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Relation of hypercytokinemia (cytokine storm) in viral respiratory SARS-COVID-2

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Abstract

COVID-19 (coronavirus disease) has ravaged the world in a way that no previous pandemic in the past 50 years has. Since the epidemic, our knowledge of the illness has advanced significantly; multiorgan involvement has the greatest influence on disease prognosis. A rapidly developing respiratory condition that is characterized by severe inflammation and damage to the lungs, resulting in difficulty breathing and reduced oxygen levels in the blood, cardiac failure, liver failure, renal damage, shock, and multi-organ failure all increase morbidity and mortality. Hyperinflammatory response, characterized by elevated cytokine levels, may have a role in the pathophysiology of COVID-19 illness. One of the most prominent markers of C is 'cytokine storm syndrome.' The link between COVID-19 interferon-alpha, beta, and interferon-gamma tumor necrosis factor and significant cytokine families are examined in this study. We examine cytokine sources and biological roles while addressing numerous changes in immune response cellular components that correlate with cytokine levels. Lastly, we briefly explore future therapeutics aimed at modulating the cytokine storm.

Keywords*: IL-6, IFN-γ, TNF-α, SARS, coronavirus COVID-19.*

1. Introduction

Wuhan, Hubei Province, China reported numerous pneumonia cases for unclear reasons in December 2019. As most pneumonia patients had attended the Wuhan wet animal market in the month preceding their diagnosis, the pneumonia was linked to it. Scientists immediately identified and named the infectious cause, SARS-Cov-2, a novel member of the Coronaviridae family. This is similar to what they did with SARS in 2002 and MERS in 2012. The estimated global mortality rate due to coronavirus 2019 (COVID-19) as of March 12, 2020 was 3.7% [1]. It remains much the same. A further 5% of the infected population is predicted to suffer catastrophic diseases requiring intensive care, with extracorporeal organ support therapy being a common necessity. This severely unwell group has a high mortality rate of 40–50% [2]. Molecular diagnostics, most commonly reverse-transcriptase polymerase chain reaction (RT-PCR), are increasingly being used to detect SARS-Cov-2, and these patients may show no symptoms at all (termed asymptomatic or presymptomatic infection). Contrarily, the most common symptoms of COVID-19 are fever (98%), cough (76%), dyspnea (55%), and myalgia or fatigue (44%). Sputum production (28%), headache (8%), hemoptysis (5%), and diarrhea (3%), are all possible symptoms. A patient with infectious pneumonia who stays in the hospital might develop acute respiratory distress syndrome

(ARDS) [4, 5], sudden cardiac damage [6, 7], and future infections [8]. In the worst cases, COVID-19 can cause ARDS, which affects 20–41% of hospitalized patients [4,8]. Multiple organ failure, including heart failure, kidney failure, liver damage, shock, and multi-organ failure, has also been described. The severity of a disease is rated according to its symptoms [9]. Adult COVID-19 instances are classified as [10-13]:

1. Mild illness: patients who exhibit any of the COVID-19 symptoms (such as a high temperature, cough, sore throat, malaise, headache, or muscular pain) but who do not have dyspnea, shortness of breath, or abnormal chest imaging.

2. Moderate illness: people with lower respiratory illness and a peripheral oxygen saturation (SpO2) of 94% (room air at sea level).

3. Serious sickness is defined as breathing rates of 30 breaths per minute, SpO2 of 94% (room air at sea level), a PaO2/FiO2 ratio of less than 300 mmHg, or lung infiltrates of more than 50%.

Critical illnesses are defined as those thathave respiratory failure (requiring mechanical ventilation), septic shock, and/or multiple organ dysfunctions [9].

Overexpression of the gene for angiotensin-converting enzyme-2 (ACE2) is associated with many organ dysfunctions. RNA expression has been found in a number of human organs [14]. High levels of ACE2, the SARS-Cov-2 entrance receptor, cause the most damage to cells, tissues, and organs. Nevertheless, earlier research has demonstrated that ACE2 is strongly expressed in human lung and small intestine epithelia, indicating that these tissues may serve as entryways for SARS-Cov-2 [15]. Nevertheless, recent studies show that lung surface expression is undetectable [16]. According to information available from the Human Protein Atlasn, the pathophysiology of COVID-19 illness is not causally related to ACE2 cell-surface protein expression [16]. Nevertheless, it is possible that the discrepancy is caused by the selective, transitory expression of ACE2 in some tissues, as was seen in the heart and kidneys [17,18].

