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Interleukin-6 (IL-6): A Major target for quick recovery of COVID-19 patients

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Abstract

The COVID-19 pandemic is now an international health emergency. The virus is highly transmitted through close contact from person to person with rapid spread in communities.COVID-19 patient may be completely asymptomatic with a positive test or mild with influenza-like illness or serious symptoms that require hospitalization. Research evidence reveals that cytokine storm result to hyper-inflammation in severe Covid-19 patients indicating interleukin-6 as the most predominant cytokine antagonizing Sars-Cov-2 from onset of Covid-19 disease to severity. Various researches have monitored levels of IL-6 in Covid-19 stages from onset, severity to recovery. IL-6 levels were high and reduced at patients recovery. Interleukin 6 (IL-6) interacts with both cells of immune system and non-immune system cells and often displays hormone-like characteristics that affect homeostatic processes, evidenced by its role in a health and in specific disease condition such as sepsis, Covid-19 etc. Studies on immunobiology of IL-6, its roles in innate and adaptive immunity, the use and advantages of various antagonists of IL-6 has shown recovery on Covid-19 patients exception of older age patients and patients with underlying immunocompromised immune status, and chronic fatal ailment. This discovery has brought about inform clinical decisions to target the inhibition of interleukin-6 (IL-6) secretion and functional inflammation signaling pathways as a therapy for quick recovery of Covid-19 patients achievable by applying strategies of laboratory investigations to monitor its secreted levels to assess COVID-19 progression, and as a prognostic predictive marker for COVID-19 patient Survival. Suppression of its release as a major target for quick recovery ofCOVID-19 patient through inhibiting Interleukin-6 (IL-6) receptors with immunomodulatory anti-IL-6 receptor monoclonal antibodies (mAbs) therapy, Inhibition of pathogenic effects of IL-6 in COVID-19.More intensive studies is needed as a major areas for searching promising candidates for immunotherapeutic interventions.

Keywords: COVID-19, influenza-like illness, Interleukin 6, monoclonal antibodies.

Introduction

Coronavirus disease 2019 (COVID-19) also referred to as SARS-CoV-2 is a disease caused by the newly discovered coronavirus specie named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which has a novel properties through variations in its original form.(Jae *et al.*,2021). SARS-CoV-2 is an envelope, non-segmented, positive sense single stranded RNA virus.(Huang *et al.*,2020).It's a novel *betacoronavirus*,SARS-CoV-2 and its mode of transmission is through exposure to respiratory droplets carrying the infectious virus from close contact or droplet transmission from presymptomatic, asymptomatic, or symptomatic individuals harboring the virus. Fomite transmission from SARS-CoV-2 contamination of inanimate surfaces has been reported

based on many studies reporting the viability of SARS-CoV-2 on various porous and nonporous surfaces (Obeagu *et al.*, 2021; Asogwa *et al.*, 2021; Obeagu *et al.*, 2020; Obeagu, 2020; Ifeanyi *et al.*, 2020; Obeagu *et al.*, 2021).

SARS-CoV-2 was noted to be stable with the viable virus being detected up to 72 hours after inoculating stainless steel and plastic surfaces with the virus, compared to copper and cardboard surfaces.(Van *et al*.,2020)

Viable virus was isolated for up to 28 days at 20^0C from nonporous surfaces such as glass, stainless steel. recovery of SARS-CoV-2 on porous materials was reduced compared with nonporous surfaces.(Riddell *et al.*,2020) Nosocomial transmission through hospital contaminated intensive care units (ICUs) general wards, floors, computer mice, trash cans, and sickbed handrails as well as in the air up to 4 meters from patients. (Guo*et al.*, 2020) fecal-oral transmission.(Yeo*et al.*,2020) From mothers with COVID-19 toneonates through vertical transmission is possible but occurs in a minority of cases.(Kotlyar *et al.*, 2021), Cascella *et al.*,(2021).This Novel *betacoronavirus*, which emerged at the end of 2019 in China and has already infected almost 3.6 million people with 60, 000 deaths reported between 13-19 September.2021. This brings the cumulative numbers of confirmed cases and deaths globally to nearly 228 million and over 4.6 million respectively.(WHO, 2021).

North America is by far the most heavily affected area, followed by Europe, Asia and South America. In September 2021 the Region of the Americans Eastern Mediterranean, South-East Asia and Western Pacific regions reported a decrease in weekly case incidence, the African and European regions reported a similar number of deaths as compared to the previous week. Similarly, COVID-19 weekly mortality decreased in the African, Eastern Mediterranean and South-East Asian regions over the past week, with the South-East Asia Region reporting the largest percentage decrease (27%). In contrast, the Western Pacific Region reported an increase (7%) in the number of deaths while the Region of the Americas and the European Region reported a similar number of deaths as compared to the previous week. The death toll from COVID-19 is higher than those from severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) combined and has become a worldwide pandemic (coronavirus disease 2019,(COVID-19) (WHOhttps://www.who.int/emergencies/diseases/novel coronavirus-2019(2021), Zhu *et al.*,2020), Song *et al.*,2020). It has affected the world in a devastating way since December 2019, It has greatfatal infectivity, causing acute respiratory distress syndrome (ARDS) and multiple organ failure (Rothan and Byrareddy 2020).

The disease-related fatality is associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections in humans is attributed in part to life-threatening hyperinflammation sustained by a cytokine storm that eventually leads to multiple organ failure (Wang *et al.*,2020) This hyperinflammatory response is associated with elevated levels of inflammatory cytokines, including interleukin-6 (IL-6) (Tanaka *et al.*, 2016).

Although most cases present only mild symptoms, 20% of the patients develop severe pathology with acute bilateral pneumonia that may evolve to acute respiratory distress syndrome and multi-organ failure. The risk of severe disease and death increases with age and the presence of comorbidities (Wiersinga *et al.*, 2020).

Infection with SARS-CoV-2 involves two overlapping phases. The first phase is characterized by a high replicative activity of the virus, followed by a counteractive host immune response (To *et al.*, 2020). This infection has been divided into three clinical stages, regarding the severity and prognosis (Siddiqi and Mehra (2020). Stage I is defined by mild unspecified symptoms, such as myalgia, dry cough, headache, and subfebrile temperature, without any laboratory and radiological abnormalities. Stage II is characterized by cough, high fever, dyspnea, abnormal thoracic imaging, lymphopenia, and increased levels of inflammatory markers. It is further divided into two groups, according to the presence (IIb) or absence (IIa) of hypoxemia. stage III as its final stage displays clinical manifestations of a severe systemic inflammatory syndrome, resulting in severe respiratory failure with an unfavorable prognosis. During this last stage of the disease, values of several inflammatory markers are extremely high and macrophage activation syndrome may occur.

Due to the above COVID-19 effect clinical deterioration become rapid, and in a large proportion of patients the severe disease course is caused by systemic hyper-inflammation,described as “cytokine storm” (Yang *et al.*,(2020). Cytokine storm is a

condition of uncontrolled systemic hyper-inflammation caused by excess cytokine secretion leading to multi-organ failure and even death (Behrens and Koretzky 2017).In COVID-19 patients, the hyperimmune response, rather than the action of the virus itself, contributes to the pathogenesis of acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndromes (Li and Fan (2020). Repurposing certain widely used immunomodulators (Kingsmore, Grammer, and Lipsky (2020). such as glucocorticoids (GC), Disease modifying anti-rheumatic drugs (DMARDs), and biologic drugs based on recombinant fusion proteins and targeted DMARDs (Rodríguez*et al.*,2020,Schett *et al.*,(2020 is a logical first step when faced with a new disease that caused a hyperimmune response.(Nasonova and Samsonove 2020). The prognosis of COVID-19 is largely dependent on various factors that include the patient's age, the severity of illness at presentation, pre-existing conditions, how quickly treatment can be implemented, and response to treatment. WHO's current estimate of the global case fatality rate for COVID-19 is 2.2%. However, the case fatality rate is affected by factors such as age, underlying pre-existing conditions, and severity of illness. Results from a European multicenter prospective cohort study that included 4000 critically ill patients with COVID-19 reported a 90-day mortality of 31%, with higher mortality noted in elderly, diabetic, obese, and severe ARDS patients(COVID-ICU 2021,Cascella *et al.*, 2021).

