SARS-CoV-2 infection: the role of cytokines in COVID-19 disease

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Abstract

COVID-19 disease, caused by infection with SARS-CoV-2, is related to a series of physiopathological mechanisms that mobilize a wide variety of biomolecules, mainly immunological in nature. In the most severe cases, the prognosis can be markedly worsened by the hyperproduction of mainly proinflammatory cytokines, such as IL-1, IL-6, IL-12, IFN-γ, and TNF-α, preferentially targeting lung tissue. This study reviews published data on alterations in the expression of different cytokines in patients with COVID-19 who require admission to an intensive care unit. Data on the implication of cytokines in this disease and their effect on outcomes will support the design of more effective approaches to the management of COVID-19.

Introduction

COVID-19 is a is a novel β-coronavirus caused by infection with SARS-CoV-2 and is closely related to SARS-CoV. It is the third zoonotic disease by coronavirus to affect humans, following Severe Acute Respiratory Syndrome (SARS) and Middle-East respiratory syndrome (MERS) [1,2].

The first cases of infection by this virus were reported in a shellfish market in south Wuhan in December 2019 [3], and it proved impossible to rule out human-human transmission. SARS-CoV-2 samples were detected in this market, but the infected animal species has not been definitively established at the time of writing [4]. One study proposed that snakes were more likely than other animals to be carriers [5], but subsequent research indicated that bats may be responsible for its transmission, given the close similarity (96.2% of genome sequence) between SARS-CoV-2 in bats and humans [6–9].

The basic reproductive number (R0) in China was reported to reach at least 2.2[10,11]. Human-human transmission started among family members, observing that 31.3 % of infected individuals in this first wave resided in Wuhan and that 72.3 % did not live there but had contact with people who did [12]. The mortality rate of the disease ranged between 2.2 and 2.84 %, and the mean age of non-survivors was 75 years [13,14]. The mean interval between initial symptoms and death was 14 days (range, 6 - 41 days) and was shorter (11.5 days) in patients aged ≥70 years [14].

The clinical manifestations of COVID-19 appear after an incubation period of around 5-6 days and most frequently include fever, coughing, and fatigue, with the possible onset of sputum production, headache, hemoptysis, diarrhea, dyspnea, and/or lymphopenia, among others [12,14–19]. Computed tomography images of patients with severe complications of COVID-19 reveal the presence of pneumonia although with abnormal characteristics, including RNAemia, acute respiratory distress syndrome, acute cardiac damage, and evidence of pulmonary ground-glass opacities. In some patients, ground-glass opacities were detected in subpleural regions in both lungs, which may lead to both systemic and localized immune responses, exacerbating inflammation. In some cases, treatment with inhalers and interferon not only had no positive effects but also worsened the clinical symptoms, with the progression of pulmonary opacities [17,20]. Patients of advanced age and those with underlying conditions (e.g., hypertension, chronic obstructive pulmonary disease, diabetes, and/or cardiovascular disease, etc.) are

at higher risk of a rapid progression to acute respiratory distress syndrome, septic shock, metabolic acidosis, coagulation dysfunction, arrhythmia, kidney damage, heart failure, liver dysfunction, and/or secondary infection, often resulting in death [17,19].

Treatment options against this new disease are mainly limited to the mitigation of clinical symptoms, especially those affecting the respiratory system, including the application of oxygen therapy, with the provision of extracorporeal membrane oxygenation for patients with refractory hypoxemia. Treatments with hyperimmune plasma and immunoglobulin G have also been received by some critically ill patients [21,22], while the administration of antivirals and corticosteroids is contraindicated [19,23]. Remdesivir, an adenosine nucleotide analog, has proven effective in *in vitro* and animal studies and in one patient in the USA [24,25]. Antiretrovirals used against the human immunodeficiency virus (HIV), such as lopinavir/ritonavir, have also been found to reduce the viral load of SARS-CoV-2 [26]. Chloroquine has also been proposed as a candidate drug for the treatment of COVID-19 based on its immunomodulatory properties and capacity to suppress tumor necrosis factor α (TNF-α) and interleukin-6 (IL-6) and to inhibit autophagy [27,28]. In general, and especially in patients suffering from a cytokine storm, clinicians should focus on the reduction of uncontrolled inflammation by blocking IL-6 and TNF-α or eliminating cytokines *via* hemoperfusion [29] (Table 1). Cytokine hyperproduction is often followed by edema, gas exchange dysfunction, acute respiratory syndrome, acute cardiac damage, and secondary infection [17].

Table 1
Experimental treatments available for SARS-CoV-2 infection.

COVID19 Treatment	Cytokine Target	Clinical effect	Reference
Tocilizumab	IL-6	Block Il-6 receptor, and revert the cytokine storm production	Luo et al. [84]
			Xu et al. [95]
			Dholaria et al. [96]
			Zhang et al. [97]
		Turn back inflammation and pulmonary fibrosis	Wang & Han [98]
			Shieh et al. [99]
Blood purification	Cytokines	Eliminate cytokines	Ma et al. [85]
Myo-inositol	IL-6	Il-6 levels reduction, and prevent the cascade inflammation response	Bizzarri et al. [102]
Azithromycin	IL-6	IL-6 and TNF-α Blockage	Schultz [103]
	TNF-α		Gautret et al. [104]
Chloroquine	IL-6	IL-6 & TNF-α supression	Wang et al. [105]
	TNF-α		
Fedratinib	IL-17	Decreasing of IL-17 (Assayed in murine model)	Wu and Yang [163]
Certolizumab & antiviral therapy	TNF-α	Antibody anti- TNF-α	Zhang et al. [188]
MSC	IL-1	Downregulation of IL-1, VEGF, IL-12, IFN-γ & TNF-α	Chen et al. [144]
	VEGF		Chen et al. [43]
	IL-12		Leng et al. [145]
	IFN-γ		
	TNF-α		