2. The Cytokine Storm

The term "cytokine storm" (CS) was first used in 1993 in relation to graft-versus-host disease (GVHD) [24,25]. Despite the fact that the concept of an uncontrolled, cytokine-mediated response was originally investigated in the 1980s in connection to malaria and sepsis [19,20], it wasn't applied to pancreatitis [21], variola virus [22], and influenza virus H5N1 [23] until the 2000s. Some medications and a variety of conditions may directly causethis = . In the latter case, the condition is known as cytokine release syndrome or infusion reaction. Adoptive T-cell treatments, such as CAR-T-cell therapy [26], monoclonal antibody drug regimens [27,28], and immune checkpoint blockade drugs [29–31] have all been linked to CS. Stressed or infected cells activate B cells, T cells, natural killer cells, macrophages, dendritic cells, and monocytes through receptor-ligand interactions. In a positive feedback loop, inflammatory cytokines are generated, stimulating additional white blood cells. After an initial infection, CS travels through the bloodstream and infects other parts of the body. Inflammation symptoms include heat, discomfort, redness, swelling, and loss of function. Localized reactions first eliminate the trigger. The release of leukocytes and the transport of plasma proteins to the injury site are both aided by an increase in blood flow. Both discomfort and an elevated core temperature serve as defensive mechanisms

against bacterial infections (notifying the host of the impending challenge). Yet, the occurrence of a pathologic trigger initiates the healing process. There are two possible results from these operations.

(1) Organ function gradually returns; (2) fibrosis develops, which may result in irreversible organ dysfunction.

Despite this, SARS-Cov-2 does not stand alone when it comes to the CS symptoms seen; similar results have been reported in SARS-Cov-1 and MERS-Cov cohorts [32,33]. A new study found that COVID-19 CS is characterized by abnormal immune activation and hyper inflammation. According to Ruan et al. [6], critically sick patients admitted to the ICU had increased levels of IL-2, IL-7, IL-10, granulocyte colony-stimulating factor, IP-10, monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1A (MIP-1A), and tumor necrosis factor-(TNF-) [6]. Uncontrolled severe inflammation has been linked to death, and data from recovered individuals contradicts that seen in critically sick patients. Key immunological components of the inflammatory environment form the basis of CS. In this article, we will examine the relationship between cytokines and intensive care unit (ICU) admission. TNF, interleukin family members, and interferon-related antiviral cytokines are among them. Lastly, we will talk about IL-6 and how we now perceive it to have contributed to the present COVID-19 epidemic.

3. Interferons (IFN)

IFN cytokines I, II, and III aid pathogen defense. Virus-infected leucocytes and fibroblasts produce type I and III interferons. Macrophages and NK cells create type II interferon to fight viral and intracellular bacterial infections (IFN-). In antigen-specific immunity, T helper (TH) CD4 [34] and CD8 CTL effector T cells produce IFN- [35]. Interferons activate a complex downstream signaling network when they connect to their receptors (IFNAR1/IFNAR2 for Type I, IFN-γR1/IFN-γR2 for Type II, and the receptor complex IL-28R/IL-10Rβ for Type III, also known as lambda interferons). Therefore, transcription factors are activated and numerous IFN-stimulated antiviral, antiproliferative, and immunomodulatory genes are expressed. It has been demonstrated that influenza defense is provided by lambda interferons (type III). an infection in a mouse model [36]. With viral load, COVID-19's IFN- levels rose [3]. The patient's condition and the delayed peak, which occurred at a time when lymphocyte numbers were down, both enhanced the amount of neutrophil infiltration in the lung's alveoli [3,37,38]. IFN- has been linked to the severity of illness in the past. Increased IFN- γ was linked to inflammation in the lungs and serious lung damage in SARS-Cov-1 and MERS-Cov [39,40], which are both signs of getting worse. IFN-, like IL-6, predicts COVID-19 worsening and ICU admission [37,38,41]. It is widely acknowledged that CD4 T cells directly produce IFN-, which enhances CD8 T cell proliferation and cytotoxicity. Supporting the development of monocytes (CD16+ CD14+ CD45+) and releasing IFN-, CD4 T cells secrete granulocyte and colony-stimulating substances into the blood.