Interleukin-6 (IL-6) plays a crucial role in the immunopathogenesis of COVID-19 and is supported by data from numerous studies who have reported increased serum concentrations of this cytokine, in severe cases (Chen,*et al.*,2019)Liu, *et al.*,*(*2020),Nasonova andSamsonove 2020).Several treatments for COVID-19 have been tested, which can be divided into three main categories drugs with direct antiviral effect, drugs with immunomodulatory effect, and neutralizing antibodies from convalescent plasma (Fragkou *et al.*,(2020). So far, among the first group, remdesivir has been considered the most prominent drug due to the evidence of faster clinical improvement and mortality reduction in the subset of hospitalized patients receiving oxygen (Beigel *et al.*,2020). However, these data are conflicting with other studies, and doubts remain about treatment efficacy and profile of patients that may benefit the most from this therapeutic (WHO 2020).

Considering the challenge of controlling virus transmission, and the lack of an unquestionably effective antiviral treatment, a therapeutic strategy of immunomodulation has been advocated (Harrison2020). This strategy is particularly relevant given the excessive production of proinflammatory cytokines recognized as crucial in the pathophysiologic process of severe COVID-19 (Huang *et al.*, 2020). In these cases, the loss of negative feedback in the immune response causes excessive production of inflammatory cytokines, leading to deleterious effects and poor prognosis (Behrens and Koretzky2017). A large group of cytokines has been recognized as significantly increased in severe COVID-19 patients which are the following; Interleukin-1β (IL-1β), IL-1RA, IL-2, IL-6, IL-7, IL-8 (CXCL8), IL-9, IL-10, IL-17, IL-18, tumor necrosis factor (TNF-α), interferon-gamma (IFN-gamma), granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), macrophage inflammatory protein 1 (MIP-1alpha/CCL3), monocyte chemoattractant protein-1 (MCP-1/CCL2), interferon gamma-induced protein 10 (IP-10/CXCL10), and fibroblast growth factor (FGF) (Y*et al.*, (2020). Most importantly, some of them (IL-6, IL-8, and TNF-α) are regarded as independent markers of the severe disease (Del-Valle *et al.*, 2020). A deeper knowledge of the SARS-CoV-2-induced cytokine storm, including its triggering mechanisms, molecular components, and kinetics, is necessary for a better understanding of the pathological process in COVID-19 and therefore for the identification of the most adequate therapeutic targets and timing of drugs administration. So far, several studies have been published on the potential effects of specific (anti-IL-6, anti-IL-1, anti-GM-CSF, and anti-TNF-α) and non-specific therapies corticosteroids. (Harrison, 2020). Among the immunomodulatory therapies for COVID-19, corticosteroids have been the most widely used, particularly dexamethasone, after growing evidence of their benefit in reducing mortality in hospitalized patients receiving oxygen and especially in patients supported with mechanical ventilation (Sterne *et al.*, 2020). Nevertheless, the most adequate dosage for each patient, precise timing of administration and duration of treatment remain to be elucidated. Also, a more selective drug would be desirable, especially considering the already existing immune dysfunction.

Among all the up-regulated cytokines that may represent selective therapeutic targets, IL-6 has been regarded as particularly important in the COVID-19 pathogenesis and may be antagonized by existing

drugs. IL-6 is an inflammatory interleukin mainly produced by macrophages and T lymphocytes in response to pathogens and is pivotal to controlling several viral infections (Velazquez-Salinas *et al.*,2019)While homeostatic values of IL-6 contribute to the resolution of infections and tissue lesions, its exacerbated production contributes decisively to cytokine storms (Tanaka *et al.,* 2016). In COVID-19, IL-6 has been positively correlated with disease stages and radiologic changes (Iannaccone*et al.*,2020). Furthermore, the potential prognostic value of IL-6 has been explored regarding the need for mechanical ventilation, mortality or both, when considered alone or in combination with other variables (Herold *et al.*,2020). Yet, most studies quantify IL-6 only at patient admission, a strategy that may not be appropriate to accurately predict the outcome or to guide treatment due to the dynamic inflammatory process occurring during infection with SARS-CoV-2. Of all the available drugs that specifically inhibit IL-6 pathway, only tocilizumab (an IL-6 receptor antagonist) has, so far, a reasonable body of evidence in COVID-19. A recently published meta-analysis on the efficacy of tocilizumab in those patients found that cumulative evidence from randomized controlled trials (RCTs) suggests a risk reduction of mechanical ventilation but no effect on mortality, while cumulative evidence from cohort studies suggests an association between tocilizumab and lower mortality (Tleyjeh *et al.*,2020, Santa *et al.*, 2021) However, only 3 of the 19 cohort studies and none of the 5 selected randomized controlled trials RCTs used elevated. IL-6 level as an inclusion criterion. A More highly Elevated Interleukin-6(IL-6) level in tandem with the severity of COVID-19 compared to other associated cytokine levelspresent Interleukin-6 (IL-6) as a major target for quick recovery of COVID-19 Patients.Scientific research often begins from a simple to complex concepts therefore some key terms that propagates this knowledge in this topic, such as coronavirus disease. coronaviruses particularly Sars-Cov-2, cytokines and its role in health and disease, Cytokine storm in Covid-19 Patient, Interleukin-6 and its role in Covid-19 immunopathogenesis, and lastly Interleukin-6 (IL-6) a major target for quick recovery of COVID-19 Patient will be discussed.

Coronavirus disease

Coronavirus disease 2019 (COVID-19) is a highly contagious viral illness caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), It has had a catastrophic effect on the world's demographics resulting in more than 3.8 million deaths worldwide, this makes it an emerging most consequential global health crisis since the era of the influenza pandemic of 1918. The first cases of this respiratory viral illness were first reported in Wuhan, Hubei Province, China, in late December 2019.(Cascella *et al.*,2021). SARS-CoV-2 rapidly disseminated across the world in a short span of time, compelling the World Health Organization (WHO) to declare it as a global pandemic on March 11, 2020. Since being declared a global pandemic, COVID-19 has ravaged many countries worldwide and has overwhelmed many healthcare systems. The pandemic has also resulted in the loss of livelihoods due to prolonged shutdowns, which have had a rippling effect on the global economy. Even though substantial progress in clinical research has led to a better understanding of SARS-CoV-2 and the management of COVID-19, limiting the continuing spread of this virus and its variants has become an issue of increasing concern, as SARS-CoV-2 continues to wreak havoc across the world, with many countries enduring a second or third wave of outbreaks of this viral illness attributed mainly due to the emergence of mutant variants of the virus.

Like other RNA viruses, SARS-CoV-2, is prone to genetic development of mutations over time, resulting in mutant variants that may have different characteristics than its ancestral strains. Several variants of SARS-CoV-2 have been described during the course of this pandemic, among which only a few are considered variants of concern (VOCs) by the WHO, given their impact on global public health. Based on the recent epidemiological update by the WHO, as of June 22, 2021, four SARS-CoV-2 VOCs have been identified since the beginning of the pandemic. Alpha (B.1.1.7): first variant of concern described in the United Kingdom in late December 2020.Beta (B.1.351): first reported in South Africa in December 2020. Delta .(B.1.617.2): first reported in India in December 2020 Gamma(P.1): first reported in Brazil in early January 2021.

SARS-CoV-2 Variants of Interest (VOIs)

SARS-CoV-2 Variants of Interest (VOIs) are defined as variants with specific genetic markers that have been associated with changes that may cause enhanced transmissibility or virulence, reduction in neutralization by antibodies obtained through natural infection or vaccination, the ability to evade detection, or a decrease in the effectiveness of therapeutics or

vaccination. The WHO Weekly Epidemiological update on June 22, 2021, described seven variants of interest (VOIs), namely **Epsilon**,Centre for disease control CDC classified this strain as a variant of concern in the US becauseit harbor specific mutations (B.1.427: L452R, D614G; B.1.429: S13I, W152C, L452R, D614G) andincreased transmissibility.(Zhang *et al.*,2021)

WHO and the CDC Identifies it as VOI Zeta (P.2)because it has key spike mutations (L18F; T20N; P26S; F157L; E484K; D614G; S929I; and V1176F)and potential reduction in neutralization by antibody treatments and vaccine sera it was first detected in Brazil in April 2020. WHO and the CDC Identifies Eta (B.1.525) and Iota (B.1.526) as variant of interestdue to its possession ofkey spike mutations(B.1.525) and Iota (B.1.526) (B.1.525: A67V, Δ69/70, Δ144, E484K, D614G, Q677H, F888L; B.1.526: (L5F*), T95I, D253G, (S477N*), (E484K*), D614G, (A701V*) andpotential reduction in neutralization by antibody treatments and vaccine sera. first detected in New York in November 2020 and classified

Theta (P.3); variant of interest also called GR/1092K.V1 carry key spike mutations (141-143 deletion E484K; N501Y; and P681H) and was first detected in the Philippines and Japan in February 2021 Iota (B.1.526); Kappa (B.1.617.1) variant harbor key mutations ((T95I), G142D, E154K, L452R, E484Q, D614G, P681R, and Q1071H) and was first detected in India in December 2021.

