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Cytokine Bombardment is the Major Cause for Morbidity in Sars-Cov-2 (Covid-19) Patients: A Review

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ABSTRACT

Cytokine bombardment is described as dysregulation and excessive production of cytokines. It causes fatal outcome in COVID-19 patients and result in acute respiratory distress syndrome. The most vulnerable group includes children, old age people and individuals with underlying conditions. In this group, COVID-19 infection initially presents with acute respiratory distress syndrome and further progresses to multiple organ dysfunction, sepsis and death. The present review describes the cytokine storm based hyper-immune response mechanisms in these patients through schematic diagrammatic representations.

Keywords
COVID-19, SARS-CoV-2, cytokine storm, interleukins, ACE-2

INTRODUCTION

The first case of coronavirus disease 2019 (COVID-19) outbreak was reported in Wuhan city, Hubei Province, China in December 2019 [1, 2]. Afterwards, on 12 January 2020,World Health Organization (WHO) coined this viral strain that causes COVID-19 as 2019-novel coronavirus (2019-nCoV) and this new strain of coronavirus was first discovered in 2019.Then, the disease was named coronavirus disease 2019 (COVID-19) by World Health Organization (WHO) and proposal for naming the virus as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was made by Coronavirus Study Group (CSG) of the International Committee, both of these were issued on 11th February 2020. SARS-CoV-2 mainly affects the respiratory system and consequently it causes pneumonia [3]. This strain was found highly contagious and it is transmitted mainly by inhalation of respiratory droplets, which contains virus rich fluid. The novel COVID-19 strain transmitted to all over the world quite fast and declared as COVID-19 pandemic by WHO on 12th March 2020 [4].

Coronaviruses (CoVs) belong to the Coronaviridae family within Nidovirales order and is well known for its crown-like spike appearance on their surface and it is best described as an enveloped virus containing single stranded RNA within a nucleocapsid [5]. These spikes are made up of glycoproteins. CoVs are categorized into 4 genus namely alpha, beta, gamma and delta-CoV (The International Committee on Taxonomy of Viruses- ICTV). Alpha and beta coronavirus are capable of infecting mammals and humans, while gamma and delta coronavirus usually infect birds. Until today, there are seven types of coronaviruses recognized that can infect humans known as Human Coronavirus (HCoV) which are alpha type HCoV-229E and HCoV-NL63, the beta type HCoV-HKU1, SARS-CoV, MERS-CoV, and HCoV-OC43 and lastly 2019-nCoV [5].

SARS-CoV-2 has four major structural proteins, which are the spike surface glycoprotein, nucleocapsid protein, small envelope protein and matrix protein. The spike protein infects the host cells using the receptor-binding domain (RBD) of angiotensin converting enzyme-2 (ACE-2). ACE-2 protein presents in various organs such as lungs, gastrointestinal tract, bone marrow, blood vessels, lymph nodes, spleen, liver, thymus, kidney and brain [6].

The specific term coined as spillover event, in which for the first time a virus is transmitted from animals to humans [7]. Later on, these diseases, denoted as zoonotic diseases. The term zoonotic virus is described as a virus that is regularly transmitted from animal to human and causes disease. Coronaviruses can cause respiratory tract infections in companions and domestic animals and can also infect humans causing respiratory diseases from mild to severe illnesses [8, 9]. In one of the studies in 2002, it has been found that several animals can transmit CoVs, as seen in the case of SARS-CoV-1 that infects both civet cats and humans together. Similarly, in 2012, MERS-CoVs infected dromedary camels and further transmitted to humans results in outbreak in Middle East.

SARS-CoV-2 (COVID-19) origin

The origin of COVID-19 is yet to be found, but research has shown that the origin is closely related to Huanan wholesale market in Wuhan, China, where the wild animals (Wild bats, Pangolins, Palm civets, Dromedary camels) were sold [11-28, 133-134].

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SARS-CoV-2 (COVID-19) transmission cycle

Studies from the past regarding earlier coronaviruses outbreak suggest that it is originated from bats and transmission of the virus to humans are passed from market civets, camels and pangolins, which act as the intermediate host [29-37]. Based on evident research data as depicted in Fig. 1, it is clear that the SARS-CoV-2 novel strain has a broad host range.