With regard to the pathophysiological mechanism of the virus, it enters the cell *via* angiotensin-converting enzyme-2 (ACE-2), mainly through the Toll-like receptor-7 (TLR-7) present in endosomes. TLR-7 activation requires the production of TNF-α, IL-

12, and IL-6 to enable the generation of specific cytotoxic CD8^{+} T cells. This involves the formation of antigen-specific B cells and antibody production through CD4^{+} helper T cells [29].

The majority of patients infected with COVID-19 have normal or reduced white cell counts and lymphocytopenia, and those with severe disease have shown significantly elevated levels of neutrophils, dimer-D, and urea in blood, with a continuing decrease in lymphocytes. Increases in certain cytokines and chemokines (e.g., IL-6, IL-10, and TNF-α) have also been observed in these patients. Thus, patients admitted to intensive care units (ICUs) have been found to have elevated serum levels of IL-2, IL-7, IL-10, macrophage colony-stimulating factor (M-CSF), granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony stimulating factor (GM-CSF), 10 kD interferon-gamma-induced protein (IP-10), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein 1-α (MIP 1-α), and TNF-α [17,30,31] (Fig. 1).
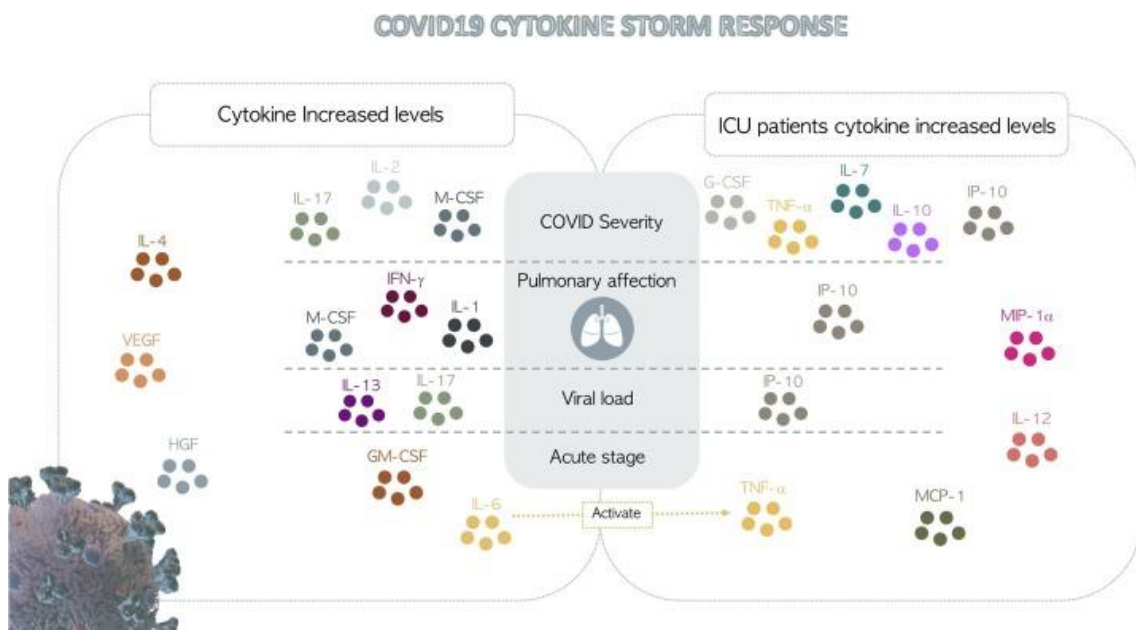

Figure 1. Cytokine storm and severity of the COVID-19 disease.

It is essential to analyze the factors underlying the physiopathology of this pandemic disease, and certain cytokines appear to play a key role. The objective of this study was to review data on the cytokines that influence the progression of COVID-19 in order to support efforts to manage this highly virulent disease.

SARS-CoV-2 and cytokines

The immediate immune response to infection by viruses, bacteria, or other microorganisms involves the mobilization of cells and molecules and draws on energetic, enzymatic, and biosynthetic resources; i.e., metabolic resources [32–34]. Metabolic dysfunctions caused by viral infection requires a reprograming of the host metabolism to generate effective antiviral defense responses. Data published on interferences between the actions of viruses and cytokines reveal the molecular mechanisms underlying the innate immune response against viral infection [35–37].

Cytokines are a group of polypeptide signaling molecules responsible for regulating a large number of biological processes *via* cell surface receptors [38]. Key cytokines include those involved in adaptive immunity (e.g., IL-2 and IL-4), proinflammatory cytokines and interleukins (ILs) (e.g., interferon (IFN)-I, -II, and -III; IL-1, IL-6, and IL-17; and TNF-α); and anti-inflammatory cytokines (e.g., IL-10). In response to stress-generating internal processes (e.g., cancer or microbial infection), host cells secrete cytokines with a highly important role in cell metabolism reprogramming as a defensive response [32,39,40].