Lambda (C.37) variant of interest was first detected in Peru and has been designated as a VOI by the WHO in June 2021 due to a heightened presence of this variant in the South American region.

There has been unprecedented speed of vaccine development against the prevention of COVID-19 and robust global mass vaccination efforts. however the emergence of these new SARS-CoV-2 variants threatens to overturn the significant progress made so far in limiting the spread of this viral illness. Nevertheless continuous effort is still ongoing in exploring immunomodulatory therapies as target for the treatment of this ailment. (Cascella *et al.*,2021).Coronaviruses (CoVs) are positive-stranded RNA(+ssRNA) viruses with a crown-like appearance under an electron microscope (coronam is the Latin term for crown) due to the presence of spike glycoproteins on the envelope. The subfamily Orthocoronavirinae of thefamily Coronaviridae, order Nidovirales and realm Riboviria. (Fan *et al.*,2019). The Nidovirales Coronaviruses are classified into four genera of Coronaviruses(CoVs)namely *Alphacoronavirus (alphaCoV), Betacoronavirus (betaCoV)Deltacoronavirus (deltaCoV)Gammacoronavirus (gammaCoV)* (Chan *et al.*, 2013*).*

SARS-COV-2.

SARS-CoV-2 is a novel betaCoV belonging to the same subgenus as the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), which have been previously implicated in SARS-CoV and MERS-CoV epidemics with mortality rates up to 10% and 35%, respectively. (Chan *et al.*, (2020) It has a round or elliptic and often pleomorphic form and a diameter of approximately 60–140 nm. Like other CoVs, it is sensitive to ultraviolet rays and heat. In this regard, although high temperature decreases the replication of any species of virus. Currently, the inactivation temperature of SARS-CoV-2 is being researched. A stainless steel surface held at an air temperature of 54.5°C (130°F) results in the inactivation of 90% of SARS-CoV-2 in approximately 36 minutes. At 54.5°C, the time for a 90% decrease in infectivity was 35.4 ± 9.0 minutes and the virus half-life was 10.8 ± 3.0 minutes. (Biryukov *et al.*,2021)Conversely, it may resist lower temperatures even below 0°C. Also, these viruses can be effectively inactivated by lipid solvents, including ether (75%), ethanol, chlorine-containing disinfectant, peroxyacetic acid, and chloroform except for chlorhexidine.

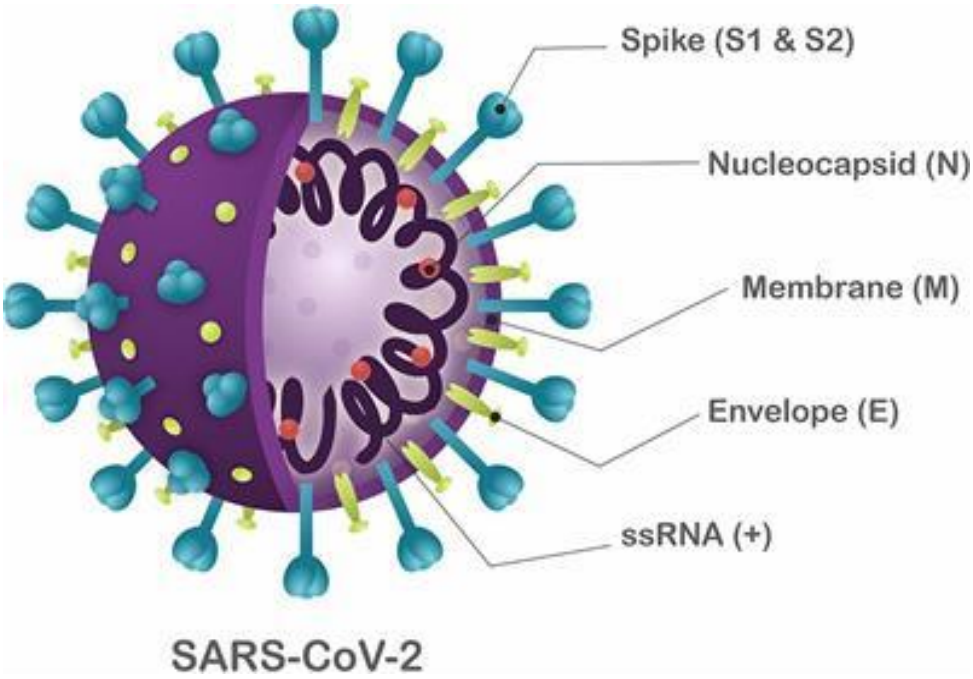

Figure 1.Schematic structure of SARS-CoV-2.Image adapted from Frontier Microbiology/ Vitology.(2020) https://doi.org/10.3389/fmicb.2020.01818.

SARS-CoV-2 structure is primarily formed by the structural proteins. it consist spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins. The S, M, and E proteins are all embedded in the viral envelope, a lipid bilayer derived from the host cell membrane. The N protein interacts with the viral RNA into the core of the virion.

SARS-CoV-2primary mode of transmission range from exposure to respiratory droplets carrying the infectious virus from close contact or droplet transmission from presymptomatic, asymptomatic, or symptomatic.Egdropletswith thevirus in the air up to 4 meters from patients,(Guo*et al.*,2020). Faecal-oral transmission(Yeo *et al.*,2020)vertical transmission occurs in a minority of cases(Kotlyar *et al.*,2021) transmission through nonporous surfaces such as glass, stainless steeland reduced transmission from porous materials.vertical transmission from mothers with COVID-19to neonates (Kotlyar *et al.*, 2021).

Clinical Manifestations of COVID-19 begins with asymptomatic or paucisymptomatic (estimated 5 days incubation period for SARS-CoV-2 while majority of patients develop symptoms within 11 days of infection,17.9% to 33.3% of infected patients remain asymptomatic(Nishiura *et al.*, 2020 Mizumoto*et al.*,2020) to symptomatic stage ofclinical illness characterized by acute respiratory failure requiring mechanical ventilation, septic shock, and multiple organ failure. Majority of symptomatic patients present with fever, cough, and shortness of breath and less commonly with a sore throat, anosmia, dysgeusia, anorexia, nausea, malaise, myalgias, and diarrhea. Stokes *et al*. reported that among 373,883 confirmed symptomatic COVID-19 cases in the US, 70% of them experienced fever, cough, shortness of breath, 36% reported myalgia, and 34% reported headache.(Stokes*et al.*,2020).Based on the severity of presenting illness that includes clinical symptoms, laboratory diagnosis and radiographic abnormalities, hemodynamics, and organ function. The National Institutes of Health (NIH) issued guidelines that classify COVID-19 into five distinct types as follows: Asymptomatic or Presymptomatic Infection in Individuals with positive SARS-CoV-2 test without any clinical symptoms consistent with COVID-19.

Mild illness: Individuals who have any symptoms of COVID-19 such as fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, anosmia, or dysgeusia but without shortness of breath or abnormal chest imaging.

Moderate illness: Individuals who have clinical symptoms or radiologic evidence of lower respiratory tract disease and who have oxygen saturation (SpO2) ≥ 94% on room air.

Severe illness: Individuals who have (SpO2) ≤ 94% on room air; a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen, (PaO2/FiO2) <300 with marked tachypnea with respiratory frequency >30 breaths/min or lung infiltrates >50%.

Critical illness: Individuals who have acute respiratory failure, septic shock, and/or multiple organ dysfunction. Patients with severe COVID-19 illness may become critically ill with the development of acute respiratory distress syndrome (ARDS) which tends to occur approximately one week after the onset of symptoms.

