ageusia) (Mungroo *et al.*, 2020) or bitter taste, loss of appetite diarrhoea, nausea and mild raised body temperature but fever is not a premier symptom of this infection (Zu *et al.*, 2020). 97.5% of COVID -19 patients show signs within 11.5 days (Tay *et al.*, 2020).

SARS-CoV-2 patients prominent clinical features, namely fever associated with a dry cough, coarse breathing sounds (shortness of breath), headache, pharyngula, myalgia, acute severe respiratory misery, aspiratory pneumonia. The symptoms are aggravated if the patient isn't properly diagnosed and treated during this stage. RT- PCR (real-time polymerase chain reaction) of the patient's sputum reports are showed the confirmation of the COVID-19 infection (Rothan and Byrareddy, 2020).

Most severe forms of COVID -19 infection and high risk of death were mainly observed in elderly (adults $\geq$ 55 years)and low immune patients with an underlying pre-existing disease like diabetes mellitus, hypertension, chronic kidney diseases, and coronary artery disease. So the recovery rate is higher in people who have healthy immune responses. Death due to progressive respiratory failure and massive alveolar damage in critically ill patients of COVID 19 is associated with hyper inflammation in alveolar tissues and aggravates in lethal pneumonia (Dhama *et al.*, 2020).

COVID-19 symptoms ranges including from asymptomatic upper respiratory tract infections to severe form of pneumonia which correlated with acute respiratory distress syndrome and fatality. The COVID-19 patients have the numerous marginal ground-glass opacities experiential in subpleural regions of both lungs (Mungroo *et al.*, 2020) that probably induced both local systemic and generalized immune response that led to accelerated inflammation. Signs and symptoms between COVID-19 and prior beta coronavirus are comparable likes fever with a dry cough, breathlessness and both sided consolidated lungs and ground-glass opacities on chest radiographs (CT scans) (Dhama *et al.*, 2020).

Severe forms of COVID-19 patients with dyspnoea or hypoxemia after one week (McGonagle *et al.*, 2020) and after which these symptoms rapidly progression and converts to septic shock, ARDS, metabolic acidosis (Medhi *et al.*, 2020) and coagulation dysfunction (Guo *et al.*, 2020) that develop injury to the kidney, heart, and other organs, and even multiple organ failures (Zu *et al.*, 2020). ARD(severe COVID-19 symptoms aggravated to ARDS around 8-

10 days after onset of symptoms) is a cause of death in COVID-19 (Mehta *et al.*, 2020) in 70% cases of fatal disease due to respiratory failure (Tay *et al.*, 2020).

Route of transmission

SARS CoV has less transmissibility and pandemic risk than to COVID-19. Because SARS CoV-2 may be transmitted quickly but not virulent than to SARS CoV and MERS CoV, that's mortality rate in COVID -19 patients is less about 3.4% but SARS (9.6%) and MERS(35% approximately) (Mona *et al.*, 2020). COVID -19 show differences in fatality between males (2.8%) and female (1.7%) (Tay *et al.*, 2020).

Generally, animal coronaviruses do not spread between humans, but SARS and MERS affect the human populations mainly through direct contact or respiratory droplets (Adhikari *et al.*, 2020).SARS CoV-2 might be transmitted to humans from bats (natural hosts of SARS-CoV-2) through an undefined intermediate host. The SARS CoV-2 virus particles transmitted from one person to another person primarily through direct contact or aerosol droplets by coughing and sneezing of symptomatic patient individuals without covering of mouth and nose with mask into the air (Mungroo *et al.*, 2020) but symptoms may develop in later who infected by asymptomatic patients. But the faecal-oral route, (recent FDA guidelines) and intermediate fomites may be other sources of viral transmission from both symptomatic and asymptomatic patients during the incubation phase of infection. SARS –CoV-2 virus infects the respiratory tract of individuals because this virus particles survival rate in the air around 14-16 hours but depending on the environmental temperature and travels a distance of 3 -4 feet (Vallamkondu *et al.*, 2020).

Currently, many countries have decided social distancing and lockdown methods for reducing mitigation and cross-transmission of this emerging disease (Nitulescu *et al.*, 2020) and the rapidly increasing cases number with high mortality rate.

WHO recommended that necessary precautions like hand washing, use PPE and face masks, self –isolation, avoid the travelling in high-risk areas of COVID -19 and contact of symptomatic patients are essential (Sohrabi *et al.*, 2020).

CONCLUSION

The pandemic by COVID-19 is a live issue distressing people globally. Estimation of the clinical and epidemiological distinctiveness of SARS-CoV-2 cases suggests that its diverse nature in producing infections. Symptomatic patients are usually considered as infectious. Research and therapeutic strategies for COVID-19 have focused on the viral genomic proteins and the development of better approaches. Understanding of clinical-etiopathogenesis is necessary to invent new vaccines and therapeutics for its control and management.

