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Abstract
The continual propagation of SARS-CoV-2 has changed health care systems globally. Ranging degrees of clinical severity in COVID-19 patients have been noted in numerous literature sources. Cytokines play a crucial role in the development of key immunological processes in COVID-19. SARS-CoV-2 causes imbalance of the immune system and might culminate in cytokine storm and multiple organ involvement. The prevailing role of some special cytokines might serve as indicators of disease severity. Further stratification of patients in the context of specific cytokines can be beneficial for diagnosing disease stages. It can prevent critical states owing to timely diagnosis and targeted therapy. Targeting peculiar cytokines can markedly reduce complications. The aim of this article is to comprehensively overview the role of the main cytokines in COVID-19 pathogenesis and distinguish prognostic factors. Insights into specific cytokine involvement in COVID-19 pathogenesis may open new avenues for diagnosing hyperinflammatory COVID-19, predicting its outcomes and providing individualized cytokine-targeted therapeutic approaches.

Keywords: COVID-19, Coronavirus, Cytokines, Cytokine release syndrome

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INTRODUCTION
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged and spread globally after the initial cases in Wuhan, China [1]. The World Health Organization termed the epidemic infection as Coronavirus Disease 2019 (COVID-19) [2].

Patients infected with SARS-CoV-2 suffer mostly from mild to moderate disease. However, severe respiratory failure (RF) and acute respiratory distress syndrome (ARDS) may also develop [3]. About 20% of patients infected with SARS-CoV-2 progress into ARDS and multiple organ damage (MOD) with cytokine release syndrome (CRS) involvement [4].

Any immune response is accompanied by intensive synthesis of proinflammatory (IL-1β, IL-6, IL-8, and TNF-α) and anti-inflammatory cytokines (IL-10) that play a pivotal role in the modulation of COVID-19 severity [5]. The uncontrolled production of proinflammatory cytokines may lead to cytokine storm manifesting as ARDS and MOD in COVID-19 [6]. COVID-19 is still a major health issue affecting the world population. The aim of this article is to comprehensively overview the role
of the main cytokines in COVID-19 pathogenesis and distinguish prognostic factors. The overview may shed light on potential markers of early diagnosis and monitoring of severe COVID-19.

SEARCH STRATEGY
Searches were performed through MEDLINE/PubMed, Scopus, and Web of Science in line with previously published recommendations [7]. Retrieval of relevant documents was completed on January 10, 2022. The following keywords were used: “COVID-19”, “coronavirus”, “cytokines”, and “cytokine release syndrome”. All retrieved abstracts were processed in view of their relevance to the topic. All original articles, reviews, and case reports were processed. Conference papers, book chapters, preprints, and editorials were filtered out.

SARS-CoV-2 BASIC CHARACTERISTICS
SARS-CoV-2 is one of the known RNA viruses characterized by large genomes (26.4-31.7 kb). The virus contains an N-terminal fragment along with a spike protein [8]. SARS-CoV-2 enters its target cells by interacting with angiotensin-converting enzyme-related carboxypeptidase (ACE2) receptor located on multiple organs such as the mucous layer of oral and nasal cavities, lungs, stomach, intestine, skin, spleen, liver, and endothelial cells [9,10]. SARS-CoV-2 entrance is enabled by the activation of Transmembrane Serine Protease (TMPRSS2) and the priming of the protease for S protein. The priming of the viral S proteins includes S protein cleavage at the S1/S2 and S20 sites. The viral spread depends on TMPRSS2 activity. Available data suggest that the viral entry can be blocked by inhibitors of the cellular serine protease TMPRSS2 [11].

IMMUNE RESPONSE IN COVID-19 PROGRESSION
In the course of infection, activated macrophages release multiple cytokines capable of enhancing inflammatory response and tissue damage. Viral danger-associated molecular patterns (DAMPs) sensed by pattern recognition receptors (PRRs) of immune cells mediate the inflammatory response. After the viral attack, Toll-like receptors activate and stimulate the release of proinflammatory cytokines [12]. Specific biological therapy targeting proinflammatory cytokines may regulate the immune response [13].

Hyperinflammatory response in subjects infected with SARS-CoV-2 merits special attention. Macrophage activation syndrome (MAS) and low expression of HLA-DR are believed to contribute to COVID-19 complicated with severe respiratory failure (SRF) [14]. The exhaustion of CD3+, CD4+, CD8+, and CD19+ lymphocytes confounds the complicated course of the disease [15]. The immune response leads to the production of IL-6 and CRP, reaching their peak level in critical conditions [16]. Severe COVID-19 is also characterized by the abundant production of IL-2, IL-6, IL-7, IL-10, and TNF-α in comparison with those who manifest mild and moderate disease [17,18].