Studies between SARS-CoV-2 and SARS-CoV have shown approximately 80% gene similarity [38, 39] and found that the horseshoe bats (*Rhinolophusaffinis*) are the primary source of this virus [24]. In addition, civet cats and raccoon dogs have been demonstrated to have genetically similar CoVs [25]. Researchers also found that animals such as ferrets and macaques could also be infected by SARS-CoVs and produce disease. However, no observable symptoms were seen in cats [40, 41]. Until today, the virus reservoir for SARS-CoV-2 remains unclear but it is reported to be either minks, snakes, or other animals [42].

The transmission cycle of SARS-CoV-2 infection from a primary host (Bats) [43] to humans is depicted in Fig. 1. Depending on the accessibility of CoVs to host cells, CoVs are able to migrate from its natural host to humans via intermediate hosts also [44]. Evolution of CoVs, particularly its spike glycoprotein allows it to adapt and binds to various mammalian host species [11].

Based on research data, potential mechanism of cross species transmission from natural to non-natural host depends on spike glycoprotein (Fusogenic or modulating) and dependency of CoV towards receptor (dependent or independent) [45-47]. It is quite possible that there is an existing receptor switch mechanism in CoVs that causes spike protein modularity and tendency of recombination. The spike glycoproteins of SARS-CoV-2 possesses high fusogenic potential, which could minimize the dependency of CoVs on receptor-based cell entry [48, 49].

Animal to human transmission

Wild bats are the natural reservoir of coronaviruses. Accumulating evidences suggest that the probable transmission of SARS-CoV-2, which is originated from bats to humans is through animal market in Wuhan China, where these wild bats are usually sold as a source of food. These markets are unhygienic and did not maintain the standard guidelines. Furthermore, it is suggested that the spillover event occurs from bats to civets and subsequently to the people who work or live near the location as there could be possibility of wildlife trade of infected animals [18-20]. The initial spread of infection was found from the animal handlers, who work in these live animal retail (wet) markets as evidence shows that they are seropositive against this novel viral strain. These handlers unknowingly transmitted the infection to the buyers [50]. Later, when they developed SARS-like illnesses, it drew the attention of public health authorities in Wuhan, China.

Current research demonstrates approximately 96% of similarity in sequence between SARS-CoV-2 and CoV (isolated from horseshoe bats; *Rhinolophusaffinis*) strongly indicates that bats are the most probable host [25]. Additionally, several other animals are also found to have a role as virus reservoir. This includes snakes, which could be a possible virus reservoir for human infection [42], pangolins that has SARS-CoV-2 related coronaviruses and minks as possible intermediate hosts for SARS-CoV-2 infection [29].

Human to human transmission

Research data from various studies so far suggest that SARS-CoV and SARS-CoV-2 are zoonotic in origin, which then spreads to humans. In Wuhan, China the human to human-transmission requires few weeks to cause the outbreak but, recently, the spread of disease occurs rapidly and this further confirms that there is human to human transmission. SARS-CoV-2 infected individual acts as the major source of infection and transmission occurs mainly via droplets (both nasal and oral) and aerosols generated during coughing, talking and sneezing according to WHO and CDC guidelines [51]. Besides that, transmission could occur via physical contact with COVID-19 patients, various surfaces, and by sharing household stuff. Some research also found that there is a possibility of COVID-19 transmitted through fecal-oral-route [52]. Furthermore, scientific literature available on NCBI shows that an enormous rate of SARS-CoV-2 infection is due to asymptomatic patients. Nearly half of the SARS-CoV-2 infected person remains asymptomatic and this poses a risk to others as a potential carrier of the virus [53]. These asymptomatic infections also escape rapid tests such as serum antibody tests.

Additionally, researchers also found that prolonged and unprotected exposure with SARS-CoV-2 infected people could cause person to person transmission. This is explained as the exposure could lead to constant pathogen pressure and subsequently, transmission of infection and disease happens [54].