Concerning COVID-19 disease, Blanco-Mello et al. described a distinctive and unsuitable inflammatory response related to SARS-CoV-2 infection. These authors revealed that an "inappropriate and weak immune response" appears more frequently in patients with comorbidities. Thus, this could favor virus replication and enhance complications related to severe cases of the disease [41].

In the short time since the emergence of COVID-19, numerous studies have described abnormal levels of the following cytokines and chemokines in the patients: IL-1, IL-2, IL-4, IL-6, IL-7, IL-10, IL-12, IL-13, IL-17, M-CSF, G-CSF, GM-CSF, IP-10, IFN-γ, MCP-1, MIP 1-α, hepatocyte growth factor (HGF), TNF-α, and vascular endothelial growth factor (VEGF) [17,30,31,42,43] (Table 2). The key point in SARS-CoV-2 infection could be the depletion of antiviral defenses related to innate immune response as well as an elevated production of inflammatory cytokines [41].

Table 2
Cytokines involved in SARS-CoV-2 infection.

Reference	Methodology	Objective	Main Results
Chen et al. [16]	Retrospective study	To describe the epidemiological and clinical features of SARS-CoV-2 pneumonia in patients from Wuhan Jinyintan Hospital	Approximately 50 % of the subjects who developed the disease had been exposed to the Huanan seafood market. It affects men more often, with an average age of 55. Approximately half of the subjects had other comorbidities. The main symptomatology is characterized by fever, cough, shortness of breath, muscle pain among others. CT scan revealed that 75% of patients developed bilateral pneumonia and some cases evolved into acute respiratory distress syndrome (ARDS) or died from multiple organ failure.
Huang et al. [17]	Descriptive study	To describe the epidemiological, clinical, laboratory and radiological characteristics, treatment and outcomes of patients infected with COVID-19 in Wuhan and make a comparison between patients in the intensive care unit (ICU) and those who are not	Infection by SARS-CoV-2 caused clusters of severe respiratory disease and was associated with ICU admission and high mortality. Most of the infected patients were male, with different comorbidities and an average age of 49 years. The disease is mainly manifested by fever, cough, and myalgia or fatigue. Dyspnea occurred in more than 50 % of the patients. Lymphopenia was present in 63 % of the cases. Patients admitted to the ICU were found to have higher plasma levels of IL2, IL7, IL10, GSCF, IP10, MCP1, MIP1A, and TNFα.
Liu et al. [30]	Descriptive study	To describe the epidemiology, clinical features, possible treatments and prognosis of patients infected with SARS-CoV-2 in Hubei	The initial manifestations of SARS-CoV-2 were fever, cough and muscle pain or fatigue. Most patients had a normal or decreased white blood cell count, and 72.3 % had lymphocytopenia. Lung involvement was observed in all cases. Treatment was based on symptom control and respiratory support. Immunoglobulin G was administered to some critically ill patients while systemic corticosteroids showed no significant benefit. The risk of death was related to age, comorbidities and the period between initial symptoms and dyspnea.
Wang et al. [31]	Retrospective study	To describe the Cytokine release syndrome-like (CRSL) that occurs in patients affected by COVID-19 pneumonia and to identify risk factors and possible treatments.	Average age: 58 years old. Gender: men mostly. Extensive pulmonary inflammation and ARDS: 83,3%. Symptoms: fever, hypoxia and shock (28,6%). Laboratory findings: Decrease of CD3, CD4, CD8, NK cells. Increase of IL-6, CD4/CD8 ratio. CRSL: 72, 7%, manifested by: pulmonary inflammation, decrease of CD4, CD8 and NK, increase of IL-6 and dysfunction of non-pulmonary organs. Management: ventilation, anti-inflammatory therapy, mechanical-ventilation
Chen et al. [43]	Literature review	To review the literature on the relationship between COVID-19 and the cytokine storm as well as the possible immutherapic treatments available	The effectiveness of some therapies was demonstrated such as the use of stem cells that inhibit the activation of T-lymphocytes, macrophages and induce their differentiation into regulatory subpopulations of T-cells and anti-inflammatory macrophages, but also inhibit the secretion of IL-1α, TNF-α, IL-6, IL-12, and γ-interferon, controlling the cytokine storm.
Conti et al. [52]	Literature review	To clarify the relationship between IL-1 and IL-6 pro-inflammatory cytokines and lung inflammation. Anti-inflammatory strategies	Infection with COVID-19 causes a release of IL-1β and IL-6 which will lead to lung inflammation, fever and fibrosis. The therapeutic potential of several cytokines, such as IL-37 and 38, capable of inhibiting molecules such as those previously mentioned, has been demonstrated
Mehta et al. [53]	Correspondence	To define the cytokine storm syndrome that occurs in severe COVID-19 states and to identify possible treatments	Cytokine storm syndrome is characterized by increased interleukin (IL)-2, IL-7, IL-6 granulocyte- colony stimulating factor, interferon-γ inducible protein 10, monocyte chemo-attractant protein 1, macrophage inflammatory protein 1-α, and tumour necrosisfactor-α. Immunosuppressors such as tozulimab or anakinra appear to work in states of hyperinflammation as described in severe COVID-19 states
Wan et al. [54]	Observational study	To characterize the state of the immune system and the implications of different cytokines in SARS-CoV-2 patients and to study their relationship with the severity of the process	Lower levels of CD4 + T and CD8 + T and higher levels of IL-6 and Il-10 were observed in the more severe NCPs. These markers may help predict the worsening of mild patients.
Yang et al. [55]	Observational study	To study the different cytokine profiles in patients infected with SARS-CoV-2 and their relationship to the severity of the disease.	A total of 14 cytokines were shown to be elevated in patients with COVID-19, with particularly high levels of IP-10, MCP-3, and IL-1ra in severe patients. These markers were predictors of the evolution of the disease towards more severe and even fatal states.
Liu et al. [56]	Retrospective study	To characterize the cytokine storm that occurs in patients with COVID-19	Patients with COVID 19 have hypercitokinaemia that manifests itself with an elevation of 38 of the 48 cytokines measured. Patients with lung lesions were observed to have an upregulation of M-CSF, IL-10, IFN-2, IL-17, IL-4, IP-10, IL-7, IL-1ra, G-CSF, IL-12, IFN-γ, IL-1, IL-2, HGF, and PDGF-BB. These biomarkers may be useful as predictors of the severity of the pathology.
Qin et al. [57]	Retrospective study	To analyze the expression of different biomarkers, inflammatory cytokines and lymphocyte subsets in patients infected with COVID-19, and to determine their relationship with the severity of the process.	An increase in neutrophil-lymphocyte-ratio and T lymphocytopenia (especially CD4 + T cells) was observed, which was more pronounced in severe patients. Elevated serum levels of TNF-α, IL-1 and IL-6 and IL-8 were also found in severe cases.
Zhang et al. [58]	Literature review	To study the use of anti-inflammatory drugs in the therapeutic approach of patients infected with COVID-19	Treatment with anti-inflammatory drugs may be useful in managing the cytokine storm that develops in critically ill