4. TNF (tumor **necrosis factor)**

There are 19 members of the TNF superfamily, all of which are type II transmembrane proteins that, after being cleaved by an extracellular proteolytic enzyme, are secreted as cytokines. TNF- is secreted by many different cell types including "macrophages, monocytes, endothelial cells,

neutrophils, smooth muscle cells, activated lymphocytes, astrocytes, and adipocytes". One of TNF-'s various roles is to control the expression of genes that encode for other proteins, including receptors, transcription factors, cytokines, and growth factors. This cytokine's widespread effects can be attributed to the presence of TNF-'s major receptor, TNFR1, on all cell types. Proteins such as "growth factors, cytokines, transcription factors, and receptors" can all have their gene expression controlled by TNF-. The impact of TNF- on CS is substantial. In COVID-19, patient deterioration was significantly influenced by TNF-, which was elevated in ICU patients compared to non-ICU patients [38,42]. TNF- levels rise early in the infection and remain high throughout, much like IL-6 and the soluble IL-2 receptor [3,38]. TNF- also increases HA-synthase-2 (HAS2) in EpCAM+ lung alveolar epithelium, CD31+ lung alveolar endothelium, and fibroblasts in the lungs of COVID19 patients [43]. The fluid inflow caused by HA (hyaluronan) in the lung alveoli is a major contributor to hypoxia and the need for mechanical ventilation. Lung epithelial cells do not produce TNF- in a highly pathogenic H5N1 influenza model. ARDS lung epithelium produces TNF-. The rise of TNF- is caused by soluble substances made by macrophages interacting with lung epithelial cells [45]. CS's pro-inflammatory cascade emphasizes its ability to cross-talk with injured mucosal tissue and self-amplify, causing systemic CS escalation. It would be interesting to determine whether SARS-Cov-2 infection also induces CS-induced TNF- generation in lung epithelial cells.

5. Interleukins

Interleukins (ILs) control immune cell development and inflammation. Many cells generate interleukin, which transmits leucocytes. IL-1 induces IL-2, which is necessary for T-cell homeostasis and T-cell-derived immunity [46] and IL-2 receptor expression [47,48]. Acute-phase signaling, immune cell trafficking to infection sites, epithelial cell activation, and the production of secondary cytokines are all enhanced by IL-1 and IL-1. Infection causes a wide range of pro-inflammatory local and systemic consequences, including an increase in particular cytokine synthesis, which may help eliminate viruses. While IL-1 does have some effect on TH1 cells, it is primarily a costimulatory factor for TH2 cells [48]. TH2 cells have theabundant expression of the high-affinity IL-1RI receptor [49]. Animal models of hypersensitivity showed that IL-1/animals had reduced IL-4 and IL-5 levels compared to controls, resulting in milder allergy responses [50]. In mouse trichuriasis muris infection, IL-1 created a TH2 immune milieu that was crucial for parasite defense [51]. Moreover, IL-1 is essential for the induction and operation of TH17. Fewer TH17 cells were generated by IL-1RI/ mice compared to wild-type controls [52]. In contrast, experimental autoimmune encephalomyelitis had no effect in IL1RI/ animals [52]. Notably, IL-1, which is made by dead, inactive Mycobacterium tuberculosis, is needed for TH17 to develop in experimental models of autoimmune diseases [53]. Mice infected with the influenza virus that have their IL-1 receptors activated in the respiratory tract have improved acute lung immunopathology and survival. This is because IL-1 receptor activation attracts CD4 T cells and boosts IgM antibody responses [54]. A rise in IL-1, IL-7, IL-8, and IL-9 levels in the initial plasma concentration is associated with a CT lung scan for COVID-19 in a patient with multiple bilateral lobular pneumonia [3]. This elevation was consistent in both ICU and non-ICU patients, indicating that COVID-19 immunopathology is important [3]. Additionally, ICU patients had greater levels of IL-2 and IL-7 than non-ICU patients [3,55]. Also, the growth of IL-10 is like that of IL-2 and

