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REVIEW ARTICLE

# "The cytokine storm and COVID-19"

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## ABSTRACT

The new coronavirus named SARS-CoV-2 was known in 2019–2020 because the precipitating agent of a many acute respiratory infections named COVID-19, that is inflicting a worldwide pandemic. The SARS-CoV-2 has reminded us of the vital role of impact host immune reaction and also the devastating effect of immune dysregulation. This year marks ten years since the primary description of a protein storm that developed once chimerical matter receptor (CAR) T-cell medical care and twenty-seven years since the term was first utilized in the literature to explain the engraftment syndrome of acute graft-versus-host malady after allogeneic biological process stem-cell transplantation. The term "cytokine unleash syndrome" was coined to explain the same syndrome once infusion of muromonab-CD3 (OKT3). cytokine storm and cytokine release syndrome are serious general inflammatory syndromes involving elevated levels of circulating cytokines and immune-cell hyperactivation which will be triggered by varied therapies, pathogens, cancers, reaction conditions, and monogenic disorders.


## BACKGROUND

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) first appeared in Wuhan, China in December 2019. It is a highly pathogenic human coronavirus (HCV) that can cause zoonotic diseases and poses a major threat to public health. The vast majority of patients with COVID-19 have a good prognosis, but there are still some critically ill patients, and even death. [1] Most of these severely ill and dead patients did not have serious clinical manifestations in the early stages of the disease. Some patients had only mild fever, cough or muscle pain. Their conditions deteriorated suddenly in the late stages of the disease or in the process of recovery. Acute respiratory distress syndrome (ARDS), and multiple organ failure occurred rapidly, leading to short-term death. [2] Cytokine storm is considered to be one of the main reasons of ARDS and multiple organ failure. [3] It plays an important role in making the disease worse. [4] Cytokine storm is the general term for the maladaptive release of cytokines in response to infection and other stimuli. The pathogenesis is complex, but involves the loss of regulatory control over local and systemic pro-inflammatory cytokine production, both at local and systemic levels. The disease progresses rapidly and the mortality rate is high. Some data show that during the COVID-19 epidemic in 2019, the severe deterioration of some patients is closely related to the excessive release and out of control of cytokines. [5]

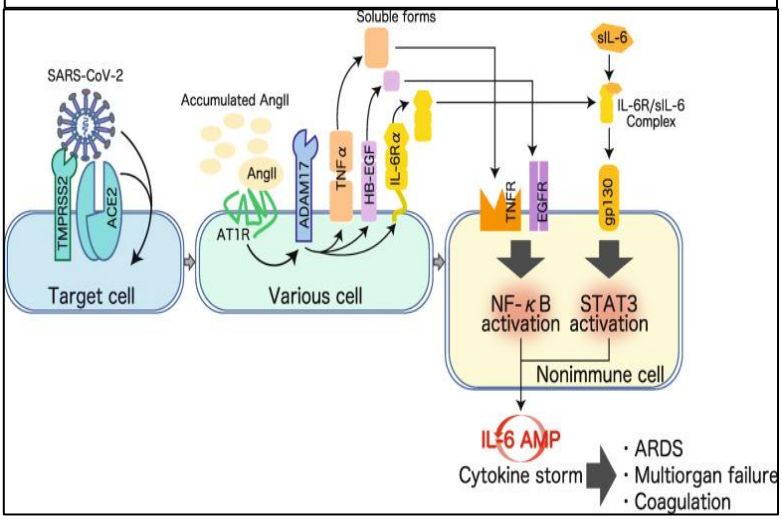
## VIRAL ENTRY OF SARS-COV-2

Within the beyond 2 decades, severe respiratory illnesses had been resulting from zoonotic infections of SARS-CoV and MERS-CoV from animals to people in endemic areas. In December 2019 in Wuhan City, China, SARS-CoV-2, belonging to the novel RNA *Beta-coronavirus*, was found to be the causative agent of COVID-19, which has presently emerged as a global pandemic. Genomic analysis found out that SARS-CoV-2 stocks approximately 80% genetic identification with SARS-CoV, about 50% with MERS-CoV, and 90% with bat-SL-CoVZC45 and bat-SL-CoVZXC21 coronaviruses, suggesting bat-to-human zoonotic transmission of this new virus [6], [7]. In addition, the proteomic characterization also showed that SARS-CoV-2 has 7 conserved non-structural domains that are similar to SARS-CoV, suggesting a relationship between the 2 beta coronaviruses. Despite the amino acid differences to SARS-CoV, SARS-CoV-2 has a similar receptor. SARS-CoV binding domain using angiotensin II converting enzyme (ACE2) for entry into the host cell **(Figure 1).** [8], [9].