Table 2 (*continued*)

Reference	Methodology	Objective	Main Results
			patients. However, possible immunological alterations of the host should be considered before starting therapy and their individual characteristics should also be considered.
Kritas et al. [60]	Literature review	To determine the cytokine potential of various cytokines of the IL-1 family as a new strategy in the management of inflammation	IL-37, which inhibits IL-1, may be considered in the treatment of patients with COVID-19 because of its anti-inflammatory activity that would help control fever and inflammation.
Chen et al. [64]	Retrospective study	To establish and compare cytokine profiles between moderate and severe stages of COVID-19 in patients from Tongji Hospital.	Severe patients more frequently presented dyspnea, lymphopenia and hypoalbuminemia, with higher levels of alanine aminotransferase, lactate dehydrogenase, C-reactive protein, ferritin and D-dimer, as well as significantly higher levels of IL-2R, IL-6, IL-10 and TNF-α. The numbers of T-lymphocytes, CD4 + T-cells and CD8 + T-cells were decreased in all cases but more markedly in severe patients. Expression of IFN-γ by CD4 + T cells was lower in severe cases
Chen et al. [65]	Retrospective study	To establish the clinical features of COVID-19 and to study the relationship between the cytokine storm detected in serum and the severity of the process in patients from Tongji Hospital.	The main symptoms of 2019-nCoV pneumonia were fever with or without respiratory symptoms and other systemic symptoms. Serum white blood cell counts were normal or decreased, lymphocyte count decreased, hs-CRP increased, procalcitonin normal, LDH increased and albumin decreased. High resolution CT showed single or multiple frosted glass shadows accompanied by septal thickening. Significantly higher levels of interleukin-2 receptor (IL-2R) and IL-6 were found in the most severe patients. No differences in serum TNF-α, IL-1, IL-8, IL-10, hs-CRP, lymphocyte count and LDH levels were found between the groups
Chu et al. [81]	Ex vivo study	To study replication, cell tropism and the route of immune activation by SARS-CoV-2 in human lung tissues	SARS-CoV-2 infected and replicated in human lung tissues more efficiently than SARS-CoV. In lung tissue, SARS-CoV-2 infected type I and II pneumocytes and alveolar macrophages but did not stimulate production of type I, II, or III interferons and only increased expression of IL6, MCP1, CXCL1, CXCL5, and IP10
Diao et al. [82]	Retrospective study	To analyze figures and markers of T-cell exhaustion in patients with COVID-19	A marked reduction in the overall T-cell count was observed in patients with COVID-19. Total T-cell, CD8 + T-cell, or CD4 + T-cell counts below 800/μL, 300/μL, or 400/μL are negatively correlated with patient survival and serum levels of IL-6, IL-10, and TNF-α. In addition, it was observed that PD-1 (a marker of T-cell exhaustion) is higher in patients with COVID 19 and that its expression is related to the severity of the process.
Dong et al. [83]	Retrospective study	Study the possible vertical transmission of the SARS-CoV-2	A newborn presented IgM antibody to SARS-CoV-2 as well as cytokine alterations although he was negative for RT-PCRs
Pedersen & Ho [86]	Literature review	To describe the cytokine storm that occurs in severe SARS-Cov-2 infected patients	Increased levels of IL-6, IL-10 and TNF-α, lymphopenia (in CD4+ and CD8 + T cells) and decreased expression of IFN-γ in CD4 + T cells in severe patients were evidenced.
Ruan et al. [87]	Retrospective study	To establish predictors of mortality in patients infected with COVID-19	Predictors of mortality in patients infected with SARS-Cov-2 include age, presence of comorbidities, presence of secondary infection, and elevated inflammatory markers in the blood such as lymphocytes, platelets, albumin, total bilirubin, blood urea nitrogen, blood creatinine, myoglobin, cardiac troponin, C-reactive protein (CRP), and interleukin-6
Sun et al. [88]	Retrospective study	To describe epidemiological and clinical features, imaging and laboratory data, clinical treatments and outcomes of severely or critically ill pediatric patients infected with COVID-19 in Wuhan.	Most of the subjects were males between the ages of 2 months and 15 years. The main manifestations included polypnea, fever and cough. Patch-like shadows and ground glass opacity were observed in most patients on chest CT scans. The analyses showed an increase in C-reactive protein, procalcitonin and lactate dehydrogenase, CD3, CD4, CD8, IL-6, IL-10 and IFN-γ and a decrease in CD16 + CD56 and Th/Ts. Treatment was based on symptom control and respiratory support. Two subjects required invasive mechanical ventilation.
Wu et al. [90]	Retrospective cohort study	To describe the clinical features and outcomes in patients with ARDS or who died from COVID-19 Pneumonia	Average age: 51 years old. Gender: men mostly. Background: Hypertension and diabetes. ARDS: 41.8 % manifested by dyspnea. Death: 52.4 %. Risk factors for ARDS and death: age, neutrophilia, organ dysfunction and coagulation, high fever (for ARDS). Treatment: Among patients with ARDS, methylprednisolone
Chen et al. [91]	Retrospective study	To analyze the relationships between the incidence of RNAaemia and the cytokine storm as well as the severity of the disease	There seems to be a relationship between RNAaemia and the severity of the patient's condition, as well as with IL-6 levels, which is particularly high in this group of subjects and may act as a therapeutic target for the management of critically ill patients.
Zhou et al. [92]	Retrospective multicenter study	To describe risk factors for mortality anD clinical course of illness in patients infected with COVID-19 in Wuhan.	Survival: 137/191 subjects. Background: hypertension, diabetes and coronary heart disease. Mortality risk factors: advanced age, high scores on the Sequential Assessment of Organ Failure scale and d-dimer greater than 1 μg/mL on admission. Time of virus excretion: 20 days in survivors although in the deceased it was detectable until death.
Zhou et al. [93]	Retrospective study		COVID-19 disease leads the activation of CD4+ T cells and generate GM-CSF, among others. The infection generates the