ARDS is characterized by a severe new onset respiratory failure or worsening of an already identified respiratory picture. The diagnosis requires a set of clinical and ventilatory criteria such as chest imaging utilized includes chest radiograph, CT scan, or lung ultrasound demonstrating bilateral opacities (lung infiltrates > 50%), not fully explained by effusions, lobar, or lung collapse. If there are clinical and radiologic findings of pulmonary edema, heart failure, or other causes such as fluid overload, they should be excluded before assessing it to be ARDS.

The Berlin definition classifies ARDS into three types based on the degree of hypoxia, with the reference parameter being PaO2/FiO2 or P/F ratio. (Ranieri *et al.*, 2012)

Mild ARDS: 200 mmHg < PaO2/FiO2 ≤ 300 mmHg in patients not receiving mechanical ventilation or in those managed through non-invasive ventilation (NIV) by using positive end-expiratory pressure (PEEP) or a continuous positive airway pressure (CPAP) ≥ 5 cmH2O.

Moderate ARDS: 100 mmHg < PaO2/FiO2 ≤ 200 mmHg

Severe ARDS: PaO2/FiO2 ≤ 100 mmHg. When PaO2 is not available, a ratio of SpO2/FiO2 ≤ 315 is suggestive of ARDS. A multicenter prospective observational study that analyzed 28-day mortality in mechanically ventilated patients with ARDS concluded that COVID-19 ARDS patients had similar ARDS features from other causes. The risk of 28-day mortality increased with ARDS severity. (Ferrando *et al.*, 2012).

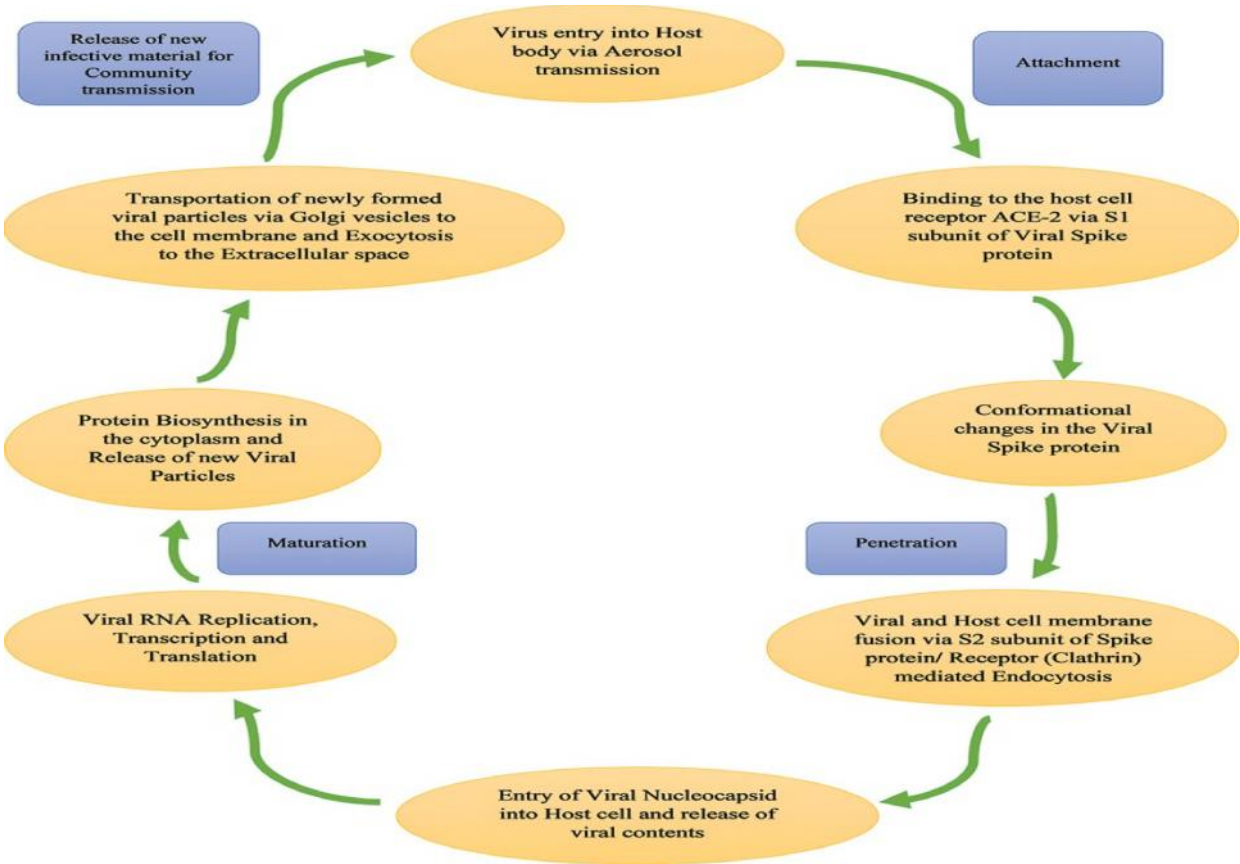

Figure2.Sars-Cov-2 life cycle.(Letko *et al.*,2020)

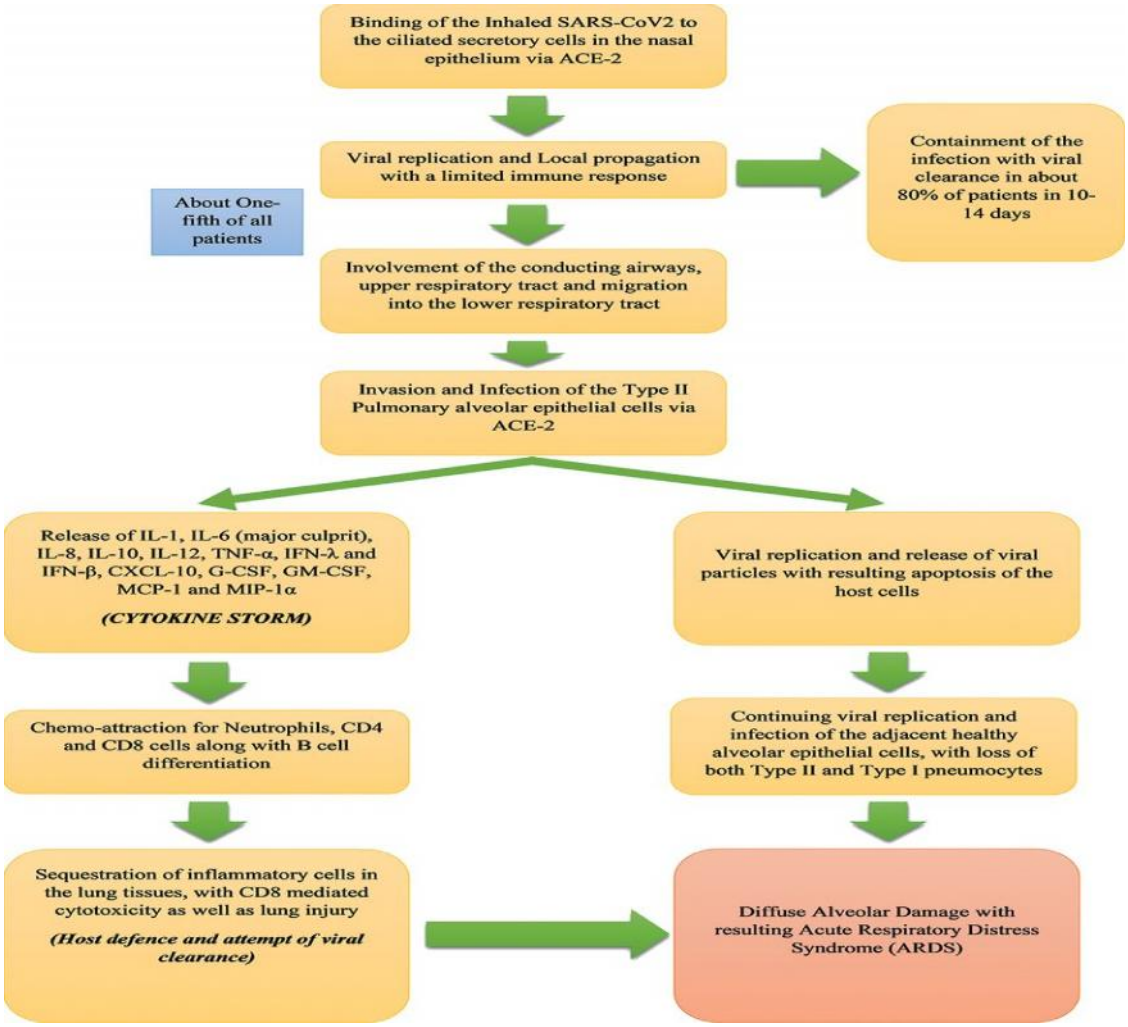

Figure 3 Pathophysiology of COVID-19. CXCL-10, C-X-C motif chemokine ligand 10; IFN, interferon; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; MIP-1α, macrophage inflammatory protein-1α; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; TNF-α, tumour necrosis factor-α; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor.(Letko *et al.*,2020)

Cytokine in health and disease

Cytokines are Non-antibody proteins secreted by inflammatory leukocytes and some non-leukocyticcells, that act as intercellular mediators. They are produced by a number of tissue or cell types rather than by specialized glands. They generally act locally in a paracrine or autocrine rather than endocrine manner.