Actually, 2 independent analysis teams already provided evidence that SARS-CoV-2 needs ACE2 to infect host cells [16, 19)]. Zhou et al. discovered that SARS-CoV-2 can enter cells expressing ACE2 originated from humans, Chinese horseshoe bats, civet, and pigs. Also, it cannot enter cells expressing either dipeptidyl peptidase 4 or aminopeptidase N, the entry receptors for MERS-CoV and HCoV-229E, respectively. SARS-CoV-2 entry via human ACE2 depends on transmembrane serine protease 2 (TMPRSS2) and therefore the endosomal cysteine proteases cathepsin B and L (CatB/L) for viral spike (S) protein priming [10].

TMPRSS2 is important for cleaving the viral envelope-located trimeric S protein on the S1/S2 and the S2' sites, main to the fusion of the viral and cell membranes mediated by the subunit S2 of protein S after the engagement of the S1 subunit to the cellular surface receptor and for the next viral internalization into the lung epithelium. [11] Particularly, ammonium chloride, an inhibitor of CatB/L, inhibited SARS-CoV-2-S protein-driven access into 293 T cells (TMPRSS2-negative) expressing ACE2, however much less so into Caco-2 cells (TMPRSS2-positive). A clinically verified TMPRSS2

**Figure 1.**
**IL-6-STAT3 signaling is a potential therapeutic target for COVID-19 mediated by cytokine storm.**

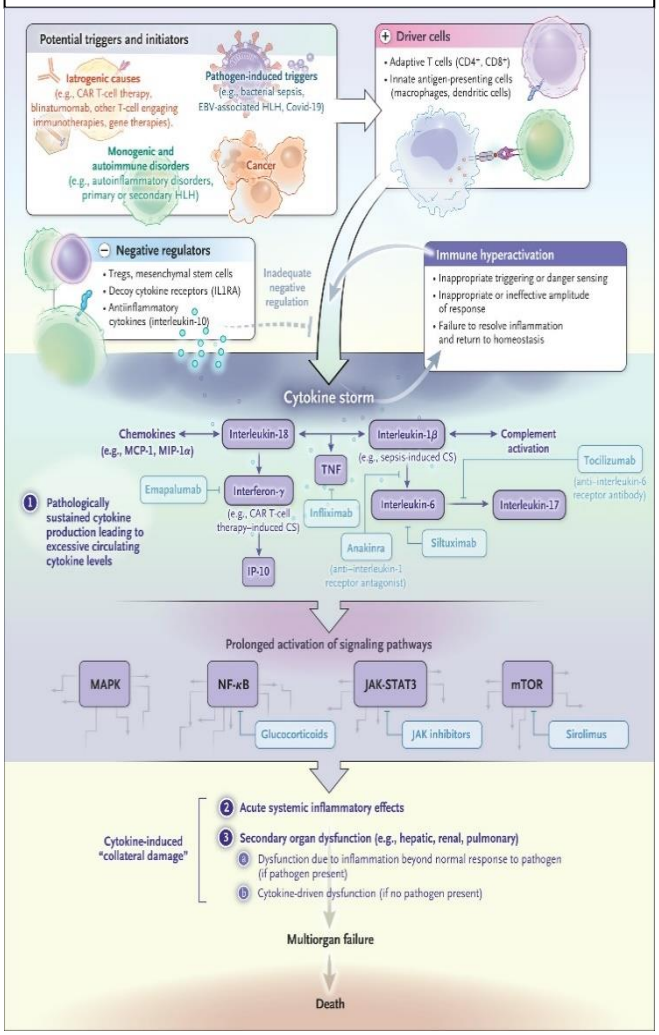


inhibitor, camostat mesylate (NCT04321096), that's authorized for medical use in Japan to deal with pancreatic inflammation, partly avoided SARS-CoV-2-pushed access into Caco-2 cells, however collectively with E-64d, an inhibitor of CatB/L completely inhibited the access. Additionally, the compelled expression of TMPRSS2 rescued themSARS-CoV-2-S-established access into CatB/L-suppressed 293 T cells, suggesting that the entry of SARS-CoV-2 is precipitated while cells specific TMPRSS2 regardless of CatB/L expression and that SARS-CoV-2 cell entry rely upon surface ACE2 and TMPRSS2 molecules. Thus, ACE2 and TMPRSS2 might be essential objectives for COVID-19 therapeutics. Of note, regardless of the genetic identification of the receptor-binding domain (RBD) structure among SARS-CoV and SARS-CoV-2, numerous reviews have proven anti-RBD monoclonal antibodies can't neutralize SARS-CoV-2 [12], [13] suggesting that cross-neutralization protection among the 2 viruses is limited. In addition, SARS-CoV-2 can infect cells that have Fc receptors (FcRs), which give the capacity of antibody-mediated internalization in macrophages, monocytes, or B cells even without ACE2 and TMPRSS2 expression especially throughout the later time point after infection [14]