Table 2 (*continued*)

Reference	Methodology	Objective	Main Results
Akhmerov & Marban [94]	Literature review	To analyze blood samples from patients with SARS-CoV-2 severe pneumonia in order to identify their immune characteristics. To describe the impact of COVID-19 at the cardiovascular level	secretion of several cytokines that induce inflammatory CD14$^+$ and CD16$^+$ monocytes with the consequent increase of IL-6 expression and the acceleration of inflammatory process. The mechanisms linking cardiac involvement and SARS-CoV-2 appear to be related to respiratory failure and hypoxemia, direct myocardial infection by the virus, indirect injury by the systemic inflammatory response, or a combination of all three. COVID-19 has been associated with myocarditis, blood pressure abnormalities and arrhythmias, acute coronary syndromes and acute myocardial infarction.
Saghazadeh & Rezaei [131]	Literature review	To describe the epidemiological and immunological features of COVID-19	COVID-19 mainly affects men. One of the main risk factors for infection and death is old age. 30 % of patients affected by COVID-19 had previous pathologies such as cardiovascular disease, diabetes, chronic respiratory disease, hypertension, and cancer. All these factors condition the transmission of the virus. The first and last alteration caused by SARS-CoV-2 is a lung lesion accompanied by the pro-inflammatory cytokine storm.
Rio & Malani [169]	Viewpoint	To describe the most relevant features of COVID-19	R0: 2.68. Compared to SARS-CoV and MERS, SARS-CoV-2 has a higher infectivity and lower-case fatality rate. Incubation period: between 5.2 days to 14 days. Clinical features: fever, dry cough, difficulty in breathing. Other symptoms are myalgia, headache, sore throat and diarrhoea. Average age: 49–56 years. Severity: most of the cases are mild, all patients admitted to the hospital have pneumonia with infiltrates on chest X-ray and ground glass opacities on chest CT scan. Evolution: ARDS and ICU admission. Treatment: symptomatic and respiratory support
Lin et al. [185]	Literature review	To clarify the pathogenesis of SARS-CoV-2 and compare it with other infections caused by coronavirus	The virus enters the body through the nasal and pharyngeal mucous membranes and reaches the lung parenchyma where it can be incorporated into the circulation causing viremia. Once in the bloodstream it can affect organs that express ACE2. The period from the first symptoms to ARDS is approximately 8 days. At this point a second, much more aggressive stage of the infection begins. In infected patients, lymphopenia and an increase in pro-inflammatory cytokines are detected.
Xiong et al. [186]	Retrospective study	To study transcriptional changes in bronchoalveolar lavage fluid (BALF) and peripheral blood mononuclear cells (PBMC) specimens from COVID-19 patients	An association was observed between the pathogenesis of COVID-19 and the excessive release of cytokines such as CCL2/MCP-1, CXCL10/IP-10, CCL3/MIP-1A and CCL4/MIP1B. In addition, it was postulated that the ability of the virus to activate apoptosis and the P53 signaling pathway in lymphocytes may be the cause of lymphopenia in patients.