Recently, several findings demonstrate that lack of proper pressure ventilation systems in intensive care units (ICU) of COVID hospitals may further increase the risk of infection. Also, there are growing research suggest that the risk

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of infection may increase due to the viability of SARS-CoV-2 in air, environment, personal protection equipment and hospital [55].
In SARS-CoV-2 infection, spike glycoprotein of virus (particularly receptor-binding domain (RBD)) binds with ACE2 receptor in human host cell in as shown in reports of SARS-CoV human-to-human transmission [56, 57]. The most peculiar feature is that SARS-CoV-2 and SARS-CoV spikes have similar RBD sequences, which strongly suggest that ACE2 receptor is the common route of entry into the host cells [57].

Human Coronaviruses (HCoVs) history
The first human coronavirus was discovered in 1965 and it was cultivated on ciliated embryonal tracheal cells from the respiratory tract of a person with common cold. Researcher named Tyrrell and Bynoe conducted the research and they found that a virus named B814 was able to grow in organ culture and when the virus was introduced (the medium was inoculated from these cultures) via intranasally to the human volunteers, it causes significant cold-like illness in some volunteers [58, 59]. In the meantime, researcher Hamre and Procknow also obtained samples from medical students with cold and they found a virus with unusual properties were able to be grown in tissue culture, the virus was named as 229E virus [60]. Both the 229E virus and B814 virus has no significant relation with any known paramyxoviruses or myxoviruses.

SARS-CoV-1
Information regarding coronavirus was limited until the outbreak of Severe Acute Respiratory Syndrome-Coronavirus (SARS-CoV-1) happened in 2002 and starting from there, the interest regarding this virus continues to rise. SARS-CoV-1 outbreak begins in Southern China in Guangdong province, and it was suggested that the virus first originated from bats and then via an intermediate host such as raccoon dog (*Nyctereutesprocyonoides*) and palm civet (*Pagumalarvata*), humans gets infected by this virus [61-63]. Last case of SARS-CoV-1 was reported in 2004 and massive efforts were made to control this infectious disease.

MERS-CoV
Then, in June 2012 outbreak of Middle East Respiratory Syndrome-Coronavirus (MERS-CoV) was first found in a Saudi Arabian patient who had severe pneumonia and died due to respiratory and renal failure, sputum sample revealed a novel corona virus strain. This strain was coined as Middle East Respiratory Syndrome-Coronavirus (MERS-CoV). MERS-CoV virus strain was closely related to several bat CoVs [64] although it was also assumed that the camels are the animal reservoirs for this contagious strain. Later on whenever the new strain of coronavirus arises, it is always thought to be related with zoonotic transmission [30-33].
Infection of mildly pathogenic HCoVs affects the upper respiratory tract and it also causes mild to moderate flu-like respiratory symptoms in healthy adults. The mildly pathogenic HCoVs are HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU. In contrast, highly pathogenic HCoVs such as SARS-CoV [65], MERS-CoV [66, 67] also SARS-CoV-2, infects lower respiratory tract causing severe pneumonia. Highly pathogenic HCoVs infection could also result in acute lung injury (ALI), acute respiratory distress syndrome (ARDS) and fatal acute lung injury, which could eventually leads to death [68-70].

Cytokine bombardment
Normally, the immune response against common viral infections is balanced or controlled in infected individuals [71, 72]. However, in the case of highly mutated viral strains, hyper-immune response is observed in the patient, which leads to multi organ dysfunction. In the case of SARS-CoV-2 (COVID-19), the hyper-immune response is denoted as cytokine storm, where the cytokines and inflammatory mediators are elevated excessively, resulting in patchy consolidation (pneumonia) in the lungs. Elevated cytokines are interferon-alpha (IFN-α), interferon-gamma (IFN-γ), interleukin-1beta (IL-1β), interleukin-6 (IL-6), interleukin-12 (IL-12), interleukin-18 (IL-18), interleukin-33 (IL-33), tumour necrosis factor-alpha (TNF-α) and transforming growth factor-β (TGF-β). These cytokines are released by natural killer cells, innate macrophages, mast cells, dendritic cells, endothelial cells and the adaptive T and B lymphocytes. At this point of time, patients develop a combination of symptoms such as shortness of breath, high grade fever, cough, confusion and generalized body weakness which is denoted as acute respiratory distress syndrome (ARDS).
SARS-CoV-2 infection activates innate and adaptive immune response which eventually leads to cytokine storm [73]. Cytokine storm is defined as dysregulation and excessive production of cytokines (particularly IL-6, IL-1, TNF- α and interferon) due to over-response of the immune system that occurs in COVID-19 patients. Cytokine storm/uncontrolled inflammatory response causes influx of several immune cells like neutrophils, macrophages and T cells into the site of infection with catastrophic effects on humans.