## PATHOPHYSIOLOGICAL FEATURES OF CYTOKINE STORM

Inflammation includes a fixed of biologic mechanisms that developed in multicellular organisms to include invasive pathogens and solve injuries by activating innate and adaptive immune responds. The immune system is predicted to recognize foreign invaders, respond proportionally to the pathogen burden, after which go back to homeostasis. This response calls for a stability among enough cytokine production to take away the pathogen and avoidance of a hyperinflammatory reaction wherein an overabundance of cytokines causes clinically great collateral harm. Cytokines play a key position in coordinating antimicrobial effector cells and providing regulatory alerts that direct, amplify, and solve the immune reaction. Cytokines have brief half-lives, which commonly prevents them from having outcomes outdoor lymphoid tissue and sites of inflammation. Although typically taken into consideration to be pathologic, sustained manufacturing of cytokines that leads to increased circulating ranges can be essential to correctly manage some disseminated infections. At elevated ranges, cytokines may have systemic outcomes and lead to collateral harm to important organ systems. Immune hyperactivation in cytokine storm can arise because of irrelevant triggering or risk sensing, with a reaction initiated with the absence of a pathogen (e.g., in genetic issues regarding inappropriate inflammation activation or idiopathic multicentric Castleman's disease); an irrelevant or ineffective amplitude of reaction, regarding immoderate effector immune-cell activation (e.g., in cytokine storm because of CAR T-cell therapy), an overwhelming pathogen burden (e.g., in sepsis), or out of control infections and extended immune activation (e.g., in HLH related to Epstein–Barr virus [EBV]); or failure to remedy the immune reaction and go back to homeostasis (e.g., in 1ry HLH) **(Figure 2).** In every of those states, there may be a failure of bad feedback mechanisms which are intended to inhibit hyperinflammation and the overproduction of inflammatory cytokines and soluble mediators. The immoderate cytokine manufacturing results in hyperinflammation and multiple organ failure. Regulatory cell kinds, decoy receptors for proinflammatory cytokines including IL1RA, and antiinflammatory cytokines including interleukin-10 are essential for antagonizing inflammatory cellular populations and stopping immune over activity.

**Figure 2.**
**Pathophysiological Features of Cytokine Storm.**




Given the lack of a unifying definition for cytokine storm [15] and confrontation regarding the difference between cytokine storm and a physiologic inflammatory reaction, we advocate the subsequent 3 hallmarks for figuring out cytokine storm: increased circulating cytokine levels, acute systemic inflammatory symptoms, and either secondary organ dysfunction (frequently renal, hepatic, or pulmonary)