IL-7 [3]. Antigen-presenting cells that activate CD8 T and TH cells may produce IL-10 in response to IFN- and IL-6. IL-10, a potent immunoregulator, may suggest COVID-19 immune insufficiency. While increased IL-10 levels are not linked to a compromised immune system, they do signal a failed attempt by the immune system to suppress the CS in the past [38]. Late immune regulation enhances IL-4, a TH2 cytokine, and inflammatory suppressor, in ICU patients [3]. ILs affect CS morbidity, even though they are not IFNs.

IL6: in the hurricane's eye

The gene for human IL-6 is on chromosome 7p21 and encodes a protein of 212 amino acids and a signal peptide of 28 amino acids. Although the core protein is 20 kDa, glycosylation accounts for the normal IL-6 size of 21-26 kDa. IL-6 has a variety of key tasks in the immune system, including aiding in the development of anti-viral immunity. The pro-inflammatory cytokine IL-6 is widely recognized for its several roles in the inflammatory process. Many different cell types can be affected by the interleukin 6 (IL-6) that is produced. A pleiotropic cytokine, that functions both pro- and anti-inflammatory (a kind of cytokine produced by muscle cells in response to muscle contraction). As soon as IL-6 is produced, it immediately binds to its soluble receptor, creating the IL6/IL6R complex. Many immune cells and tissues have a place where they can get IL-6. The IL-6 receptor-signaling complex (gp130) is made up of two transmembrane-IL-6 binding chains, soluble IL-6 receptors, and cytoplasmic signaling molecules. Leukemia inhibitory factors, IL-22, IL-27, and IL-25 share the cytoplasmic signaling molecule IL-6R. Hence, receptor co-sharing may explain IL-22, IL-27, IL-25, and IL-6 redundancy and pleiotropy. Soluble IL-6 and its ligand increase gp130. IL-6/IL-6R complex creation initiates the cell's IL-6 signaling pathway. The intracellular cascade that occurs following the creation of a complex activates both the Janus kinase (JAK)-STAT3 pathway and the JAK-SHP-2-MAP kinase pathway. Through stimulating the Suppressor of cytokine signaling 1 (SOCS1) and Suppressor of cytokine signaling 3 (SOCS3), STAT3 is able to control the IL-6 response by inhibiting intracellular feedback loops and IL-6 signaling. In addition to macrophages, neutrophils, dendritic cells, and lymphocytes, there are many more immune cells that produce IL-6. In an inflammatory setting, IL-6 is produced by a broad variety of cells, not just those of the immune system. They include mesenchymal cells, endothelial cells, and fibroblasts. These findings underscore IL-6's prevalence and deep potential in inflammatory conditions. IL-6 enters the liver via the bloodstream and immediately stimulates hepatocytes, causing them to generate C-reactive proteins, serum amyloid A, and fibrinogen. In addition, a decrease in albumin levels after hyperinflammation may point to liver injury and, more significantly, systemic illness. Central differentiation of naive CD4 T cells into effector and helper cells is promoted by IL-6 [56]. IL-6 promotes TH7 production [57] and the activation and development of cytotoxic CD8 T cells [58] by linking innate immunity with adaptive immunological responses. In addition, IL-6 prevents the maturation of T Regulatory T CD4+ CD25+ FOXP3 cells [59], which promotes the onset of autoimmune conditions. Via promoting the expansion of T-follicular helper cells, B cells, plasma cells, and IL-21, IL-6 has a secondary effect on immunoglobulin production. Apart from that, some viruses have the ability to alter the intracellular cascade of events involved in inflammation and the production of IL-6. HIV-1, for example, increases the ability of NFkB and NF-IL-6 to bind to DNA. This increases IL-6 RNA transcription, which causes too much IL-6 to be released. In human airway epithelial cell cultures,