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Cytokine bombardment triggers the bronchoalveolar damage (apoptosis of endothelial and epithelial cells), fibrosis of lungs and vascular leakage, which results in acute respiratory distress syndrome (ARDS), multi organ dysfunction syndrome (MODS), severe other syndrome and ultimately death as depicted in Fig. 2 [74]. One of the consequences of cytokine bombardment is lung injury and it can progress into acute lung injury or in more severe cases, ARDS [75]. Dissemination of viral particles through blood circulation leads to viremia and consequently it causes multi organ dysfunction syndrome (MODS) [76, 77]. Studies regarding cytokine profiles of COVID-19 patients demonstrated that cytokine bombardment is directly correlated with unfavourable prognosis of severe COVID-19, lung injury and multi organ failure as depicted in Fig. 2 [78-83].

Several studies reported that, increase in serum Ang II induces apoptosis in alveolar epithelial cells, resulting in lung fibrogenesis [84]. This enzyme also mediates cytokine signalling and oxidative stress, which contributes to several pathophysiology of lung diseases [85].

In COVID-19 cytokine bombardment, angiotensin converting enzyme-2 (ACE-2) plays an important role. ACE-2 enzyme is a membrane protein that metabolizes angiotensin II (ANG II). Abundance of ACE-2 receptors could be found on smooth muscle cells of the lungs, pulmonary endothelium, type II alveolar epithelial cells and enterocytes [86]. In SARS-CoV infection, ACE-2 acts as a functional receptor [87], it is then occupied and endocytosed together with the virus. This causes reduction of ACE-2 (ACE-2 downregulation) and increase of serum ANG II (Reduction of ACE-2 mediated degradation of ANG II) as depicted in Fig. 3 [88].

SARS-CoV-2 enters the throat via droplet or aerosol transmission and it travels to the lungs and gastrointestinal system due to abundance of ACE-2 receptors. S protein (spike glycoprotein) of the virion then binds to these cellular ACE-2 receptors [89]. Transmembrane serine protease-2 (TMPRSS2) and endosomal cysteine proteases cathepsin B and L (CatB/L) are used for S protein priming. Invasion of SARS-CoV-2 in the respiratory epithelial cells stimulates immune response that results in cytokine production along with weak interferon (IFN) response (may be an important cytokine production amplifier). Furthermore, SARS-CoV-2 are able to activate pathogenic Th1 cells rapidly, Th1 cells then secretes interleukin-6 (IL-6) and granulocyte-macrophage colony-stimulating factor (GM-CSF). Subsequently, GM-CSF stimulates intermediate monocytes (CD14+, CD16+) to produce copious amounts of tumor necrosis factor-α (TNF-α), IL-6 and other cytokines [90]. High expression of IL-6 and TNF-α is typical in cytokine storm of COVID-19 patients.

Cytokine bombardment in COVID-19 mainly causes pneumonia and subsequently results in acute respiratory distress syndrome (ARDS), which is a major cause of mortality in severe cases of SARS-CoV-2 infection, just as in SARS-CoV and MERS CoV infection [91-93]. Mechanism of ARDS in COVID-19 includes excessive production of cytokine as one of the major contributing factors [78, 94, 95]. In later stages of infection, impaired tissue remodelling, and uncontrolled epithelial cells proliferation contributes to ARDS. Death due to ARDS is mainly caused by hypoxia which occurs in relation to apoptosis of epithelial and endothelial cells that disturbs lung microvascular and alveolar epithelial cell barrier resulting in vascular leakage and alveolar edema. In addition, post-mortem examination of lung of COVID-19 patient shows there is existence of acute respiratory distress syndrome (ARDS) and T-cell over activation due to high cytotoxicity of the CD8+ T cells and increase in the number of T-helper (Th) 17 cells [96].