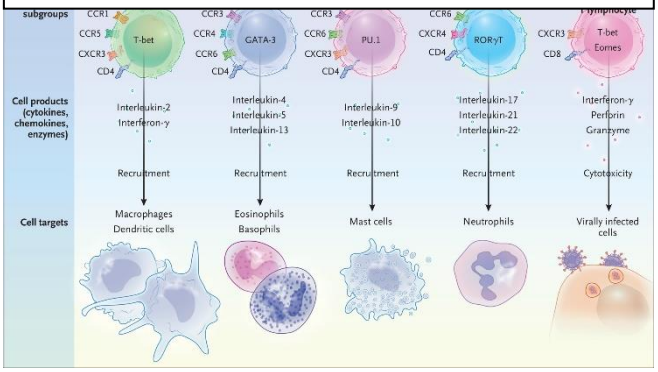
because of inflammation beyond which might be attributed to an ordinary response to a pathogen (if a pathogen is present), or any cytokine-driven organ dysfunction (if no pathogen is present). Improvement in results with cytokine neutralization or antiinflammatory agents similarly supports The pathologic role of extreme cytokines and the classification of a situation as a cytokine storm. However, decrease level of a treatment response does now no longer obligatorily rule out cytokine storm, due to the fact underlying situations are possibly to play a part, a unique cytokine can be the disorder driver, or the timing of remedy may also be poor. In brief, cytokine storm includes an immune reaction that leads to collateral breakdown, which can be more than the instantaneously gain of the immune reaction. Thus, an exuberant inflammatory reaction to a massive pathogen burden can be suitable for controlling the infection if increase secondary organ dysfunction does no longer occur, while further excessive ranges of cytokines in cancer-related HLH or idiopathic multicentric Castleman's disease might be taken into consideration a pathologic condition of cytokine storm due to the fact of no pathogen requiring an immune reaction is concerned and patients benefit from treatment with cytokine neutralization and another antiinflammatory agents. Circulating cytokine ranges may be tough to measure due to the fact cytokines have brief half-lives, circulating ranges might not as it should be mirror local tissue ranges, and measurements might not be effortlessly received worldwide. We do now no longer recommend a selected threshold for elevations in cytokine ranges above the everyday range, and we do now no longer endorse particular cytokine panels or listing precise cytokines whose ranges ought to be elevated, given the shortage of to be had evidence. However, we trust that that is a vital region for destiny studies and will gain from systematic evaluation through a multidisciplinary consortium.

## CELL TYPES INVOLVED IN CYTOKINE STORM

The cells of the innate immune system are the primary line of protection towards pathogens. Neutrophils, monocytes, and macrophages apprehend pathogens, produce cytokines, and engulf pathogens and cells through phagocytosis. There are many different innate immune cells, such as dendritic cells, γ–δ T cells, and natural killer (NK) cells. [16] Innate immune cells use pattern-recognition receptors, which aren't particular for any specific antigen, to apprehend and reply to an extensive type of microbial invaders through generating cytokines that prompt cells of the adaptive immune system. Innate cells which can be most usually implicated in the pathogenesis of cytokine storm consist of neutrophils, macrophages, and NK cells. Neutrophils can produce neutrophil extracellular traps, a network of fibers that make a contribution to thrombi formation and increase cytokine production throughout cytokine storm. Macrophages, that are tissue-resident cells which can be frequently derived from circulating monocytes, do now no longer divide; they have got diverse capabilities, from the elimination of senescent cells with the aid of using engulfment, to tissue repair and immunoregulation, to antigen presentation. In many styles of cytokine storm, macrophages emerge as activated and secrete immoderate quantities of cytokines, in the long run inflicting extreme tissue harm which can result in organ failure. Hemophagocytic macrophages are regularly found in bone marrow biopsy specimens from sufferers with cytokine storm. Interferon-γ can induce hemophagocytosis with the aid of using macrophages, and this may also make a contribution to the cytopenias usually found in sufferers with cytokine typhoon. [17] The cytolytic characteristic of NK cells is faded in a few styles of cytokine typhoon, which can result in extended antigenic stimulation and issue resolving inflammation. [18] Excess interleukin-6 may also mediate the impairment in NK-cell function through decreasing perforin and granzyme production.

The adaptive immune system consists of B cells and T cells. T cells differentiate into a wide variety of subsets with wonderful effector-cell functions probably concerned in cytokine storm **(Figure 3).**

**Figure 3.**
T-Cell Effector Subgroups Involved in Cytokine Storm.




Type 1 helper T cells and cytotoxic T lymphocytes are typically liable for the host protection against viral infections. Th1 cells modify the recruitment of macrophages, whereas type 2 helper T cells recruit eosinophils and basophils, type 9 helper T cells recruit mast cells, and type 17 helper T cells recruit neutrophils. [19] An exaggerated Th1-type inflammatory reaction frequently takes place in the course of cytokine storm. Th1 cells produce huge amounts of interferon-γ, result in not on time hypersensitivity reactions, prompt macrophages, and are important for protection against intracellular pathogens. [20] Iatrogenic reasons of cytokine storm concerning increase T-cell activation, as CAR T-cell and anti-CD28 antibody therapy, point to the capacity of activated T cells to provoke cytokine storm. Impaired granule-mediated killing of contaminated

cells or tumor cells via CTLs is a key element of a few varieties of cytokine storm. [21] Data from mouse models of HLH and patients with cytokine storm suggest that the lack of ability of CTLs for killing successfully leads to extended activation of T cells, triggering a cascade of inflammatory tissue damage. [22] [23] [24] Th17 cells have an important function in host protection, mainly antifungal protection, and abnormal Th17-cell feature can cause autoimmunity. [25]

An experimental version of macrophage activation syndrome (a type of secondary HLH) presents proof that Th17 cells can be drivers of a cytokine storm this is unbiased of interferon-γ. [26] B cells aren't frequently related to the pathogenesis of cytokine storm. However, the effectiveness of B-cell depletion in treating a few cytokine storm disorders, as HHV-8 related multicentric Castleman's disease, suggests that those cells are successful of starting up or propagating cytokine storm, specifically while virally infected.