when the SARS-Cov-1 structural protein N (nucleocapsid) bound to the NFkB regulatory region on the IL-6 promoter, it significantly turned on the promoter. This was not the case for the SARS-Cov-1 structural proteins S (spike), E (envelope), or M. (membrane) [60]. This might counteract IL-6 control mechanisms, ending IL-6-mediated activation once the risk is gone. COVID-19's long-term effects must be examined in light of environmental factors and temporary autoimmune illnesses that follow viral infections. COVID-19 has focused on IL-6 [61]. Early on in the pandemic, IL-6 levels were a great indicator of how bad the disease was and how much help was needed for breathing [6, 62, 63]. Pedersen and his colleagues show that high levels of IL-6 (along with TNF- and IL10) are linked to a lower chance of getting better and the need to stay in the ICU [38]. Researchers found a statistically significant correlation between low to moderate IL-6 and other levels, and mild to moderate occurrences. Prompetchara et al. found a 52% rise in IL-6 levels between ICU and non-ICU patients [41]. The elevated CRP levels decreased lymphocyte count, and increased neutrophil count were all linked to this. According to the research of Zhao et al., GM-CSF production by CD4 TH cells is responsible for the indirect upregulation of IL-6 and IFN- [64]. IL-6 is released into the pulmonary environment after GM-CS stimulates the generation and recruitment of CD14+CD16+ monocytes. Upon viral protein identification, innate, MyD88-dependent immunological receptors activate to generate IL-6 early in SARS-Cov-1 and MERS. Data showing enhanced IL-6 production in SARS-Cov-1 pathogenesis [60] lend credence to the idea that the two members of the Coronaviridae family may have identical physiopathological mechanisms.

7. Antigen-independent, cytokine-dependent inflammatory loop amplification

Innate and adaptive immune responses are frequently started off by viral antigens [66]. HLA class I and II predicted peptide'mega pools showed 100% and 70% of COVID-19 convalescent patients have SARS-Cov-2-specific CD4 and CD8 T cells, respectively. These reactions were connected to anti-SARS-Cov-2 IgG and IgA levels in every case. The spike protein elicited the majority of CD8 T-cell responses. The M (membrane) protein was discovered as the second most prevalent antigen [66]. The findings from this study provide credence to the ongoing efforts to create a vaccination against the SARS-CoV-2 Spike protein [67]. Naive T cells acquire a wide variety of phenotypic and functional characteristics and effector activities after being activated and differentiated in response to TCR recognition of HLA/peptide-epitope complexes [68-70]. Modeling T-cell responses in COVID-19 suggests that naïve T-cell cytokine programming may have an effect on disease severity [71]. Interferons I and III, IL-2, and mild sickness are all linked. During T-cell priming, severe illness is associated with IL-6, IL-10, IL-1, TNF, CXCL8, and other CXCLs. Antigen exposure and viral persistence alter clinical outcome [72]. Furthermore, pro-inflammatory cytokines impact viral load [73,74]. In spite of this, antigen-independent, cytokine-dependent immune amplification may maintain COVID-19 hyperinflammation. In Lescure et alcase .'s series, late respiratory worsening in the absence of nasopharyngeal viral RNA supports immunologically driven late, severe symptoms [75]. As healthy donors have cross-reactive Cov memory T cells, memory T cells may play a role in COVID-19 illness [66]. Memory that is homeostatic and antigen-independent IL-7 and IL-15 have been demonstrated to enhance the proliferation of T-cells and bystander T-cells [77–80]. Furthermore, IL-2 produced by activated T cells may promote bystander activation [79-81]. According to Lucas et al. [73], COVID-19