IL-6 IN COVID-19
The course of COVID-19 is strongly dependent on IL-6 level [19]. The initial stages of COVID-19 are characterized by the overproduction of IL-6 by activated T-helper 17 (TH17) cells [20]. The role of IL-6 is critical in COVID-19 complicated with pneumonia and ARDS [21]. Overall, the disease progression from mild to severe forms coincides with a marked increase in IL-6 owing to the imbalance between CD4+ and CD8+ cells [22]. Interestingly, IL-6 correlated positively with IL-8 in severe COVID-19 [23].

A single-center prospective cohort study has demonstrated an association between high IL-6 and mortality from COVID-19 [24]. In a Receiver Operating Characteristic (ROC) curve analysis, IL-6 was found to be a specific predictor of mortality with high sensitivity (0.88) and specificity (0.89) [24]. IL-6 pretreatment levels may predict the development of post-COVID arthritis [25].

Several studies have explored the benefits of targeting IL-6 receptors (IL-6R) in COVID-19 [26]. Tocilizumab (TCZ) has proved particularly beneficial for COVID-19 patients requiring mechanical ventilation [27].

Patients with severe COVID-19 pneumonia who received TCZ therapy within the first 48 hours after admission had better prognosis [28].

Patients with severe COVID-19 who received TCZ therapy earlier than those with non-severe forms survived the disease [29]. Patients on mechanical ventilation treated with TCZ had a survival rate of 74% [30].

Elevated IL-6 may inhibit HLA-DR expression on the monocytes of patients infected with SARS-CoV-2 [31]. In fact, IL-6 is negatively correlated with HLA-DR expression [32] while TCZ therapy is accompanied by an
increased expression of HLA-DR on monocytes of COVID-19 patients [14].

A retrospective multicenter case-control study demonstrated that COVID-19 patients treated with TCZ are unlikely to get intubated (OR 0.37, 95% CI 0.18–0.78) [33]. Their course of disease on biological therapy can be monitored by levels of ferritin [33].

**IL-1BETA**

*Interleukin 1 beta (IL-1B)* is one of the proinflammatory cytokines that can be originated from monocytes, dendritic cells, tissue macrophages, NK cells, and B lymphocytes [34]. Increased activity of monocytes is believed to be the main source of elevated circulatory cytokines, particularly *IL-1B*, and related hyperinflammation in COVID-19 [35]. Specifically targeting *IL-1B* may avert the development of hyperinflammation [36]. Higher *IL-1B* levels were reported in severe COVID-19 patients compared with those with mild forms [37]. In a cohort study, the IL-1 inhibition in COVID-19 was associated with a significant mortality reduction [38].

**sST2**

The suppression of tumorigenicity-2 (ST2), particularly its secreted soluble isoform (sST2), has been examined in the course of COVID-19 progression [39]. High serum sST2 positively correlated with CRP and negatively correlated with CD4+ cells, contributing to the immune dysregulation [40]. Severe COVID-19 cases were characterized by persistently high sST2 that was predictive of critical illness [40].

**IL-8**

Elevated IL-8 has been reported in case-control studies of COVID-19 [41]. IL-8 was found to be the best predictive marker of COVID-19 with AUC 0.88 (95% CI 0.81–0.96) [37], although the level of elevation was similar across groups with mild, moderate, and severe COVID-19 [37].

When compared with IL-6 in the context of COVID-19, IL-8 demonstrated a higher predictive value in an ROC curve analysis: AUC 0.9776 vs 0.8417 [42].

Notably, IL-8 levels tend to increase during COVID-19 progression from mild to severe forms. Taken together, IL-6 may be a marker of severe COVID-19 whereas IL-8 may be a better marker for all forms of the disease and its predictor [42].

**IL-32**

Epithelial and immune cells are the main sources of IL-32. It regulates inflammatory response via TNF-α, IL-2, and IL-1b signaling [43]. In case of influenza, elevated IL-32 may prevent virus spread [44]. Significantly elevated IL-32 levels were reported in healthy controls compared with COVID-19 patients [37]. Moreover, IL-32 could be viewed as a marker distinguishing healthy subjects from those with COVID-19 (IL-32 AUC 0.71, 95% CI 0.64–0.77) [37].