# CLINICAL, IMMUNOLOGICAL AND PATHOLOGIC FEATURES OF COVID-19 ASSOCIATED CYTOKINE STORM

In China, categorized the stage of COVID-19 in keeping with the guidelines [27] issued via the National Health Commission of the Peoples Republic of China (NHC). in accordance with the instructions, NHC defines severe infection of COVID-19 as one of the following conditions: RR ≥30 breaths/min in resting state; O2 saturation ≤93%; $PaO_2$/fraction of inspired $FiO_2$ ≤three hundred mmHg. Critical infection as one of the following conditions: respiratory failure and requiring mechanical ventilation; shock; complication of another organ failure, and desires intensive care. The most common signs and symptoms of COVID-19 had been fever, cough, shortness of breath, fatigue, and myalgia [28], [29], [30], [31], and severe instances have a tendency to be older with extra primary illnesses and be afflicted by dyspnea, extra complications [28], [31]. In COVID-19, 14% progress to intense sickness and 5% to essential infection [32]. A potential study pronounced that the computerized tomography of the lungs of COVID-19 [33]. The lung lesions growth and the scope expands because the disorder progresses, and ground-glass opacity coexisted with consolidation or striated shadow. Some patients represented diffuse lesions in lungs. Up to date, the inflammatory problems (insufficient in chemokines) in COVID-19 have been reported in lots of scientific researches. The COVID-19 is willing to reason a lower of lymphocyte count and an increase of C reactive protein (CRP), specifically in seriously sick patients [28], [33], [29], [34], [35], [36]. The main subsets of the T lymphocytes (T cell) ($CD3^+$ $CD4^+$ T cell and $CD3^+$ $CD8^+$ T cells) are decreased in COVID-19 and are substantially decrease in severe cases [28], [37], [34], [35], [38], [39]; however, controversial outcomes are also stated in a few research [29], [31]. The outcomes of the alternative immune cells, the B cell and natural killer (NK) cell, have greater inconsistency in recent researches. IL-6 was determined elevated in all research, and only one study show IL-10 was no longer elevated. About 1/2 of the researches we gathered confirmed TNF-α was elevated. Only Huang et al. [40] inspected the multiple sorts of chemokines and discovered that severe patients had more ranges of G-CSF, GM-CSF, IP-10, MCP-1, MIP-1a, MIP-1b, RANTES, and IL-8. The inflammatory problems of COVID-19 were summarized in **(table 1).**

Cytokine, chemokine, and leukomonocyte responses detected in COVID-19 patients.

| Comparison objects | IL-6 | IL-1β | IL-10 | TNF-α | IFN-γ | IL-2(R) | IL-4 | IL-8 | IL-17 | $CD3^+$ $CD4^+$ T cell | $CD3^+$ $CD8^+$ T cell | B cell | NK cell | References |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SC ($n$ = 11) vs. MC ($n$ = 10) | I | ND | I | I | D | I | ND | ND | ND | D | D | ND | ND | (5) |
| SC ($n$ = 9) & CC ($n$ = 5) vs. MC ($n$ = 15) | I | – | – | – | ND | I | ND | – | ND | ND | ND | ND | ND | (6) |
| SC (n−27) vs. MC ($n$ = 17) | I | – | I | I | ND | ND | ND | I | ND | D | – | – | – | (7) |
| ICU care ($n$ = 13) vs. No ICU care ($n$ = 28) | I | – | I | I | – | ND | I | I | – | ND | ND | ND | ND | (9) |
| SC ($n$ = 37) & CC ($n$ = 16) vs. MC ($n$ = 57) | I | – | I | ND | ND | ND | ND | – | ND | D | D | ND | ND | (12) |
| $SpO_2$ < 90% (n = 7) vs. $SpO_2$ ≥90% ($n$ = 36) | I | ND | I | – | ND | – | – | ND | ND | – | – | – | ND | (40) |
| SC ($n$ = 34) vs. MC ($n$ = 67) | ND | ND | ND | ND | ND | ND | ND | ND | ND | D | D | D | D | (42) |
| SC ($n$ = 30) vs. MC ($n$ = 125) | I | ND | ND | ND | ND | ND | ND | ND | ND | D | D | ND | ND | (43) |
| SC ($n$ = 269) vs. MC ($n$ = 279) | I | – | I | I | ND | I | ND | – | ND | ND | ND | ND | ND | (44) |
| SC ($n$ = 21) vs. MC ($n$ = 102) | I | ND | I | – | – | – | – | ND | – | D | D | – | – | (45) |
| SC ($n$ = 45) & CC ($n$ = 62) vs. MC ($n$ = 80) | I | – | I | ND | ND | ND | ND | ND | ND | D | D | D | D | (46) |