Immunologically Cytokines are identified as cell-signaling group of low molecular weight extracellular polypeptides/glycoproteins synthesized by different immune cells, mainly, by T cells, neutrophils and macrophages, which are responsible to promote and regulate immune response in terms of activity, differentiation, proliferation and production of cells and other cytokines.These polypeptides act on signaling molecules and cells, stimulating them toward sites of inflammation, infections, traumas, acting on primary lymphocyte growth factors and other biological functions. Cytokines may act in the site where they are produced (autocrine action), in nearby cells (paracrine action) or in distant cells (endocrine action). In this sense, they are important in the development and regulation of immune system cells. Different types of cytokines had been discovered, including chemokines, interferons (IFN), interleukins (IL), lymphokines and tumor necrosis factor (TNF)(zhang and An 2007, Turner *et al.*,2018,Vinicius *et al.*,2018).

Cytokines are produced by a number of cell types, such as leukocytes which regulate immunity, inflammation and hematopoiesis (Deverman and Patterson 2009) About 200 cytokines are recognized to date. They have a high degree of a helical structure and the molecules share a similar polypeptide fold with four a helical bundles. They are categorized on the basis from which they are produced either from Th1 cells , Th2 cells. Th17 and T regulatory cells (Treg). It secretes IL-17, IL-17F, IL-22 and IL-25. Treg cells type 1 (Tr1) secrete mainly IL-10and IFN-γ, IL-5 in lesser amount and very low level of TGF-β and IL-2. Tr3 subset of Treg (also called Th3 cells) produces preferentially TGF-β and lesser amounts of IL-10

According to their secretion they are classified into lymphokines (cytokines that are secreted by T cells and regulate the immune response, Pro-inflammatory cytokines (cytokines that amplify and perpetuate the inflammatory process), Growth factors cytokines (cytokines that promote cell survival and result in structural changes in the airways), Chemokines (cytokines that are chemotactic for inflammatory cells) and Anti-inflammatory cytokines (cytokines that negatively modulate the inflammatory response) (Deverman and Patterson 2009). Inflammatory Cytokines. Proinflammatory cytokines are immunoregulatory cytokines that amplify and perpetuate the inflammatory process whichfavour inflammation. They are produced predominantly by activated macrophages and are involved in the up-regulation of inflammatory reactions.Proinflammatory cytokine-mediated inflammation is a cascade of gene products usually not produced in healthy persons. Its effective in stimulating the expression of these genes. endotoxins trigger Proinflammatory cytokines production. The major proinflammatory cytokines. Proinflammatory cytokines are responsible for early immune responses. Proinflammatory cytokines are IL1-alpha, IL1-beta, IL6, and TNF-alpha. Other proinflammatory mediators include members of the IL20 family, IL33 LIF, IFN-gamma, OSM, CNTF, TGF-beta, GM- CSF, IL11, IL12, IL17, IL18, IL8 and a variety of other chemokines that chemoattract inflammatory cells. These cytokines either act as endogenous pyrogens (IL1, IL6, TNF-alpha), upregulate the synthesis of secondary mediators and proinflammatory cytokines by both macrophages and mesenchymal cells including fibroblasts, epithelial and endothelial cells, It stimulate the production of acute phase proteins, or attract inflammatory cells.(Gulati K *et al.*,2016)

Cytokine storm

The pathogenetic origin of cytokine storm cyndrome (CSS) is associated with the dysregulated synthesis of a wide range of cytokines involving pro-inflammatory, immunoregulatory, anti-inflammatory and chemokines, reflecting the pathological activation of innate and acquired (Th1 and Th17) immunity. These include IL-1, IL-2, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-17, IL-18, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), tumor necrosis factor (TNF)-α, interferon (IFN)γ-induced protein 10, monocyte chemoattractant protein (MCP)-1, macrophage inflammatory protein (MIP)-1α, chemokines (CCL1, CCL3, CCL5, CXCL8, CXCL9, CXCL10, etc.) from the role of IL-6 in covid 19 inhibitors in the treatment of Covid -19 patient.(Liu *et al.*,2020)

Interleukin-6

Interleukin-6 (IL-6) is a member of the pro-inflammatory cytokine family, It induces the expression of a variety of proteins responsible for acute inflammation, and plays an important role in the proliferation and differentiation of cells in humans. (Schelle*et al.*, 2011) IL-6 signaling is mediated by building a complex of IL-6, the transmembrane IL-6 receptor (mIL-6R) or with soluble forms of IL-6R (sIL-6R), and the signal-transducing subunit molecule gp130. Therefore, three modes for IL-6 signaling may occur in which IL-6 is binding to mIL-6R (classic), to sIL-6R (trans-signaling), or is joined through IL-6R to gp130 on nearby located cells (trans-presentation). These pathways, and the fact that gp130 is ubiquitously expressed, lead to the pleiotropic functions of IL-6. The control of IL-6 signaling is regulated through the induction of suppressor molecules after activation of the IL-6 pathways as well as through the presence of sIL-6R and gp130 forms in the blood. Vice versa, an overproduction of IL-6 and dysregulation of the IL-6 signaling pathways can result in inflammatory and autoimmune disorders as well as cancer development suggesting that IL-6 plays a significant role in the human cytokine network. Several therapeutic agents have been evaluated for inhibiting the cytokine itself, the signaling via the IL-6 receptor, or target kinases (e.g., JAK/STAT) associated with the signaling pathways.(Peter and Wolfram 2020).

Interleukin-6 (IL-6) is produced by almost all stromal and immune system cells, including B lymphocytes, T lymphocytes, macrophages, monocytes, dendritic cells, mast cells, and other nonlymphocytic cells, such as fibroblasts, endothelial cells, keratinocytes, glomerular mesangial cells and tumor cells. As a multifunctional member of the cytokine network, IL-6 acts as a mediator between pro- and anti-inflammatory reactivity by initiating trans- and classical signaling, respectively (Hunter and Jones2017). In addition, IL-6 is responsible for bridging the gap between the innate and adaptive arms of the immune response (Schelle*et al.*, 2011, Du *et al.*,2021)

Interleukin-6 is a pro-inflammatory cytokine.Previous research on bioavailability of Interleukin-6 (IL-6reveals that Interleukin-6 (IL-6) is produce by almost all stromal and hematopoietic cells, and its expression is highly regulated by microRNAs, RNA-binding proteins, RNases and circadian response factors. Physiological concentrations of IL-6 in human serum are normally low (1–5 pg/ml), but during disease, IL-6 is rapidly induced and in extreme circumstances (such as septic shock or cytokine-release syndrome) itreaches µg/ml quantities. Data from patients with COVID-19 show that IL-6 concentrations in SARS-CoV-2 infection are comparable to those in patients with other forms of sepsis or acute respiratory distress syndrome but are far lower than those observed in cytokine-release syndromes associated with polyclonal T cell activation.(Du*et al* .,2021)