It then involves multi organ system dysfunction as it disseminates to organs such as the kidney, vascular system and central nervous system. It could cause renal insufficiency and failure in the kidney. In the vascular system, it could lead to vasculitis which can be seen as a chilblain lesion in toes known as ‘coronavirus toes’ or it can also manifest as a pernio lesion and sometimes large blood vessels are also involved. As for the central nervous system, patients could also experience symptoms commonly loss of sense of smell and taste, headache (13%), dizziness (17%), confusion, unable to arouse also muscle inflammation and nerve pain (19%). 36% of patients had neurologic symptoms. Autopsy shows brains tissue edema partial brain neuronal degeneration [97].

Moreover, cytokine storm also diminishes cytotoxic T cell response due to over-response of the immune system caused by pathogenic HCoV. For instance, in SARS-CoV infection, T cells underwent apoptosis that is mediated by TNF-α. CoV-specific T cells are essential to prevent further damage of infection to the host cell and ultimately clears off the virus [98, 99]. Besides that, cytotoxic T cell are needed to suppress overactive innate immune response [100, 101].

Current updates on SARS-CoV-2 (COVID-19)

WHO defines SARS-CoV-2 (COVID-19) deaths as, in probable or confirmed cases, where there is no other clear-cut alternative cause of death reported other than COVID-19. Majority of deaths reported were due to excessive inflammatory immune response denoted as cytokine storm and severity of the disease [102]. This is characterized by elevated levels of circulating cytokines, acute lymphopenia and post-mortem examination of COVID -19 patients shows that there is substantial mononuclear cell infiltration in the lungs, kidneys, heart [103], spleen, and lymph

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nodes [104, 105]. Pandemic COVID-19 remains a major threat to public health [132-134]. Manifestation of COVID-19 differs in each person from asymptomatic, mild, severe illness and in some, SARS-CoV-2 infection (COVID-19) even results in death [132-134].
Centres for disease control and prevention (CDC) also mentioned that some underlying conditions increase the risk of patient to develop severe illness, such as chronic kidney disease, chronic obstructive pulmonary disease (COPD), heart condition (coronary artery disease, heart failure), immunocompromised state due to solid organ transplant, smoking, diabetes mellitus type 2, obesity, sickle cell disease, cancer and pregnancy [104, 106-109].There are several potential factors related in recovery which are early treatment, strong immune system among the population, good dietary habits and Bacillus Calmette-Guérin (BCG) vaccination policy in some countries, which shows less COVID-19 cases than countries without BCG vaccination policy [110]. Up to date, there is no specific treatment available for COVID-19. However, Food and Drug Administration (FDA) suggested some of the treatment strategies, such as plasma therapy and the use of certain antibiotics.

Potential antibiotics against SARS-CoV-2 (COVID-19)
Hydroxychloroquine and Remdesevir antibiotics significantly inhibit SARS-CoV-2 (COVID-19) viral replication. Hydroxychloroquine (HCQ) is an analogue of chloroquine (CQ) and it is a broad-spectrum antibiotic. It is mainly used for the treatment of malaria but also inhibits COVID-19 viral replication significantly [111]. The possible antiviral mechanism of CQ includes interference of glycosylation of ACE-2 at the time of viral entry [112] and increasing endosomal pH needed cell/virus fusion [113]. Besides that, CQ could reduce the damage of cytokine storm (Hyper inflammatory response against SARS-CoV-2 viral infection) by down-regulating the production of cytokines and expression of TNF-α receptor [111].
Research findings demonstrated that in vitro, CQ was highly useful in controlling viral entry and post entry stages of SARS-CoV-2 infection [114]. Also, it is shown that CQ phosphate is beneficial for improving lung imaging findings, preventing exacerbation of pneumonia, promoting a virus-negative conversion and shortening disease course [115]. In context of cytokine storm, it is found that low doses of HCQ might reduce cytokine storm in severe COVID-19 patients [116]. However, CQ has a relatively narrow margin of therapeutic and toxic dose, in which CQ poisoning could lead to death [117].
Remdesevir is a broad-spectrum antibiotic and a nucleotide analogue, which act as RNA replication blocker (polymerase inhibitor). This antibiotic interacts with the viral RNA-dependent RNA polymerase and delays chain termination. Thus, the SARS-CoV-2 viral replication stops and subsequently the complications of the viral infection can be prevented in the patients [118-122].