IL-1

IL-1 actively participates in the inflammatory response to infection [39], and its main sources are activated monocytes and macrophages [44]. SARS-CoV-2 appears to act on the activation and maturation of IL-1β, which in turn activates other proinflammatory cytokines, such as IL-6 and TNF-α [45–47]. Hence, IL-1β forms part of the cytokine storm produced by coronavirus infections [48–54]. Yang et al. detected elevated levels of the antagonistic receptor of IL-1 (IL-1Ra) in 14 severe cases of COVID-19, and this marker has been associated with increased viral load, loss of pulmonary function, lung damage, and mortality risk [55]. Liu et al. also found elevated IL-1α levels in patients with severe COVID-19, and these were strongly associated with lung injury [56]. IL-1 levels are related to the virulence of the process, and significantly higher serum levels have been observed in SARS-CoV-2 cases with severe symptoms than in mild cases or in those infected with the 2003 SARS-CoV or 2012 MERS coronavirus [57]. Most COVID-19 patients with severe symptoms have elevated levels of IL-1β, which has been associated with SARS, hypercoagulation, and disseminated intravascular

coagulation [58]. For this reason, some therapeutic strategies have used the inhibition of IL-1 in an attempt to avoid the cytokine storm [59,60]. In this way, mesenchymal stem cells (MSCs) have been used to inhibit proinflammatory cytokines such as IL-1α and TNF-α [43].

IL-2

IL-2 plays a key role in the proliferation of T cells and in the generation of effector and memory T cells [61]. It is involved in adaptive immunity and increases glucose metabolism to promote the proliferation and activation of T, B, and NK cells [39]. Hence, IL-2 participates in the prevention of autoimmune diseases and is essential to control immune responses and maintain self-tolerance [62]. The absence of this interleukin has been associated with a poor control of effector cells and the consequent development of autoimmunity [63].

Huang et al. detected elevated levels of IL-2 or its receptor IL-2R in patients with COVID-19, and it has been reported that these increases are directly proportional to the severity of the disease [17,30,43,52–54,56,57,64,65]. Elevation of this interleukin and its association with disease severity have also been reported in patients with other types of coronavirus [66–68].

IL-4

IL-4 is also involved in adaptive immunity, playing a crucial role in the immune regulation governed by activated T helper (Th) cells. It preferentially acts through activation, proliferation, and differentiation of B lymphocytes and promotion of the immunoglobulin E isotype. It therefore decisively intervenes in the induction of humoral immunity-regulating Th2 cells [39,69].

It has been proposed that IL-4 has an anti-inflammatory function that is specific to the tissue in which it is present, reflecting the metabolic plasticity of different tissues [70]. With respect to viral infections that target the respiratory system, Bot et al. observed that its expression during infection with an influenza virus had negative effects on CD8^{+} memory T cells [71].Various studies of COVID-19 patients have detected elevated IL-4 levels as part of the cytokine storm associated with severe respiratory symptoms [16,17,43,72].

L-6

IL-6 is involved in inflammation, the immune response, and hematopoiesis [73]. This pleiotropic biomolecule is secreted by multiple cell types and regulates a wide variety of physiological processes [74]. During initial stages of inflammation, secreted IL-6 travels to the liver and induces a large number of acute-phase proteins, including C-reactive protein (CRP), serum amyloid A (SAA), fibrinogen, haptoglobin, and α1-antitrypsin. In addition, IL-6 has been found to diminish the production of fibronectin, albumin, and transferrin [75]. It has been reported that it has regenerative and anti-inflammatory effects mediated by the conventional signaling process, although it also exerts proinflammatory effects mediated by trans-signaling, as in the case of viral infections [76].

In relation to the different types of coronavirus, elevated IL-6 levels have been observed in SARS cases and related to the severity of symptoms [48,77,78] and in SARS-CoV, being implicated in possible T-cell dysfunctionality. It has been observed that SARS-CoV-induced cytokines may damage the capacity of T cells in relation to dendritic cells, compromising the viability of these cells and macrophages to eliminate the pathogen [49,79]. Similar observations have been made in relation to MERS [50,80].

Elevated IL-6 levels have been found in patients with COVID-19 and related to a poor prognosis [16,31,53,65,81–90]. Wan et al. detected elevated IL-6 levels in one-third of patients with mild symptoms and three-quarters of those with severe symptoms, concluding that IL-6, alongside IL-10, may be of prognostic value in patients with COVID-19 [54]. Among patients admitted to ICU, Diao et al. found an inverse proportional association between elevated IL-6 levels and T cell counts [82], and another study of patients with severe symptoms described elevated serum levels of IL-6 and CRP [91]. A study of 452 patients infected with SARS-CoV-2 also reported that the elevation of IL-6 levels was more marked with more severe symptoms [57]. These levels have been higher than those observed in patients with SARS-CoV or MERS [77,80]. IL-6 levels were also found to be markedly higher in patients who died from COVID-19 than in those who recovered [92]. As noted above, activation of IL-1β by SARS-CoV-2 in turn activates IL-6 and TNF-α [45–47]. It has also been demonstrated that a high expression of IL-6 in patients with COVID-19 can accelerate the inflammatory process, contributing to the cytokine storm and worsening the prognosis [93]. The cytokine storm, including

elevated levels of IL-6, has also been associated with cardiac damage in these patients [94].