contains high quantities of IL-7, IL-15, and IL-2, all of which have been shown to trigger IFN production in an antigen-independent way [82]. With cytokine combinations such as IL-12 + IL-18, it is feasible to activate CD8 T cells specific for naive and memory viruses without an antigen [83]. During infections with intracellular pathogens, these cytokines could trigger fast antigen-nonspecific IFN secretion [84]. Considering the high levels of numerous cytokines during COVID-19, the synergistic potential of cytokine "cocktails" must be noted. In comparison to IL-12 alone, subthreshold TNF coupled with IL-12 leads to a more than 20-fold increase in IFN-producing CD8 T cells [83]. There was a TCR-independent IL-12-dependent mechanism for IFN- production by CD4 and CD8 T cells in a dengue virus model [85]. Chronic viral infections present antigens for a long time, generating CD8 T cells that react to cytokines without TCR activation [83]. COVID-19 IL-1 elevations may reflect inflammasome activity [86,87]. Nonetheless, it has been shown that cognate interactions between effector CD4 T cells and myeloid cells increase IL-1 production via the TNF/TNFr axis [88]. An immature form of natural killer cells, those responsible for producing IL-22, are given a boost by IL-1 and are maintained throughout the body. When bacteria and fungi infect the exterior of cells, IL-22 is involved in the development of Type 3 immune responses. Type 3 responses, such as elevated IL-17 and IL-22 levels, are more common in patients with severe cases of COVID-19 [73]. In some cases, cytokines can stimulate both antigen-specific and antigen-independent immune responses. Cytokine storms can occur without regulating systems.

8. Discussion

Secondary haemophagocytic lymphohistiocytosis (HLH) is similar to the hyperinflammatory condition [89]. Some people think COVID-19 should be categorized with other hyperinflammatory diseases [90]. Hepatomegaly and splenomegaly are associated in the clinic with HLH. A risk algorithm based on recognized diagnostic criteria can be used to evaluate the probability of HLH in COVID-19 [91-93]. Regarding biochemistry, COVID-19 has been linked to hypertriglyceridemia [94], an additional characteristic that overlaps with hyperinflammatory illnesses such as HLH. Hyperferritinemia is another resemblance to HLH. Ferritin levels in persons with severe COVID-19 are greatly elevated [6]. It is outside the scope of this investigation to examine ferritin's function in cell biology during infection. However, Kernan et al. [95] give a more in-depth look. COVID-19's uncontrolled immune response is significantly connected to the aforementioned clinical symptoms. COVID-19 causes two-stage immune responses. The adaptive immune response destroys infected epithelial cells and stops viral multiplication in the early (asymptomatic, pre-incubation) phase [43]. As SARS-Cov-2 was able to spread during the second phase, this suggests that adaptive immunity was unable to eradicate the virus. During budding, viruses are demonstrated to induce immunogenic cell death [87] and to activate the NACHT, LRR, and PYD domain-containing protein 3 (NLRP3) inflammasome [86]. Zhou et. al., and Hoffmann et. al., discovered SARSCov-2 cell entrance mechanisms [96, 97]. Both investigations demonstrated that SARS-Cov-2 employs ACE2 as an entry receptor and, more importantly, that viral spike (S) protein binding to cellular receptors requires priming by the serine protease TMPRSS2. The scientists showed that a widely available TMPRSS2 inhibitor can block theviral entrance, speeding up COVID-19 clinical trials [98]. Virus entry and replication can activate many TLRs and signaling pathways. TLR sensing study aims to boost antiviral immunity [99-101]. Van