*SC, severe cases; CC, critical cases; MC, moderate cases; I, increased; D, decreased; –, not elevated; ND, not done.*

The pathologic capabilities of COVID-19 confirmed that the lungs had been infiltrated with extreme CCR6+ Th17 cells and excessive cytotoxicity of CD8+ T cells [45]. But excessive cytotoxicity of CD8+ T cells does now no longer suggest that

they exert the ordinary function. The SARS-CoV-2 might cause cytotoxic lymphocytes (mainly concerning NK cells and CD8+ T cells) exhaustion, which is manifested because the upregulated exhaustion markers, such NKG2. The exhaustion markers return to normal in patients who've recovered or are convalescent [46], [47]. BALF cells had been located excessive cytokine releases, such CCL2, CXCL10, CCL3, and CCL4 [48]. Furthermore, Xiong et al. [48] use the transcriptome dataset technique to find out that SARS-CoV-2 can activate apoptosis and P53 signaling pathway (one of the pathways liable for the survival of the cell) in lymphocytes. These outcomes might offer a few reasons for the reason of patients lymphopenia. Another group of Chen and his colleagues studied the mechanisms for lymphopenia [49]. Their consequences reveal that SARS-CoV-2 infected the $CD169^{+}$ macrophages in spleens and lymph nodes (LNs), and cause lymphoid tissue damage, such splenic nodule atrophy and lymph follicle depletion, etc. The $CD169^{+}$ macrophages explicit excessive Fas and lead to activation-induced cell death (AICD) through Fas/FasL interactions. Furthermore, SARS-CoV-2 selectively triggered macrophages to provide IL-6, not TNF-α and IL-1β, to immediately promotes lymphocyte necrosis. The evaluation of peripheral blood mononuclear cells (PBMCs) found out that non-structural protein (nsp) 9 and nsp10 of SARS-CoV-2 target NKRF (NF-κB repressor) to promote IL-6/IL-8 production [46]. As a consequence, it recruits neutrophils and induces uncontrollable host inflammatory response. Overall, the clinical, immunological, and pathologic features of COVID-19 have a thing common with SARS and MERS. For example, all of the viruses can lead to lymphopenia and influenza-like signs in early stage. SARS and COVID-19 do not lead to the upgrade of TNF-α, but high levels of IL-6 and IL-10 is greater prevalent in COVID-19. The IL-6 performs an essential function in the pathologic of COVID-19, which includes the chemotaxis of neutrophils and lymphocyte necrosis. Importantly, COVID-19 is extra capable of purpose cytotoxic lymphocytes exhaustion