Interleukine-6 mediated cytokine storm in COVID-I9 patient

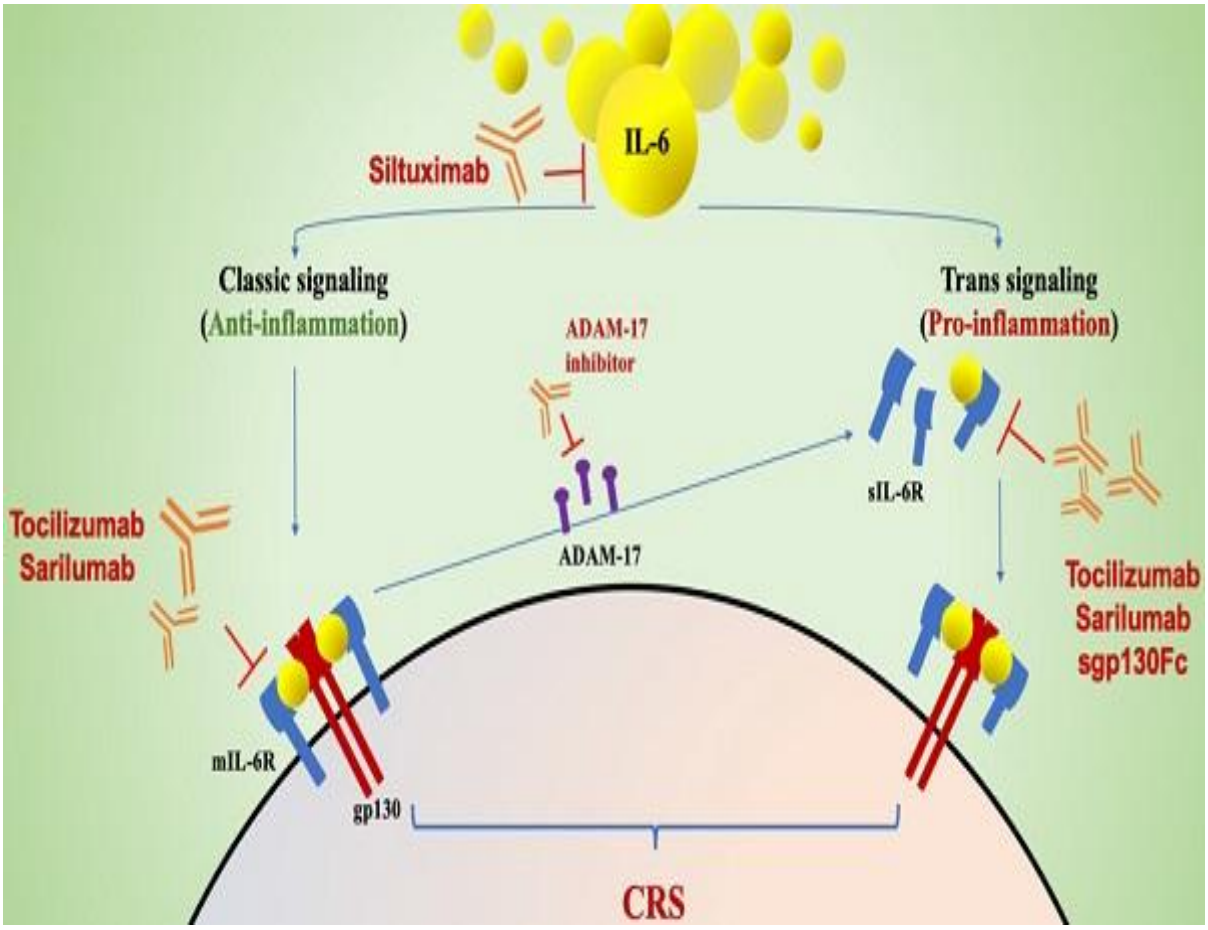

Figure 4.Cytokine release syndrome (CRS) and Paces *et al.*, 2020, Du *et al.*,2021 Cytokine release syndrome (CRS) may be the key factor in the pathology of severe coronavirus disease 2019 (COVID-19). As a major driver in triggering CRS in patients with COVID-19, interleukin-6 (IL-6) appears to be a promising target for therapeutics. The results of inhibiting both trans- and classical- signaling with marketed IL-6 inhibitors (tocilizumab, siltuximab and sarilumab) in severe COVID-19 patients are effective based on several small studies and case reports so far (Paces *et al.*, 2020, *Du et al.*, 2021).

Figure 4 above illustrates IL-6 response in patients with COVID-19, and the pathogenesis role of IL-6-mediated CRS in severe COVID-19, and the rationale for the use of anti-IL-6 agents and key information regarding the potential features of these IL-6 inhibitors in COVID-19 patients.

Huang *et al.* (2017) reported the clinical features and cytokine profile of critically ill patients with COVID-19 in Wuhan, China, and suggested that a cytokine storm, also known as cytokine release syndrome (CRS), could be associated with disease severity. After virus infection, dendritic cells, macrophages, and neutrophils, as the first line of defense, start the immune reaction and affect its type and intensity. Autopsies on patients who died of COVID-19 revealed a high infiltration of macrophages within the area of bronchopneumonia (Barton *et al.,* 2020). These macrophages significantly produce IL-6, suggesting that they may be the cause of excessive inflammation in COVID-19 disease. Similarly, in SARS disease, which represents the closest disease to COVID-19 in humans, high production of IL-6 was also previously described. SARS produces even more intense IL-6 than common viral respiratory diseases (e.g., influenza and parainfluenza)(Pace*set al.,* 2020). Recent studies have implied the possibility that inflammatory cytokine storms and inflammatory events are responsible for severe COVID-19 pathology .Thus, IL-6 should not be ignored in the treatment of severe COVID-19.

According to a recent meta-analysis, significantly higher levels of IL-6 in serum are demonstrated to be predictors of the disease severity and prognosis of patients with COVID-19 (Chen *et al.*,2020, Du *et al.*,2020), Another meta-analysis indicated that elevated IL-6 levels occur more often in severe and critically ill COVID-19 patients than in mildly ill COVID-19 patients, and they occur more often in patients who die from the disease than in those who survive (Zhu *et al.*,2020) This might help clinicians identify critical patients in a timelier and more effective manner.

However, before regarding IL-6-mediated CRS as the pathological driver of severe COVID-19, caution should be warranted. It is noteworthy that COVID-19 patients lack most of the hallmarks of CRS, including hypotension, capillary leak syndrome, and neurotoxicity [35]. In addition, the clinical course of CRS is much more acute than that of COVID-19 (Hay *et al.*,2017) Evidence shows that, compared with 1,000-10,000 pg/ml in CRS, serum IL-6 levels are far lower in COVID-19, with peak levels typically less than 100 pg/ml in COVID-19(.(Zumla *et al* .,2020, Du *et al* .,2021)

The ability to discern the role of IL-6 in COVID-19 is indicated by the presence of soluble cytokine receptors (sgp130 and sIL-6R), which affect the bioavailability and signaling properties of IL-6.

How these factors shape IL-6 activities in COVID-19 help establish whether IL-6 activities are abnormally regulated in COVID-19 or whether the maintenance of circulating IL-6 is more significant. This is achieved by genetic studies of patients with COVID-19 using Genome-wide association studies and functional analyses of SNPs which identify disease susceptibility loci affecting the IL-6 cytokine cassette. For example, a specific IL6R mutation (rs2228145), which results in elevated circulating sIL-6R, protects patients from SARS-CoV-2 infection and reduces the need for hospitalization. These results could be viewed as surprising, as sIL-6R maintains the circulating half-life of IL-6 and drives inflammatory signals through IL-6 trans-signaling. However, the IL-6–sIL-6R complex is also susceptible to antagonism by sgp130, inhibiting IL-6 trans-signaling and sequestering IL-6 from the membrane-bound IL-6R. There are also IL6ST polymorphisms affecting sgp130 levels, which often associate with indices of cardiometabolic disorders, but it is not clear whether they have any impact on COVID-19. Thus, there is genuine complexity that makes it difficult to determine whether genetic mutations influence underlying health conditions or enhance early IL-6 production that promotes viral control. These considerations may provide additional support for the idea that IL-6 blockade can be beneficial.

Clinical trials with olamkicept (derived from sgp130) might offer additional insights by targeting IL-6 trans-signalling as opposed to a more global IL-6 blockade (Du *et al.,* 2020).

Despite multiple trials in the past 12 months, it is still difficult to judge who will benefit from IL-6 blockade in COVID-19. This type of more effective approach may help to identify patients that would respond to IL-6 targeted therapy. Unlike IL-6 and sIL-6R, sgp130 is less prone to inflammatory regulation, and changes in the circulating IL-6:sIL-6R:sgp130 ratio may offer a more informed view of IL-6 bioactivity (Du *et al.*,2020).