der Made et al. showed that X-chromosomal TLR7 loss-of-function variants reduce type I and II IFN responses and lower IRF7 mRNA expression, which affects COVID-19 disease severity (figure 4). Increasing anti-viral immunity with the TLR7 agonist imiquimod has been suggested as a therapeutic because of TLR7's significance [102]. Customized nanoparticle vaccines [103] might be used to investigate the efficient in vivo distribution of vaccines to dendritic cells and the induction of a robust adaptive immune response [104]. Both the apoptotic cascade and widespread death of infected tissues cause inflammation that is reminiscent of the body's innate immune response [100,105,106]. Early in the infection, endogenous viral proteins activate immune receptors through the innate, MyD88-dependent pathway, leading to the production of IL-6 [107]. SARS-Cov-2 infection activated the respiratory system's IL-6 amplifier (IL-6 Amp) via NFB and STAT3. IL-6 amplification may cause COVID-19 hyperinflammation in several inflammatory and autoimmune disorders [61,108]. A variety of immune cells, such as activated CD4 T cells [66], monocytes, and macrophages [110], are drawn to the local inflammatory milieu [109], which may enhance IL-6 Amp in a potentially harmful positive feedback loop. Infectious epithelial cells generate IL-6, which allows activated pro-inflammatory immune cells to invade and increase local cytokine levels. Lung inflammation causes ARDS The link between COVID-19 and lung illness is well-established; however, recent research suggests that other organ abnormalities, including acute kidney injury (AKI), may also be present. [111,112]. Despite this, COVID-19-induced AKI etiology and pathogenesis are still poorly understood [113,114]. Several studies [115-117] have linked IL-6/IL-6r to AKI pathogenesis. Additionally, IL-6 levels in kidney damage patients have a substantial concentration-dependent correlation with mortality [118]. Many ideas have been proposed to explain how IL-6 contributes to renal impairment. For example, IL-6 may cause renal illness by elevating tubular epithelial cell sensitivity to pro-fibrotic cytokines like TGF-. Moreover, IL-6 has been demonstrated to worsen mesangial proliferative glomerulonephritis by increasing the proliferation of mesangial cells [117,119]. Moreover, prolonged cytokine stimulation of the liver results in the liver manufacturing more clotting factors, which leads to COVID-19-induced coagulopathy [120,121], which has been associated with hyperinflammation [122]. Moreover, thromboembolic symptoms are evident in post-mortem reports [123]. We [124] and others [125] found that hospitalized COVID-19 patients had highly elevated levels of D-dimers (more than 500 ng ml1) and fibrinogen (greater than 5.5 g l1). Some extremely unwell people have D-dimers more than 20,000, indicating a severe hypercoagulable condition.

COVID-19 for possible treatments

COVID-19 treatments are not FDA-approved [126]. Many studies and observations have shown that lowering SARS-Cov-2-induced hyperinflammation in COVID-19 patients may decrease disease development [6]. Modern COVID-19 therapy emphasizes respiratory support. We advocate immune-modifying medication research based on cytokine data and clinical findings of COVID-19's immunological genesis. In fact, immunomodulatory are the most rapidly investigated treatments thus far [126]. Tocilizumab, a recombinant humanized anti-IL-6 receptor (IL-6r) mAb, and siltuximab, a recombinant human-mouse chimeric monoclonal antibody that binds IL-6, may lessen CS [127,128] and prevent renal function deterioration [129]. One such treatment option for IL-1 inhibition is anakinra. Interleukin-1 receptor (IL-1r) antibodies are often used to treat hyperinflammatory diseases, and their use has a favorable safety profile even at large doses,

indicating potential as a treatment option for COVID-19 [130]. Anakinra is used to counteract the negative effects of IL-1 and IL-1. Two cohort studies [131-133] looked at clinical efficacy and found it to be effective. Without randomized studies, the FDA encourages clinicians to exercise cautious [134]. Preventing systemic inflammation with antibody-mediated neutralization of particular cytokines has given mixed outcomes in clinical settings [135-138] or success in limited subgroups. Hence, blood purification by filtration, dialysis (diffusion), and adsorption have been key study areas for non-specific inflammatory mediator sequestration [139-142]. The ultimate goal of blood purification is to reduce potentially harmful concentrations of pro-inflammatory mediators. By reducing IL-6 levels [116], which restores immunological homeostasis, we hope to reduce the prevalence of COVID-19-induced acute kidney injury and improve patient outcomes and survival. Recent research suggests that cytokine adsorption, blood purification, and IL-6 reduction in advanced COVID-19 illness can diminish hyperinflammation [124,130,143]. To evaluate the effectiveness of blood purification techniques in fostering clinical recovery in COVID-19 patients, randomized controlled studies are nonetheless required.

10. Conclusions

In this work, we identify the most prominent targets in the deadly cytokine response in severe COVID-19 patients by athorough analysis of the rapidly growing data. Several therapeutic drugs were being examined in clinical trials at the time of writing; surprise, IL-6 blocking was the primary focus [144-146]. TNF blockade, on the other hand, should be investigated [147,148]. While clinical trials are still in their early stages, they hold great promise for alleviating the pain of COVID-19 sufferers.

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