# IL-6-STAT3 SIGNALING AS A POTENTIAL CAUSE OF THE ARDS VIA CYTOKINE STORM IN COVID-19 PATIENTS

## IL-6 amplifier, machinery for excessive inflammation

SARS-CoV-2 infection induces the endocytosis of ACE2 collectively with SARS-CoV in target cells which includes epithelial cells and endothelial cells, resulting in an increase of serum angiotensin II (Ang II) ranges because of the reduction of ACE2 surface expression **(Figure 1).** [12], [51]. Ang II increment is likewise acquired in lung-harm models, wherein ACE2 is dramatically reduced upon acid treatment [48]. Ang II acts not simplest as a vasoconstrictor however additionally as a pro-inflammatory cytokine thru Ang II kind 1 receptor (AT1R) [49]. Therefore, it is hypothesized that a renin-angiotensin system (RAS) can be worried in the ARDS improvement following SARS-CoV-2 infection [50]. In fact, treating mice with AT1R inhibitors or exogenous recombinant ACE2 suppresses ARDS improvement triggered via SARS-CoV infection [8]. In addition, a feasible advantage of RAS inhibitors in COVID-19 patients has been reported [51], [52]. The Ang II-AT1R signaling axis turns on ADAM metallopeptidase domain 17 (ADAM17), which in flip digests the membrane sorts of epidermal growth factor family members (EGF, epiregulin, amphiregulin, transforming growth factor-alpha, etc.) and TNF-α, all of which stimulate the NF-κB pathway **(Figure 1).** [53], [49], [54]. ADAM17 is likewise an enzyme that approaches membrane-bound IL-6Rα to the soluble form (sIL-6Rα) collectively with ADAM10. Therefore, we hypothesize serum Ang II and sIL-6Rα might be predictive markers of COVID-19 severity. Once sIL-6Rα is generated, the sIL-6R-IL-6 complex transduces intracellular signaling thru its binding to gp130, a signal transducer of IL-6, that's expressed on non-immune cells which includes endothelial cells, epithelial cells, and fibroblasts even with no membrane IL-6R expression, observed with the activation of Janus kinase (*JAK*)/*STAT3* [55]. so, Ang II-AT1R signaling can create an IL-6-mediated effective feedback loop of NF-κB signaling, a mechanism referred to as the IL-6 amplifier, at some point of lung infection accompanied with ARDS with multiorgan failure and coagulation **(Figure 1).** The IL-6 amplifier is a hyper NF-κB activation machinery in the non-immune cells triggered via the synchronous activation of NF-κB and STAT3. It is inducing a huge and sustained production of NF-κB goal genes, such as IL-6, chemokines, and growth factors, that's critical to develop numerous disorder models such as lung transplantation, rheumatoid arthritis, and multiple sclerosis [56], [57]. moreover, we have demonstrated that the co-activation of NF-κB and STAT3, that's proof of activation of the amplifier, is determined in scientific specimens from patients with inflammatory diseases [56], [58]. in addition, the expression of target molecules of the infection amplifier is better in the serum of patients with rheumatoid arthritis or multiple sclerosis [56], [58]. Furthermore, the amplifier activation relies upon the concentrations of NF-κB stimulators and of IL-6 round non-immune cells, however those concentrations range among cells. Indeed, activation has a tendency to arise greater without problems in tissue-specific the non-immune cells including tracheal basement cells, synovial fibroblasts, keratinocytes, kidney tubule cells, and chondrocytes. Therefore, via the IL-6 amplifier, those cells should modify numerous tissue specific-inflammatory diseases [56], [57]. Moreover, activation of the IL-6 amplifier relies upon on numerous environmental and genetic factors. Besides, we have mentioned that stress and ache may be precipitated for the activation of the IL-6 amplifier at particular blood vessels [59], [60], and a few SNPs have an impact at the activation, mainly thru the NF-κB pathway [56], [58].

# CLINICAL POSSIBLE THERAPEUTICS FOR COVID19

As stated above, high IL-6 levels are particularly correlated with the deadly complications of COVID-19 patients [61], [62], [63]. Specially, a preceding record confirmed that inhibition of the NF-κB pathway in animals infected with SARS-CoV reduces mortality and IL-6 levels [64]. As mentioned above, the IL-6 amplifier performs an important part in chronic inflammatory diseases. The activation of the IL-6 amplifier may also result in a cytokine storm, a phenotype of dysregulated inflammation. If that is the case, the cytokine storm in severe COVID-19 may be inhibited via blockade of the IL-6 amplifier [50]. Consistently, chimeric antigen receptor (CAR)-T cell-induced deadly cytokine storm was avoided via an IL-6-STAT3 blocker [65], [50], [66]. As the IL-6 amplifier is activated via the coactivation of NF-κB and STAT3 in non-immune cells, NF-κB and STAT3 ought to be potential regulators of the COVID-19-mediated cytokine storm displayed in **(Figure 1).**