Interleukin-6 (IL-6) A major target for quick recovery of COVID-19 patient

Coronavirus disease 2019 (COVID-19) has very rapid infectivity and its fatal, causing acute respiratory distress syndrome (ARDS) and multiple organ failure (Rothan and Byrareddy, 2020). In serious cases, clinical deterioration is rapid, and in a large proportion of patients the disease severity is caused by systemic hyper-inflammation called "cytokine storm" (Yang *et al.,* 2020) Several research reveals that interleukin-6 plays a unique role in the cytokine storm occurring in patients with COVID-19, its good correlation to the disease severity, the risk of needing mechanical ventilation, or death, the life threatening effect of interleukin-6 storm evidenced in its high levels in cytokine release syndrome recommends it as a pharmacological target for quick recovery ofCovid-19 patients.(Huang *et al.,*2020, Han *et al.,*2020, Herold *et al.,*2020). The target of interleukin-6 for quick recovery of Covid-19 patients through research has led to the use of the following Immunological Strategies:

Monitoring interleukin-6 levels as a tool in determining COVID-19 progression from Acute to severity stage of coronavirus disease 2019 in Patients.

Monitoring interleukin-6 levels as a Prognostic Marker for COVID-19 patient Survival.

Suppression of Interleukin-6 (IL-6) release as a major target for quick recovery of Covid-19 patients.

The use of biologics immunomodulatory therapy example Anti-IL-6 receptor Monoclonal Antibodies (mAbs) inhibiting Interleukin-6 (IL-6) receptors.

The use of personalized immunomodulatory therapy, with respect to the role of cytokines in pathogenesis are derived from studies aimed to find other relevant therapeutic targets for the treatment of CSS in patients with COVID-19. These therapeutic targets include inhibition of IL-6

Inhibition of pathogenic effects of IL-6 in COVID-19 patient.

How the above strategies are utilized to targets interleukin-6 for quick recovery of COVID-19 patients are discussed below.

Monitoring interleukin-6 levels a tool in determimingCOVID-19 progression from Acute to severity stage of coronavirus disease 2019 in Patients

Monitoring interleukin-6 levels is a potential to predict the recovery and non-recovery stage outcome of COVID-19 patients. Among the elevated levels of inflammatory mediators in COVID-19 patients, the blood levels of IL-6 are noticeably higher in non-survivors compared to survivors (Zhou *et al.,*2020, Tay *et al*.,(2020) and predict the need for mechanical ventilation. (Herold *et al.,* (2020; Hojyo *et al.,* 2020).

The advancement of COVID-19 disease from severe to critical stage is strongly associated with cytokine storm. Cytokine storms cannot only lead to apoptosis of epithelial and endothelial cells but also causes vascular leakage, leading to acute respiratory disease syndrome (ARDS) and other severe syndromes and even death.(Channappanavar and Perlman, 2017).According to research review data by Xiaohui*et al.* (2021) on association between IL-6 levels in severe disease and mortality in COVID-19 disease: a systematic review and meta-analysis. In this study for predicting the severe Covid-19 stage using IL-6, 12 studies reported the values of IL-6 levels. (Nagant *et al.,*2020; Shi *et al.,*2020) His data was arrived at using analysis from Spearman's correlation coefficient of logarithm SEN and (1-SPE) is 0.790 (p=0.002), which suggested the existence of a threshold effect.

The forest plot of the diagnostic odd ratio(DOR) of IL-6 for predicting the severe disease in patients with COVID-19 is shown in figure 5.

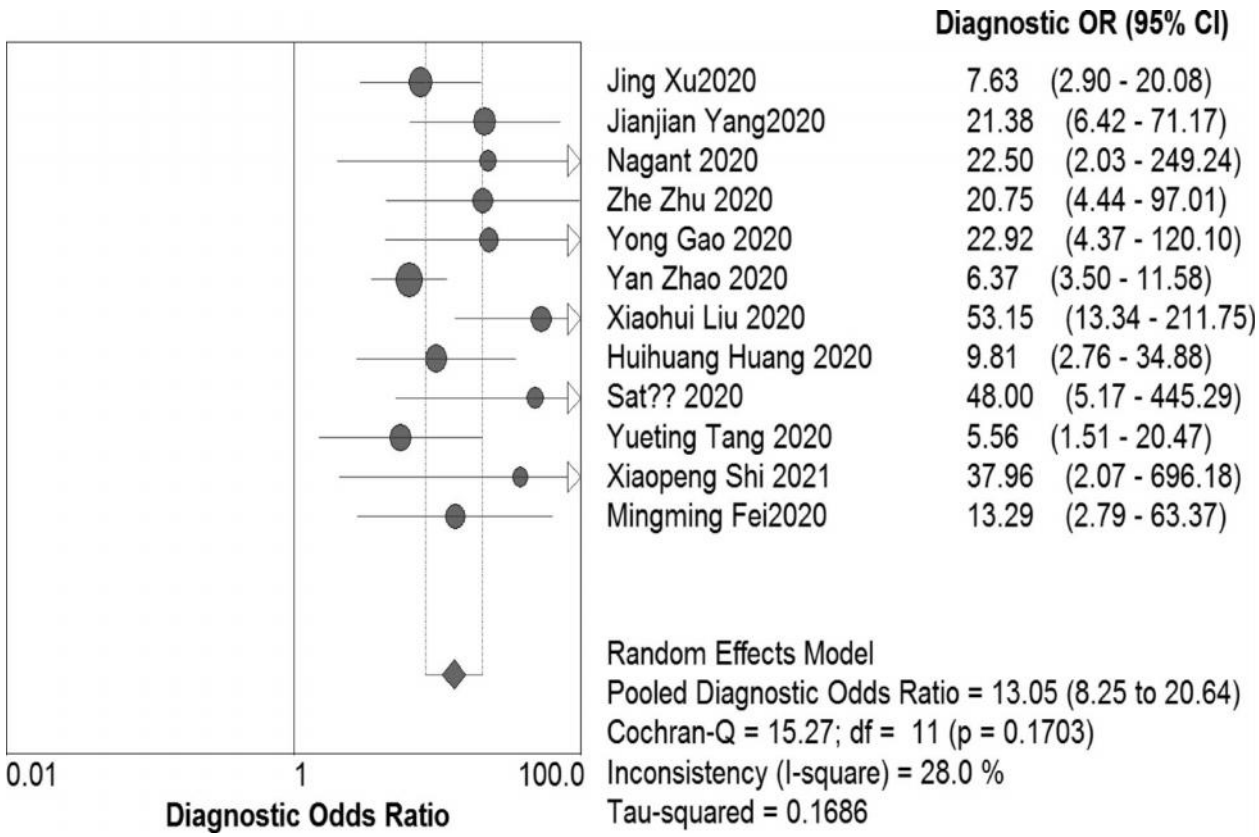

Figure 5.Forest plot of the DOR of IL-6 for predicting the severe disease in patients with COVID-19.DOR, diagnostic OR; IL-6, interleukin-6.Xiaohui et al., (2021),

The pooled diagnostic odds ratio (DOR) was 13.05 (95% CI 8.25 to 20.64, I2=28.0%), and there is no obvious heterogeneity among the studies. The summary of operating characteristic (SROC) curve is shown in figure 3