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Conflict of Interest

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REFERENCES

Adhikari, S. P., Meng, S., Wu, Y.-J., Mao, Y.-P., Ye, R.-X., Wang, Q.-Z., Sun, C., Sylvia, S., Rozelle, S., Raat, H., Zhou, H. 2020. Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease (COVID-19) during the early outbreak period: a scoping review. *Infectious Diseases of Poverty*, 9(1):29–29.

Al-Qahtani, A. A. 2020. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): Emergence, history, basic and clinical aspects. *Saudi Journal of Biological Sciences*.

Dariya, B., Nagaraju, G. P. 2020. Understanding novel COVID-19: Its impact on organ failure and risk assessment for diabetic and cancer patients. *Cytokine & Growth Factor Reviews*, 53:43–52.

Dhama, K., Patel, S. K., Pathak, M., Yatoo, M. I., Tiwari, R., Malik, Y. S., Singh, R., Sah, R., Rabaan, A. A., Bonilla-Aldana, D. K., Rodriguez-Morales, A. J. 2020. An update on SARS-CoV-2/COVID-19 with particular reference to its clinical pathology, pathogenesis, immunopathology and mitigation strategies. *Travel Medicine and Infectious Disease*, pages 101755–101755.

Fiesco-Sepúlveda, K. Y., Serrano-Bermúdez, L. M. 2020. Contributions of Latin American researchers in the understanding of the novel coronavirus outbreak: a literature review. *PeerJ*, 8:e9332–e9332.

Guo, Y.-R., Cao, Y. R., Hong, Q. D., Tan, Z. S., Chen, Y. Y., Jin, S. D., Tan, H. J., Wang, K. S., Yan, D. Y. 2020. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. *Military Medical Research*, 7(1):11–11.

He, F., Deng, Y., Li, W. 2020. Coronavirus disease 2019: What we know? *Journal of Medical Virology*, 92(7):719–725.

Helmy, Y. A., Fawzy, M., Elaswad, A., Sobieh, A.,

Kenney, S. P., Shehata, A. A. 2020. The COVID-19 Pandemic: A Comprehensive Review of Taxonomy, Genetics, Epidemiology, Diagnosis, Treatment, and Control. *Journal of Clinical Medicine*, 9(4):1225–1225.

Henry, B. M., Vikse, J., Benoit, S., Favaloro, E. J., Lippi, G. 2020. Hyperinflammation and derangement of renin-angiotensin-aldosterone system in COVID-19: A novel hypothesis for clinically suspected hypercoagulopathy and microvascular immunothrombosis. *Clinica Chimica Acta*, 507:167–173.

Huang, J., Song, W., Huang, H., Sun, Q. 2020. Pharmacological Therapeutics Targeting RNA-Dependent RNA Polymerase, Proteinase and Spike Protein: From Mechanistic Studies to Clinical Trials for COVID-19. *Journal of Clinical Medicine*, 9(4):1131–1131.

Jin, Y., Yang, H., Ji, W., Wu, W., Chen, S., Zhang, W., Duan, G. 2020. Virology, Epidemiology, Pathogenesis, and Control of COVID-19. *Viruses*, 12(4):372–372.

Kai, H., Kai, M. 2020. Interactions of coronaviruses with ACE2, angiotensin II, and RAS inhibitors—lessons from available evidence and insights into COVID-19. *Hypertension Research*, 43(7):648–654.

Khan, S., Liu, J., Xue, M. 2020. Transmission of SARS-CoV-2, Required Developments in Research and Associated Public Health Concerns. *Frontiers in Medicine*, 7:310–310.

Li, H., Zhou, H., Zhang, Y., Wang, M., Zhao, H., Liu, Q. 2020a. Updated Approaches against SARS-CoV-2. *Antimicrobial Agents and Chemotherapy*, (6):64–64.

Li, X., Geng, M., Peng, Y., Meng, L., Lu, S. 2020b. Molecular immune pathogenesis and diagnosis of COVID-19. *Journal of Pharmaceutical Analysis*, 10(2):102–108.

Lotfi, M., Hamblin, M. R., Rezaei, N. 2020. COVID-19: Transmission, prevention, and potential therapeutic opportunities. *Clinica Chimica Acta*, 508:254–266.

McGonagle, D., O'Donnell, J. S., Sharif, K., Emery, P., Bridgewood, C. 2020. Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. *The Lancet Rheumatology*, 2(7):e437–e445.

Medhi, B., Mahalmani, V. M., Mahendru, D., Semwal, A., Kaur, S., Kaur, H., Sarma, P., Prakash, A. 2020. COVID-19 pandemic: A review based on current evidence. *Indian Journal of Pharmacology*, 52(2):117–117.

Mehta, P., McAuley, D. F., Brown, M., Sanchez, E., Tattersall, R. S., Manson, J. J. 2020. COVID-19: consider cytokine storm syndromes and immunosuppression. *The Lancet*, 395(10229):1033–1034.