With regard to the important role of IL-6 in the SARS-CoV-2-induced cytokine storm and its evasion, it has been reported that the monoclonal antibody tocilizumab acts by blocking the receptor of IL-6 and has been reported to reverse cytokine hyperproduction [84,95–97], inflammation, and pulmonary fibrosis [98,99]. In fact, a multicenter clinical trial is under way in China on the usefulness of tocilizumab to treat patients with COVID-19 (NCT04252664 & NCT04257656), and it has already been included in clinical practice guidelines in China and Italy [100,101]. The polyol myo-inositol was also described by Bizzarri et al. as a potential candidate drug to reduce IL-6 levels and the risk of cytokine storm [102]. In addition, the capacity of the macrolide azithromycin in combination with hydroxychloroquine, to reduce nasopharyngeal levels of SARS-CoV-2 has been attributed to its capacity to block IL-6 and TNF-α [103,104]. Chloroquine also has the capacity to inhibit IL-6 and TNF-α, and is being tested against COVID-19 [104,105]. Finally, blood purification therapy has been proposed to eliminate pathological antibodies and IL-6, among other cytokines, given its successful application against other diseases [85].

IL-7

IL-7 plays an important role in lymphocyte differentiation, participating in the development of T cells and peripheral homeostasis [106]. All of the main CD4 T cell subgroups (CD4+ immature, memory, and Th17 cells) depend on this cytokine for peripheral homeostasis [107–110]. IL-7 activates T cells, increases the production of proinflammatory cytokines, and negatively regulates transforming growth factor beta (TGF-β). The role of this biomolecule depends on IL-6 [111], and it has been suggested that IL-7 secretion can be induced by viral infections [112].

As in the case of other cytokines, it has been reported that IL-7 levels are elevated in patients with COVID-19 and directly related to disease severity [17,53,54].

IL-10

IL-10 is a type 2 cytokine that inhibits the production of proinflammatory cytokines (e.g., IFNγ, TNFα, IL-1β, and IL-6) in various cell types and prevents dendritic cell maturation by blocking IL-12. It hampers expression of the major histocompatibility complex and costimulatory molecules, which have an important role in cell immunity. However, IL-10 can have immunostimulatory effects, including the stimulation of IFNγ production by CD8^{+} T cells. It is also a powerful factor for the growth and differentiation of B cells, mast cells, and thymocytes [113–119]. Numerous authors have described viruses (Epstein Barr virus, cytomegalovirus and herpesvirus) that contain IL-10 homologs, which may contribute to the presentation of different binding profiles to receptors and biological activities that can increase viral resistance [72,114,120–125].

However, IL-10 regulation is decreased in infection with some viruses, such as HIV, contributing to T-cell depletion [126–128]. Animal studies have shown that the antibody-mediated inhibition of IL-10 signaling improves the T-cell response and contributes to eliminating viral resistance. Hence, the effective blocking of IL-10 signaling may be useful against resistant viral infections [129,130].

Various authors have detected this interleukin in patients with COVID-19 and related its levels to disease severity and progression, as in the case of other cytokines [17,43,57,64,82,83,86,88,89] and it has been reported to have possible prognostic value [54]. In fact, some authors indicate that IL-10 may be hyper-expressed in anti-SARS-CoV-2 immunity, being higher in patients of advanced age with respect to a "hyperinflammatory response", possibly related to the reduction of T-cell receptors in the elderly [131]. As with other cytokines, IL-10 levels were found to be higher in patients with COVID-19 than in those with SARS-CoV or MERS [17].

IL-12

IL-12 is one of a group of heterodimeric biomolecules with distinctive characteristics, including pairing versality (also observed for IL-23, IL-27, and IL-35), which are involved in molecular processes and functions with a crucial role in positive and negative feedback [132,133]. IL is a proinflammatory/prostimulatory cytokine produced in response to microbial agents by dendritic cells, B cells, monocytes, and macrophages, among others. It has key functions in the development of Th1 and Th17

cells [134–137]. IL-12 also induces the production of IFN-γ by T and NK cells in a positive feedback mechanism [138].

The action of this cytokine in viral infections is based on its direct chemotactic effects on the infiltration of NK cells, increasing their binding to vascular endothelial cells. NK cells secrete IFN-γ, which participates in positive feedback by increasing the production of IL-12 [139,140]. Viral infections rapidly induce the gene expression of IL-12, which also acts after viral replication [141–143]. For instance, IL-12 is endogenously induced during the pneumonia produced by influenza and activates NK cells, which secrete IFN-γ and thereby inhibit viral replication. IL-12 has been found to produce some improvement in the response of CD8+ T cells [140].

Elevated serum IL-12 levels have been observed in patients infected with SARS-CoV-2, [16,17,43] and in those infected with other coronaviruses such as SARS-CoV [77].

MSCs inhibit the secretion of IL-12, as well as IFN-γ and TNF-α, and have been proposed as an effective therapy against COVID-19 [144,145].

IL-13

IL-13 is secreted by activated Th2 cells, constituting a counter-regulatory system for the Th1-type immune response. It is considered an important regulator of immune responses mediated by Th2-type cytokines [146]. IL-13 has varied functions and has been implicated in the development of bronchial asthma by inducing the production of TGF-β, eotaxin-3, and mucin [147–150]. It also participates in the activation of mast cells (de Vries JE, 1996). Both IL-13 and IL-4 are involved in allergic processes, asthma, and the regulation of Th2 lymphocytes [151]. IL-13 mediates tissue responses to infections, including the mobilization of eosinophils and the expulsion of parasites [152].