There are a lot of NF-κB activators, as PRRs, AT1R, ADAM17/10, TNF-α-TNFR, and EGF-EGFR. Some may be therapeutic targets for the cytokine storm. However, IL-6 is the important STAT3 activator through inflammatory responses. Considering the provision of IL-6 inhibitors, IL-6-STAT3 blockade may be a simple choice to avoid COVID-19-induced cytokine storm. TCZ is a recombinant humanized monoclonal anti-IL-6R antibody and presently authorized to be used in patients with CAR-T cell-induced severe cytokine storm or CRS with fever, hypoxia, acute renal failure, hypotension, and cardiac arrhythmia that often warrants ICU admission [65], [66]. The effectiveness of TCZ has been also mentioned in CRS associated with numerous different conditions, as sepsis, graft-versus-host disease, and macrophage activation syndrome [67], [68]. Common side effects of TCZ are increased upper respiratory tract infections. Therefore, it is probably hard to apply TCZ for COVID-19 patients on the early phase of the disease. However, the inhibition of the signal transduction mediated via IL-6, the critical STAT3 inducer for the IL-6 amplifier, via binding to both mIL-6Rα and sIL-6Rα is an affordable technique to remember for treating cytokine storm in COVID-19 patients [50], [54]. In fact, Luo and colleagues mentioned that TCZ administration stabilizes clinical results with a reduction of increased C-reactive protein ranges in greater than 1/2 of COVID-19 patients liable to a cytokine storm [69]. Furthermore, Xu et al. investigated whether or not TCZ treatment effectively improves the respiratory function in a total of 21-hospitalized COVID-19 patients. Indeed, amongst those 21 patients, 20 had been recovered after the TCZ therapy [70]. Toniati et al. also confirmed that 77% of patients out of one hundred unexpectedly improved clinical and respiratory state after TCZ treatment [71]. These series of study propose that IL-6-STAT3 signaling may be a promising target for the clinical intervention of COVID-19. Several ongoing clinical trials for TCZ in COVID-19 patients were documented (phase II; NCT04317092, NCT04445272, NCT04377659, phase III; NCT04320615, NCT04330638, NCT04345445) (https://clinicaltrials.gov/ct2/results?cond=COVID-19). Another anti-IL-6R antibody, SAR, used for rheumatoid arthritis [72], has been examined in a multicenter, double-blind, clinical phase II/III study in patients with severe COVID-19 (NCT04315298) [73]. Although Roche has now no longer reached significant consequences of TCZ in phase III study (NCT04320615), greater cautious have a look at for patient choice is important. We hypothesize that the timing of the treatment must be substantial to suppress the cytokine storm triggered via SARS-CoV-2 infection. Because patients with severe COVID-19 signs and symptoms have multiorgan failure because of the high expression level of cytokines, a number of which adjust the function of the organs directly or indirectly through blood endothelial cells that explicit ACE2, we hypothesize that IL-6 inhibitors which includes TCZ should mitigate cytokine storms in COVID-19 patients earlier than multiorgan failure. As defined in the review, the study that discovered IL-6 inhibitors should suppress cytokine storms in patients after CAR-T cell therapy should probably did so through blocking off the IL-6 amplifier [66]. Indeed, on 18th of September 2020, phase III study met its primary endpoint, displaying that patients with COVID-19 associated pneumonia who received TCZ had been 44% much less probably to develop to mechanical ventilation or demise in comparison to patients who took placebo. Other therapeutic options that probably inhibit JAK kinases associated with IL-6 signaling, such baricitinib (phase II/III; NCT04340232) [74], are also potential therapeutic candidates.

# CONCLUSION

The cytokine storm and CRS in fatal COVID-19 are represented via numerous pathological capabilities as ARDS, coagulation, and multiorgan dysfunctions. Since blood IL-6 levels are highly correlated with the deadly complications of COVID-19, we recommend that IL-6 performs a pivotal role in the disorder augmentation and may be hence a useful biomarker for figuring out the disorder severity. With this regard, TCZ is a good therapeutic choice for disrupting the IL-6 amplifier, an IL-6-mediated hyper-inflammatory mechanism that may be caused via innate immune signaling upon viral infection collectively with Ang II-AT1R-mediated signaling because of the reduction of Ang II-quencher ACE2. However, generally, monoclonal antibody-based therapeutics impose a significant value burden on patients and society. Therefore, future research must be directed to the identity of accountable molecules that adjust the IL-6 amplifier in severe COVID-19, thereby allowing the development of latest clinical interventions the use of small molecules against those targets. Intriguingly, SARS-CoV, MERS-CoV, and SARS-CoV-2 show excessive genomic diversity and are taken into consideration to have originated from bats. Given that those viruses share viral spike proteins and utilize human ACE2 receptor for their entry, it is distinctly feasible that a novel bat coronavirus may also had been transmitted to human beings

that cause emerging infectious diseases. Therefore, clarification of the molecular mechanism for the way CRS promotes a couple of signs and symptoms in coronavirus-associated sicknesses is needed. Better understanding of this problem will facilitate the development of novel therapies in preparation for future COVID outbreaks.

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