**IL-10**

In a study with healthy controls, severe COVID-19 patients had significantly lower levels of IL-10, suggesting the exhaustion of anti-inflammatory reserves with the progression of the disease [37]. In another case-control study, IL-10 was increased in COVID-19 patients while IL-10 positively correlated with CRP (r = 0.41, P < 0.01) [45].

Serum IL-10, along with IL-6 and TNFα, gradually increased in a study comparing non-survivors with survivors during their ICU stay [46]. Significant differences in IL-10 levels were noted on day 3 after ICU admission (P < 0.01) [46]. The elevated serum IL-10 in critically ill COVID-19 patients possibly restrain the area of SARS-CoV-2 damage and initiate restoration interrelated with both proinflammatory and anti-inflammatory processes throughout the disease progression [46].

**IL-37**

IL-37 is a newly discovered cytokine, a member of the IL-1 family, characterized by anti-inflammatory and immune suppressive properties [47]. Such properties are confounded by suppression of the production of proinflammatory cytokines and chemokines such as IL-1β, IL-1Ra, IL-6, IL-8, IL-23, and TNF-alpha [48]. High IL-37 is associated with low proinflammatory cytokines in COVID-19, possibly restricting the virus replication [49]. COVID-19 patients with high IL-37 had a significantly shorter hospitalization than those with low IL-37 (mean 14.8 vs 20.3 days, P < 0.001) [49].

**INNATE IMMUNE RESPONSE IN COVID-19**

T cells are intimately involved in the development of immune response in COVID-19. Patients with COVID-19 present with decreased T cells and increased levels of T cell-produced cytokines [50]. T cells are particularly dysfunctional over the course of the disease progression [51]. A marked imbalance of CD4+ and CD8+ cells is
evident in severe COVID-19, pointing to the exhaustion of innate immunity and the reduction in circulating T cells [52]. CD4+ T cells activate B cells to produce virus-specific antibodies. This pathway is particularly deficient in patients with depleted CD4+ T cells [53].

In a study of 123 patients with mild and severe COVID-19, markedly lower levels of lymphocytes, platelets, and hemoglobin were noted in patients with severe disease [22]. Both CD4+ and CD8+ T cell counts were markedly reduced in the severe group, and their survival prognosis was worse when compared to the mild group [22].

Interestingly, T cell counts reach their lowest levels in severe COVID-19 when IL-10, IL-2, IL-4, TNF-α, and IFN-γ reach their peaks [18]. Severe COVID-19 also leads to the lowering of CD3+, CD8+, and CD4+ T cell counts [18].

Combined analyses of complement anaphylatoxins along with inflammatory cytokines in COVID-19 pointed to the additive roles of both protein groups [54]. C5a and C3a proteins are proinflammatory mediators in COVID-19 that enable recruitment of neutrophils, activation of mast cells, and induction of cytokine production [55]. Severe COVID-19 tends to elevate both C3a and C5a levels, leading to systemic vascular affections and deterioration of the disease course [54].

**THROMBOSIS IN COVID-19**

Patients infected by SARS-CoV-2 present with enhanced prothrombotic features. Thromboses are described in numerous reports of COVID-19 [56,57]. Prothrombotic autoantibodies such as anticardiolipin IgG, IgM, and IgA; anti-β2 glycoprotein I IgG, IgM, and IgA; and anti-phosphatidylserine/prothrombin (aPS/PT) IgG and IgM have been detected in hospitalized COVID-19 patients [58]. Elevated D-dimer is characteristic of COVID-19 patients treated in the ICU [17].

Compared with COVID-19 survivors, non-survivors present with significantly higher prothrombin time (PT), international normalized ratio (INR), D-dimer, and fibrin/fibrinogen degradation products (FDP) [24]. The ROC curve analysis has revealed AUC 0.816 for D-dimer and 0.830 for FDP, suggesting that both markers could predict COVID-19 mortality [59].

Coagulation parameters in ICU patients correlated significantly with proinflammatory cytokines [60]. Also, disseminated intravascular coagulation (DIC) was more frequent in COVID-19 patients with ARDS [61]. Those with ARDS frequently presented with septic shock, DIC, and acute kidney and heart failure [62]. Critically ill COVID-19 patients tended to have higher D-dimer, lactate dehydrogenase (LDH), CRP, and ferritin as constituent components of hyperinflammatory response [53].

**VASCULAR REMODELING IN COVID-19**

Vascular remodeling in COVID-19 is associated with Platelet Derived Growth Factor-AA (PDGF-AA), Platelet Derived Growth Factor-AB-BB (PDGF-AB-BB), Fibroblast growth factor (FGF), and IFN-γ-inducible protein 10 (IP-10) [63]. Soluble CD40 ligand (sCD40L), which is abundantly produced by the platelets of COVID-19 patients, stimulates endotheliocytes, pericytes, and smooth muscle cells [64].