Plasma therapy for SARS-CoV-2 (COVID-19) patients
Plasma therapy includes intravenous immunoglobulin administration into the COVID-19 patients and provides passive immunity against the SARS-CoV-2 viral infection. The antibodies bind to specific target antigen via humoral and cellular arms of the immune system and block the cell-cell interaction by cell-surface receptors mediation. IgM and IgG antibodies also reduce mortality in adults with severe sepsis [123-126].

DISCUSSION

SARS-CoV-2 (COVID-19) infection presented as mild to severe form in different individuals. Infection of SARS-CoV-2 leads to cytokine bombardment. It is characterized by excessive production of inflammatory mediators, mainly IL-6, IL-10 and TNF-α, which triggers the bronchoalveolar damage, fibrosis of lungs and vascular leakage. Combination of these pathological features are denoted as acute respiratory distress syndrome (ARDS). The patients with underlying diseases develop, ARDS progresses to multiple organ dysfunction syndrome (MODS) and sepsis, which results in death of the patients [127-132].
The research data found till date, suggests that the mortality of COVID-19 patients is due to over immune response denoted as cytokine bombardment. Cytokine bombardment / storm is major pathological cause in the progression of this disease. Wan *et* al. found significant IL-6 elevation in most of the COVID-19 patients with severe disease [26, 27, 127-131]. Moreover, excessive production of cytokines (IL-6 and IL-10) results in immune dysfunction due to T-cells impairment [17].
In one of the studies in China, researchers reported that T lymphocytes, ($CD4^+$ and $CD8^+$) are the primary immunological marker responsible for fatal outcome in COVID-19 patients [127]. However, in contradiction Ghazazia et al. reported, TGF-β elevation in COVID-19 patients [128]. In a nutshell majority of research findings confirm the role of cytokine storm (IL-6, IL-10 and TGF-β) in COVID-19 patients.

CONCLUSION

The wild bats that had been sold in the wet market of Wuhan, China are the major reservoir for SARS-CoV-2 (COVID-19) strain. This contagious viral strain transmitted to humans from wild bats and gradually the chain reaction from human to human continued and affected all over the world. Studies suggest that SARS-CoV-2 strain infect humans by interacting with the host respiratory membrane protein via S spike, results in ACE-2 down regulation. The present review focuses on cytokine storm-based mechanism of hyper-immune response (Elevation of IL-6, IL-10 and TNF-α) in COVID-19 patients.

Author's contributions
All authors contributed to the present review. The idea of the article was originally suggested by Dr. KartikeyaTiwari and the literature search along with the data analysis was performed by KhadijahbintiZainal, SaralaPergasa and ShazwinaIzzatibintiSamah. All authors revised and approved the final review manuscript.

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Availability of data and material All the data was collected from WHO.

Code availability Not applicable.

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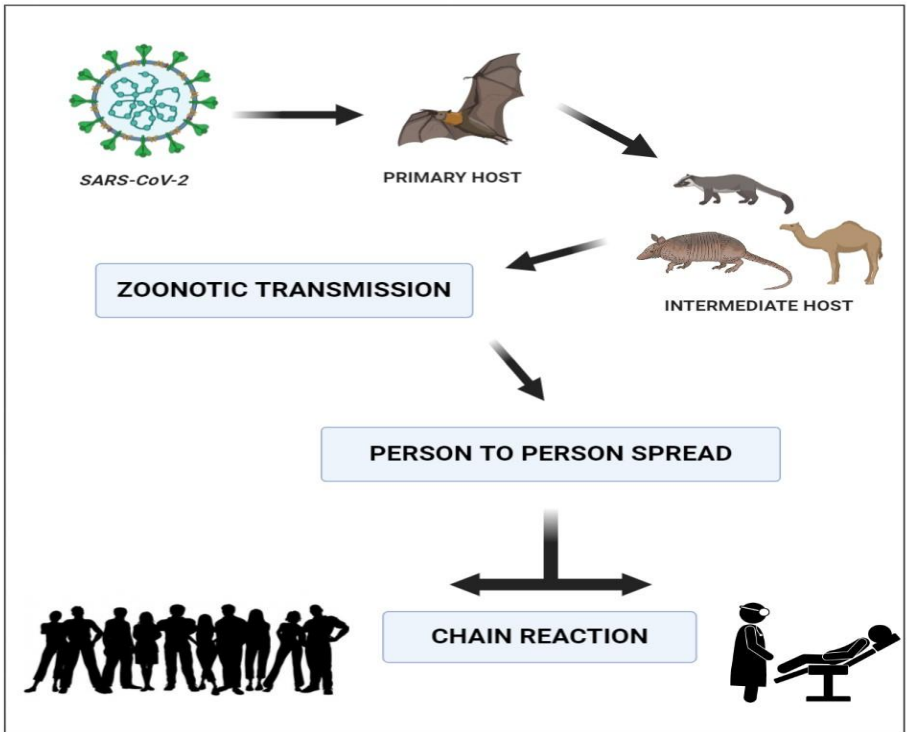