Merad, M., Martin, J. C. 2020. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. *Nature Reviews Immunology*, 20(6):355–362.

Mona, F., Ali, T., Shokouh, G. 2020. Comparison of the COVID-2019 (SARS-CoV-2) pathogenesis with SARS-CoV and MERS-CoV infections. *Future Virology*, 15(5):7238751–7238751.

Mungroo, M. R., Khan, N. A., Siddiqui, R. 2020. Novel Coronavirus: Current Understanding of Clinical Features, Diagnosis, Pathogenesis, and Treatment Options. *Pathogens*, 9(4):297–297.

Naqvi, A. A. T., Fatima, K., Mohammad, T., Fatima, U., Singh, I. K., Singh, A., Atif, S. M., Hariprasad, G., Hasan, G. M., Hassan, M. I. 2020. Insights into SARS-CoV-2 genome, structure, evolution, pathogenesis and therapies: Structural genomics approach. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, 1866(10):165878–165878.

Nitulescu, G., Paunescu, H., Moschos, S., Petrakis, D., Nitulescu, G., Ion, G., Spandidos, D., Nikolouzakis, T., Drakoulis, N., Tsatsakis, A. 2020. Comprehensive analysis of drugs to treat SARS-CoV-2 infection: Mechanistic insights into current COVID-19 therapies (Review). *International Journal of Molecular Medicine*, 46(2):467–488.

Ortiz-Prado, E., Simbaña-Rivera, K., Gómez-Barreno, L., Rubio-Neira, M., Guaman, L. P., Kyriakidis, N. C., Muslin, C., Jaramillo, A. M. G., Barba-Ostria, C., Cevallos-Robalino, D., Sanches-SanMiguel, H., Unigarro, L., Zalakeviciute, R., Gadian, N., López-Cortés, A. 2020. Clinical, molecular, and epidemiological characterization of the SARS-CoV-2 virus and the Coronavirus Disease 2019 (COVID-19), a comprehensive literature review. *Diagnostic Microbiology and Infectious Disease*, 98(1):115094–115094.

Rothan, H. A., Byrareddy, S. N. 2020. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *Journal of Autoimmunity*, 109:102433–102433.

Shi, Y., Wang, Y., Shao, C., Huang, J., Gan, J., Huang, X., Bucci, E., Piacentini, M., Ippolito, G., Melino, G. 2020. COVID-19 infection: the perspectives on immune responses. *Cell Death & Differentiation*, 27(5):1451–1454.

Sohrabi, C., Alsafi, Z., O'Neill, N., Khan, M., Kerwan, A., Al-Jabir, A., Iosifidis, C., Agha, R. 2020. World Health Organization declares global emergency: A

review of the 2019 novel coronavirus (COVID-19). *International Journal of Surgery*, 76:71–76.

Tang, D., Comish, P., Kang, R. 2020. The hallmarks of COVID-19 disease. *PLOS Pathogens*, 16(5):e1008536–e1008536.

Tay, M. Z., Poh, C. M., Rénia, L., MacAry, P. A., Lisa, F. P. 2020. The trinity of COVID-19: immunity, inflammation and intervention. *Nature Reviews Immunology*, 20(6):363–374.

Vallamkondu, J., John, A., Wani, W. Y., Ramadevi, S. P., Jella, K. K., Reddy, P. H., Kandimalla, R. 2020. SARS-CoV-2 pathophysiology and assessment of coronaviruses in CNS diseases with a focus on therapeutic targets. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, 1866(10):165889–165889.

Wu, L., O'Kane, A. M., Peng, H., Bi, Y., Motriuk-Smith, D., Ren, J. 2020. SARS-CoV-2 and cardiovascular complications: From molecular mechanisms to pharmaceutical management. *Biochemical Pharmacology*, 178:114114–114114.

Xu, Z., Shi, Z., Wang, L., Zhang, Y., Huang, J., Zhang, L., Liu, C., Zhao, S., Liu, P., Zhu, H., Tai, L., Bai, Y., Gao, C., Song, T., Xia, J., Dong, P., Zhao, J., Wang, J. 2020. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *The Lancet Respiratory Medicine*, 8(4):420–422.

Yan, Y., Shin, W. I., Pang, Y. X., Meng, Y., Lai, J., You, C., Zhao, H., Lester, E., Wu, T., Pang, C. H. 2020. The First 75 Days of Novel Coronavirus (SARS-CoV-2) Outbreak: Recent Advances, Prevention, and Treatment. *International Journal of Environmental Research and Public Health*, 17(7):2323–2323.

Zu, Z. Y., Jiang, M. D., Xu, P. P., Chen, W., Ni, Q. Q., Lu, G. M., Zhang, L. J. 2020. Coronavirus Disease 2019 (COVID-19): A Perspective from China. *Radiology*, 296(2):E15–E25.