Thrombin-antithrombin complexes (TATc) and soluble tissue factor were significantly elevated in the BALF of COVID-19 patients and demonstrated predictive value in COVID-19 [65].

Accordingly, severe COVID-19 cases may need long-term monitoring after hospital discharge [63].

**AUTOIMMUNITY IN COVID-19**

Neutrophilic extracellular traps (NET) are believed to be the main sites for autoantibody production and accumulation in COVID-19 [66]. Complement activation and overly produced anti-nuclear antibodies, anti-52 kDa SSA/Ro, anti-60 kDa SSA/Ro, antiphospholipid antibodies, and anti-interferon antibodies have been reported in patients infected with SARS-CoV-2 [67,68]. All these factors may induce various autoimmune disorders [69].

COVID-19 manifestations are often viewed through the prism of autoimmunity and inflammatory rheumatic diseases. Also, COVID-19 may manifest with rheumatic symptoms and syndromes such as secondary hemophagocytic lymphohistiocytosis, arthralgias and myalgias, cytopenia, and acute interstitial pneumonia-like presentation [70,71,72]. Likewise, COVID-19 may develop cytokine release syndromes with complicated course owing to immunosuppression [73].

**COMPLETE BLOOD COUNT IN COVID-19**

A sizeable proportion of patients with COVID-19 present with a low white blood cells (WBC) count below 4×10^9/L and lymphopenia below 1.0×10^9/L. However, severe COVID-19 often result in higher WBC and neutrophil
counts and lower lymphocyte counts than moderate cases [74]. LDH and aspartate aminotransferase (AST) are often elevated in severe and critically ill COVID-19 patients [17, 53].

Overall, severe COVID-19 is characterized by elevated AST, alanine transaminase (ALT), LDH, creatine kinase, CRP, ferritin, and serum amyloid A (SAA) [18].

**STRATIFICATION OF COVID-19 PATIENTS**

Numerous studies have reported an association of proinflammatory cytokines with severe COVID-19, ARDS, and poor outcomes [62,76]. COVID-19 patients with ARDS had elevated IL-6, IL-8, IL-10, and TNF-α on days 1, 3, and 5 [62]. Comparing severe and mild COVID-19, IL1β, IL-6, IL-8, and TNF-α were significantly higher in critically ill patients [75]. Additionally, higher IL1β, IL-6, and IL-8 positively correlated with the number of critical COVID-19 cases and in-hospital deaths. All these factors may be used for patient stratification and mortality prediction [54].

One report demonstrated elevation of 16 soluble factors in patients infected with SARS-COV-2 [63]. The same report pointed to the lowering of 2 antibacterial factors such as macrophage-derived chemokine (MDC22) and hematopoietic growth factor FMS-like tyrosine kinase 3 ligand (FLT-3L). Some of these soluble factors (cytokines) may act as chemokines attracting immune cells to inflammation sites. Also, IL-10 and IL-1RA with potentially antimicrobial and anti-inflammatory properties were elevated in COVID-19 [63]. MDC22, FLT-3L, and IL-12 were markedly lowered in ARDS [63]. All these findings may help suggest stratification schemes.

**CONCLUSION**

A better understanding of the various involvements of cytokines in COVID-19 pathogenesis can be beneficial in identifying the stage of disease progression, predicting the disease course, and enabling personalized treatment approaches. Thus, clinical markers may serve as valuable indicators for monitoring the virus spread in humans with COVID-19.

**AUTHOR CONTRIBUTIONS**

YF drafted the initial version of the manuscript. OZ conceptualized and edited the initial version. Both authors significantly revised the manuscript. They take full responsibility for the integrity and accuracy of all aspects of the review.