Fig. 1 Zoonotic transmission of novel SARS-CoV-2 (COVID-19) strain.

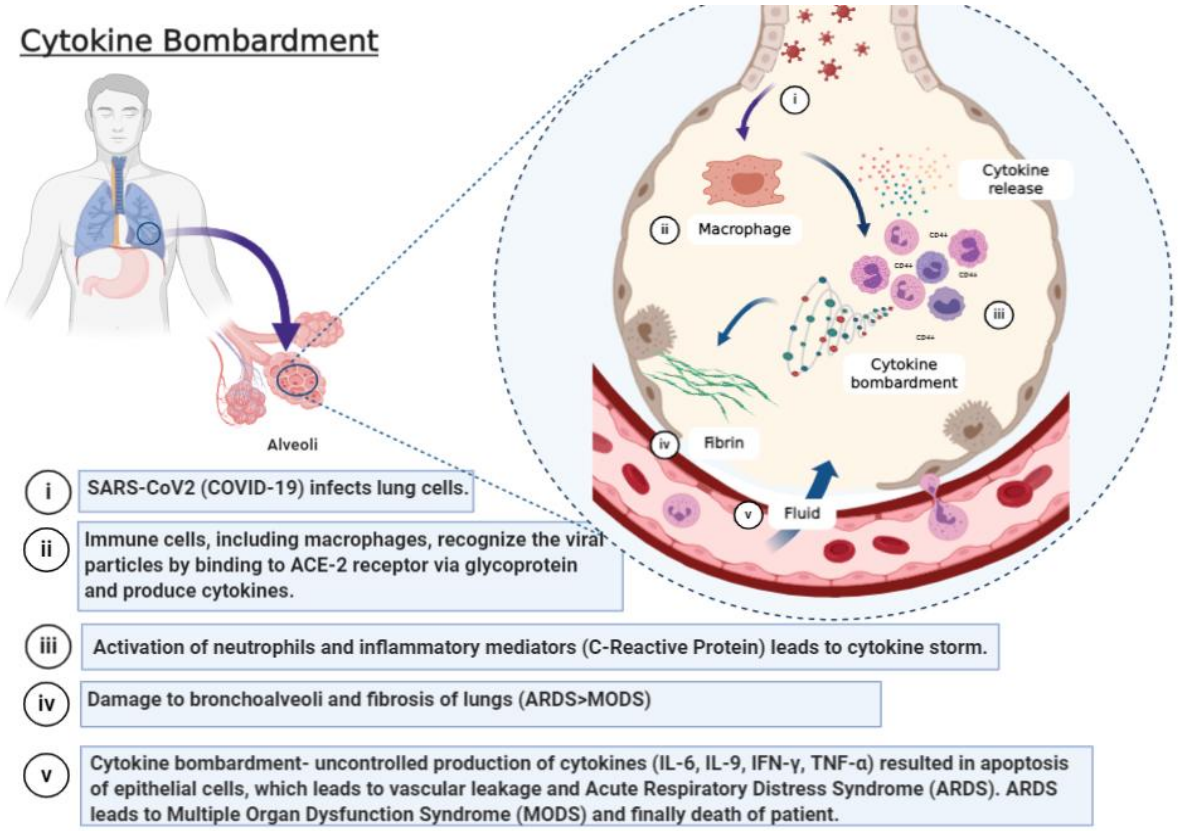

Fig. 2 Cytokine bombardment stages in COVID-19 patients.