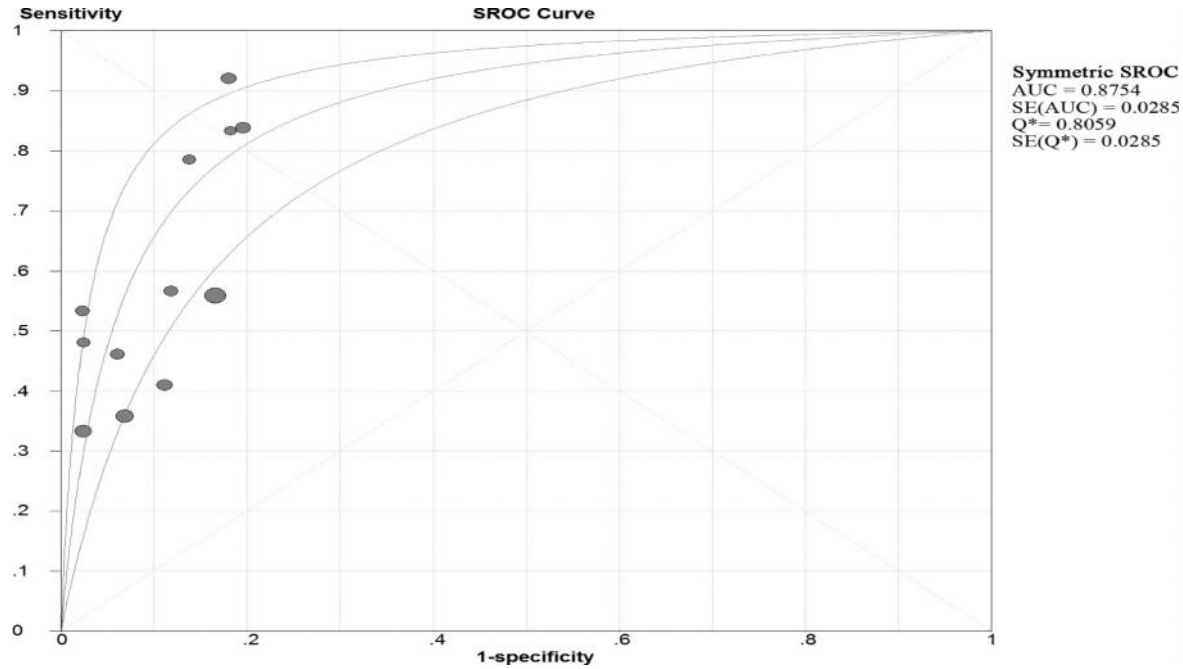

Figure 6.The summary of operating characteristic curve (SROC) showing predictive value of IL-6 in severe disease in patients with COVID-19.SROC, summary of operating characteristic IL-6, area under the curve AUC.(Xiaohui e*t al.*,2021).

In critically ill COVID-19 patients, abnormal cytokine production and uncontrolled regulation were observed. (Wu *et al.,* 2020) This out of control cytokine storm is not only the core factor responsible for disease progression and symptom deterioration in patients with COVID-19 but also the main factor leading to COVID-19 death. In this sense, COVID-19 is a disease similar to other viral ailments likes Middle East respiratory syndrome, 2020 SARS and avian influenza, all of which are characterized by the development of cytokine storms as a warning sign of disease escalation (Wu *et al.,* 2020).

Interleukin-6 as a Prognostic and predictive Marker for COVID-19 patient Survival

Research by Santa *et al.,* depicted IL-6 kinetics throughout the infection based on the onset of symptoms and the admission day. Patients were then grouped according to the shape of their IL-6 level curve, Matching profile and outcome, all patients in profile one died in the first week of hospitalization (non-survivors). All patients in the other profiles survived. In survivors' group 1 peak of IL-6 was observed around day ten after the onset of symptoms, but after admission, IL-6 levels decreased gradually as patients recovered. In survivors group two a peak of IL-6 level was observed approximately at day seven after the onset of symptoms and was also detected around day four of hospitalization, followed by decreasing values of IL-6 as patients recovered. It shall be noted however that patients in the survivors group one were admitted three days later (median difference) than patients in the survivor"s group two counting from disease onset. In both groups, all individuals displayed a peak of IL-6, which was limited in time. Importantly, after the 10th day of hospitalization, all these patients showed an IL-6 value close to normal. (Santa *et al.*,2021).From this researches reviewed above it showed that the level of IL-6 at admission is useful to predict the risk of patients needing mechanical ventilation or high-flow oxygen during hospitalization and its decrease due to treatment indicates it as a target for quick recovery of Covid-19 patients

Inhibition of pathogenic effects of IL-6 in COVID-19 patient by Targeting Only sIL-6R-dependent Trans-signaling pathway

Pathogenic effects of IL-6 in COVID-19 are mostly determined by trans-signaling rather than cis-signaling. At the same time, "classical" (cis) signaling is also involved in the induction of acute-phase response, the production of pathogenic Th17 and Th22 cells, and suppression of T regulatory cells. Therefore, trans and cis-signaling provide a multidirectional contribution to the development of the immunopathological process in the course of disease progression.

Key cytokines involved in infection-induced cytokine storm is interleukin 6 (IL-6) (Scheller and Rose-John, 2006; Zhang et al., 2020a). Tocilizumab is an IL-6 receptor antagonist approved by the US FDA for the treatment of severe CRS (Grupp*et al.,* 2013) and figures as an interesting drug to treat the cytokine storm caused by SARS-CoV-2 (Zhang *et al.,* 2020). The treatment of patients with severe COVID-19 with Tocilizumab presented no complications in the 21 assisted patients, with an average age of 56.8 ± 16.5 and no history of illness deterioration or death. Thus, it immediately improved the clinical outcome and appeared to be an effective treatment for reducing mortality (Xu et al., 2020). Another study employing the treatment of COVID-19 patients with Tocilizumab for 14 days reinforced these observations. The treatment was observed to cause an effective decrease in inflammatory markers, radiological improvement, and a reduction in ventilatory support requirements for these patients (Alattar et al., 2020). Additionally, Toniati and collaborators administered Tocilizumab in 100 patients in Italy (average age of 62 years old) who had been diagnosed with COVID-19 pneumonia and ARDS and required ventilatory support. Overall, at 10 days of follow-up, the respiratory condition was improved or stabilized in 77% of the patients, and, based on these data; the response to this drug in patients with severe COVID-19 was rapid, sustained, and associated with significant clinical improvement (Toniati *et al.,* 2020).

Immunological Strategies to Suppress Interleukin-6 (IL-6) release as a major target for quick recovery of Covid-19 patients

The development and use of personalized immunomodulatory therapy, with respect to the role of cytokines in pathogenesis, requires the studies that aimed to find other relevant therapeutic targets for the treatment of CSS in patients with COVID-19. These therapeutic targets include inhibition of IL-1, IL-6, with Siltuximaba chimeric human-mouse monoclonal antibody.

Anti-IL-6 receptor Monoclonal Antibodies

Research Data related to biological effects and molecular mechanism of action monoclonal antibody (MOA) of IL-6 which led to the discovery of Anti-IL-6 receptor Monoclonal Antibodies are understood and are summarized in a number of published reviews The use of monoclonal antibodies (mAbs) inhibiting Interleukin-6 (IL-6)receptors. Medicines such as Tocilizumab and Sarilumab, has been used in clinical practice to achieve this strategy as a major achievement in treating immune-mediated inflammatory disease (IMIDs) and in recent years in the management of critically ill patients with CSS including COVID-19.(Peter and Wolfram 2020)

Limitations /challenges in the use of biologics immunomodulatory therapy to target IL-6 for quick recovery of covid-19 patients

Although biologics provide a very useful addition to our therapeutic library, evidence suggests that they should not be considered a panacea. Serious adverse events have been reported and long-term safety data are lacking. Furthermore, a substantial number of patients demonstrate a poor response to these agents, confirming that our understanding of IMID immunopathogenesis is not complete.

The current challenge is to identify exactly when to introduce biologics into the therapeutic algorithm. Traditionally they have been used in those least likely to respond, that is, those who have failed multiple DMARDs and still have active disease. Certainly in rheumatology, the prevailing philosophy is to treat as early as possible in order to avoid the potential sequelae of joint destruction and functional loss. While in Covid-19 patients its also required to diagnose promptly and treat to avoid fatality.

Conclusion

In recent years and the discovery of biologic therapies and immunotherapies has become an exciting innovation in the treatment of diseases. For millions of patients, treatment success translate to rapid suppression of inflammation, prevention of disability, improved quality of life, and the goal of complete disease remission.

Clinical researches shows that cytokines contribute to immunopathology and that targeting these proteins can re-direct the course of disease. High levels of secreted interleukin-6 have been discovered at the course of identifying covid-19 prognostic markers as a means of monitoring covid-19 progression, prediction of patient recovery and survival. Interleukin 6 (IL-6) has a broad beneficial and non-beneficial effect on both cells of immune system and non-immune system cells and often displays hormone-like characteristics that affect homeostatic processes. This is evidenced by its role in a healthy state and in specific disease condition such as sepsis. Covid-19etc.The study of immunobiology of IL-6, the roles of IL-6 in innate and adaptive immunity, the use and advantages of various antagonists of IL-6 has shown recovery on Covid-19 patients, exception of older age patients and patients with underlying immunocompromised immune status, and chronic fatal ailments. Recent studies have proved the possibility that inflammatory cytokine storms and inflammatory events are responsible for severe COVID-19 pathology. Therefore IL-6 should not be ignored in the treatment of severe COVID-19.This research discovery has brought about inform clinical decisions to target the inhibition of interleukin-6 (IL-6) secretion and its functional inflammation signaling pathways with immunomodulatory agents and antagonist monoclonal antibodies as a therapy for quick recovery of Covid-19 patients.

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