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**CONFLICTS OF INTEREST**

Both authors have completed the ICMJE Disclosure of Interest Form (http://www.icmje.org/disclosure-of-interest/; available from the corresponding author). Both authors declare no potential conflicts of interest.

| Markers | Serum levels | Notes | Refs |
|---------|--------------|-------|------|
| IL-6    | Elevated (↑) | ↑ in the severe patient group (p=0.001); ↑ in mild-moderate severity group compared with healthy controls (p=0.001) | 23   |
| IL-1B   | ↑            | ↑ in severe group compared with mild group (p < 0.05) | 37   |
| sST2    | ↑            | Positively correlated with CRP and negatively with CD4+ and CD8+ T cells | 40   |
| IL-8    | ↑            | The best discriminatory marker for differentiation of COVID-19 patients from healthy controls (AUC=0.88, 95% CI 0.81–0.96). | 37   |
| IL-32   | Reduced (↓)  | Valuable discriminatory marker for distinction between COVID-19 and healthy control groups (AUC=0.71, 95%CI 0.64–0.77). | 37   |
| IL-10   | ↓            | suggestion of exhaustion of anti-inflammatory properties in covid-19 patients | 37   |
| IL-37   | ↓ or ↑ depending on severity | Defining role in COVID-19 prognosis. Patients with elevated IL-37 had significantly shorter hospitalization (p<0.001) | 49   |
Viral entry through ACE2 receptors on target cells surface

Priming of viral S spike protein by TMPRSS2

Activation of endosome through Toll-like receptors

cytokine storm, multiple organ damage

massive release of proinflammatory cytokines: IL-1β, IL-6, sST2, IL-8

CD4+T cells reduction:

T cells dependent B cells activation and stimulation of virus-specific antibody production

*low IL-10 levels: exhaustion of anti-inflammatory properties

*high IL-10 levels: limitation area of damage and initiation of restoration

Figure 1. Pathogenetic mechanisms of cytokines involvement in COVID-19

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ЦИТОКИНДЕР COVID-19 АУЫРЛЫГЫНЫҢ ЖӘНЕ НӘТИЖЕЛЕРІНІҢ ӘЛЕЮЕТТІ МАРКЕРЛЕРІ
Түйіндеме
SARS-CoV-2-нің таралуы бұқіл алемдегі денсаулық сақтау жұысінің өзгерті. Көптеген әдеби өкіншіздерде COVID-19 шалдықтан науқастарда клиникалық ауырлықтың әртұрлі денгейі байқылды.

Цитокиндер COVID-19 кезінде негізін генетикалық процестердің дамуында шешуші роль атқарады. SARS-CoV-2 иммунды жүйенін төнгерімсіздігін тудырады және цитокиндік дәуылға, көптеген органдардың зақымдалуына алып келуі мүмкін. Кейбір арнайы цитокиндердің басым рөлі аурудан ауырлығының индикаторы бола алады. Нәкты цитокиндер тұрғысына науқастардың басым әрі стратификациялау аурулық кезіндерін диагностикалау үшін пайдалы бұлға мүмкін.

Бұл ұактылы диагноз қою және мәсілетті терапия арқылы сыны жағдайлардың алынуы алуға мүмкіндік береді. Ұағаш сілді аурулар мен жаңа аурулардың ерекшелікті сәйкесінің жаңа және кеңінен колдонылған COVID-19 диагнозының қолға, оның нәтижелерін болғауға және цитокиндерге бағытталған жеke терапевтик тәсілдерді ұсынуға жақа мүмкіндіктер ашуы мүмкін.

Түйін сөздер: COVID-19, коронавирус, цитокиндер, цитокиндерді бөсіту сілді
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ЦИТОКИНЫ КАК ПОТЕНЦИАЛЬНЫЕ МАРКЕРЫ ТЯЖЕСТИ И ИСХОДОВ COVID-19

Резюме
Распространение SARS-CoV-2 изменило системы здравоохранения во всем мире. В многочисленных литературных источниках отмечена различная степень клинической тяжести течения COVID-19 у пациентов. Цитокины играют решающую роль в развитии ключевых иммунологических процессов при COVID-19. SARS-CoV-2 вызывает дисбаланс иммунной системы и может привести к цитокиновому шторму, поражению многих органов. Преобладающая роль некоторых особых цитокинов может служить индикатором тяжести заболевания. Дальнейшая стратификация пациентов в разрезе конкретных цитокинов может быть полезной для диагностики стадий заболевания. Это позволяет предотвратить критические состояния благодаря своевременной диагностике и целенаправленной терапии. Ориентация на специфические цитокины может заметно уменьшить количество осложнений. Цель этой статьи — всесторонне рассмотреть роль основных цитокинов в патогенезе COVID-19 и выделить прогностические факторы. Понимание участия специфических цитокинов в патогенезе COVID-19 может открыть новые возможности для диагностики гипервоспалительного COVID-19, прогнозирования его исходов и предоставления индивидуальных терапевтических подходов, нацеленных на цитокины.

Ключевые слова: COVID-19, коронавирус, цитокины, синдром высокого кровяного давления цитокинов
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