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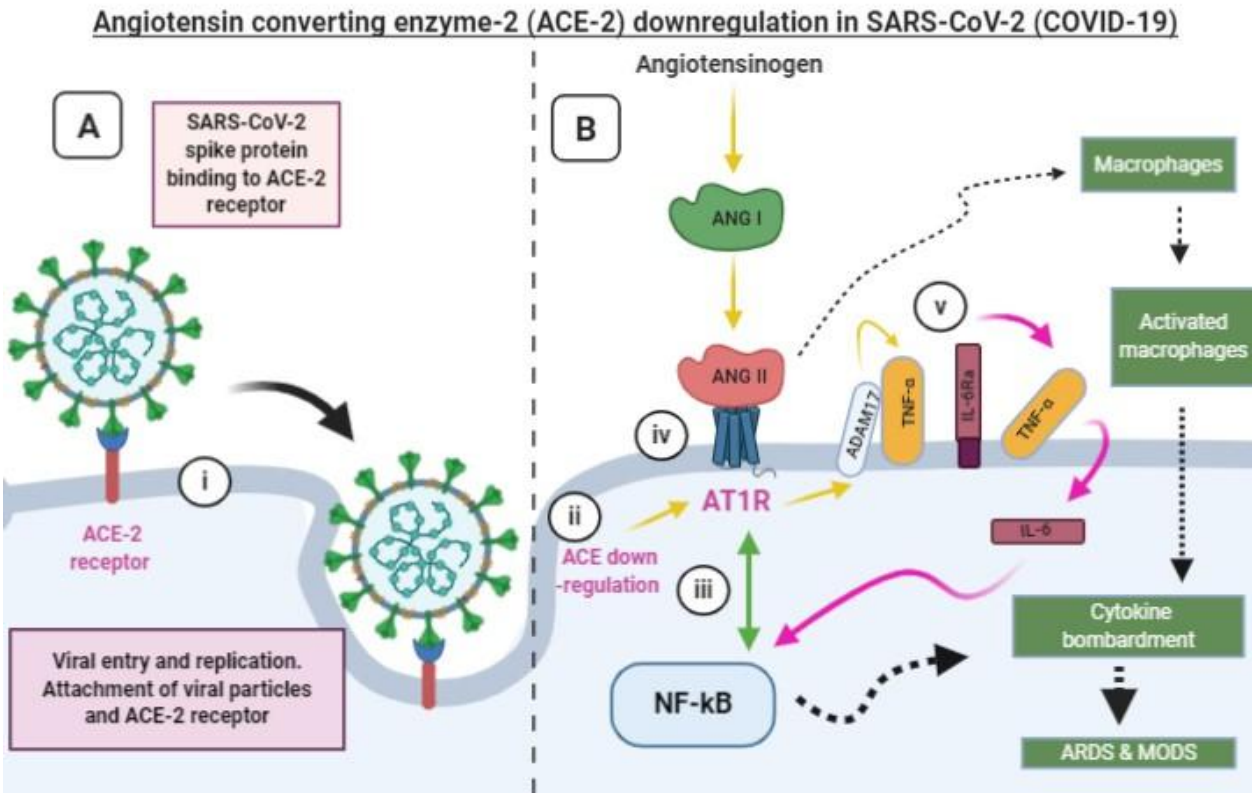

Fig. 3 Angiotensin converting enzyme-2 (ACE-2) downregulation mechanism in SARS-CoV-2 (COVID-19) patients

I. The virion particles enter the host cell by interacting with the ACE-2 receptor via its spike protein.
II. The ACE-2 expression is downregulated by the virus through the upregulation of angiotensin II (ANG II). Cleavage of ANG I by angiotensin converting enzyme-2 (ACE-2) results in ANG II.
III. Through NF-kB signalling, upregulated ANG II act on AT1R receptor and modulate the gene expression of several inflammatory mediators (IL-6, IL-9 and TNF-α).
IV. The interaction between ANG II / AT1R also affects the activation of macrophages and triggers cytokine bombardment, which results in uncontrolled activation of macrophages (macrophage activation syndrome) and leads to Acute Respiratory Distress Syndrome (ARDS).
V. ADAM17 (metalloprotease) also releases these pro-inflammatory cytokines and ACE-2 receptors to the soluble form, which facilitates the loss of the protective function of surface ACE-2 and probably increases SARS-CoV-2 pathogenesis.