Few data are available on the presence of IL-13 in patients with COVID-19. Huang et al. found no difference in serum IL-13 levels between those requiring ICU admission and those who did not [17]. However, Liu et al. observed a directly proportional association between IL-13 levels and the viral load of SARS-CoV-2 [56].

IL-17

IL-17 is synthetized by Th17 lymphocytes and is elevated in inflammatory processes and autoimmune diseases [153–156]. It is also produced by CD8^{+} cells and by various sets of immature lymphocytes, including gamma-delta T cells, NK cells, and group 3 innate lymphoid cells [157]. IL-17, alongside IL-22 and TNF-α, also induces the production of antimicrobial peptides [158]. Hence, IL-17 is a proinflammatory cytokine that plays a role in tissue damage, physiological stress, and infection. These functions vary according to the tissue in which IL-17 is expressed, being particularly important in the gastrointestinal tract and skin [159,160].

Elevated IL-17 levels have been reported in patients with SARS-CoV-2 as part of the cytokine storm [17], and they have been associated with the viral load and disease severity [56]. In contrast, Wan et al. found that IL-17 levels were normal in patients with COVID-19, with no significant differences between patients with severe *versus* mild symptoms [54]. Elevated IL-17 levels were previously described in patients with SARS-CoV or MERS [161,162]. The fact that Th17 cells can produce IL-17, among others, has led to proposals for a therapeutic approach to COVID-19 focused on Janus kinase 2 (JAK2) inhibitor named Fedratinib. This JAK2 inhibitor decreases IL-17 expression by Th17 cells in murine models [163].

M-CSF

M-CSF, also known as colony-stimulating factor-1, is a primary growth factor that belongs to the family of colony-stimulating factors [164]. It regulates the growth, proliferation, and differentiation of hematopoietic cells, including monoblasts, promonocytes, monocytes, macrophages, and osteoclasts. It is secreted by various cell types, including monocytes, fibroblasts, osteoblasts, stromal cells, endothelial cells, and tumor cells. The actions of M-CSF are mediated by a type III tyrosine-kinase receptor. It requires the synergic action of IL-1 and IL-3 during the early differentiation of myeloid line cells, while at subsequent stages it can directly control the proliferation and differentiation of mononuclear cells of the phagocytic system [165]. M-CSF expression increases during infectious processes, augmenting the production of myeloid cells [166].

Liu et al. found significantly elevated levels of this factor in patients with COVID-19 and associated the hyperexpression of this and other cytokines with lung damage, which may assist in predicting disease severity [56].

G-CSF

G-CSF is essential for the proliferation and maturation of polymorphonuclear granulocyte cells (PMNs), preparing the organism for defense against invasion by certain pathogens. The immunological functions of PMNs in infections include chemotaxis, phagocytosis, and the release of lysosomal enzymes and other signaling molecules. Thus, G-CSF has hematopoietic growth factor properties and simultaneously functions as a mediator of anti-infectious and anti-inflammatory responses [167]. It is the main determinant of the number of circulating neutrophils and is a key mediator in physiological responses that require the action of these cells. Increased levels of endogenous G-CSF have been reported in infectious and traumatic processes and in patients with neutropenia or fever with/without neutropenia. G-CSF levels have also been correlated with bacteremia by Gram-negative organisms [168].

Huang et al. found that G-CSF levels were elevated in patients with COVID-19 and even higher in those requiring ICU admission [17]. This could lead the multiorgan failure related to severe cases [90,169]. Wu D and Yang XO (2020) associated G-CSF levels with the response of Th17 lymphocytes in patients with SARS-CoV-2, finding that the IL-17 produced by these cells can induce the production of G-CSF, among others. They also reported that Th17 contributes to the cytokine storm triggered by SARS-CoV-2 [163]. Liu et al. directly related G-CSF levels to the viral load of SARS-CoV-2 and the associated lung damage [56].

GM-CSF

GM-CSF is a heterodimeric complex that consists of a specific alpha chain of GM-CSF and a signal transduction subunit shared with IL-3 and IL-5 receptors. It is a single-membrane protein that homodimerizes after binding to G-CSF [170–172]. The main sources of this biomolecule are fibroblasts and endothelial, epithelial, stromal, and hematopoietic cells [164], and it is secreted by epithelial cells in the lung [173,174]. Unlike M-CSF and G-CSF, GM-CSF is virtually undetectable in the blood, although it

has been found to be locally produced and activated in tissues affected by inflammatory processes. Serum GM-CSF levels can also be elevated in response to endotoxins. Hence, GM-CSF plays an important role in the inflammatory process [175–177], stimulating the proliferation and activation of macrophages, eosinophils, neutrophils, monocytes, dendritic cells, and microglial cells. Besides its role as a hematopoietic growth factor, this cytokine increases the production of proinflammatory cytokines, favors antigenic presentation and phagocytosis, and promotes chemotaxis and leukocyte adhesion. It is of major importance in maintaining immune homeostasis in lung and gut [178].

Elevated serum GM-CSF levels have been detected during the acute phase of infection by SARS-CoV-2 in comparison to healthy individuals, both in those who required ICU admission and those who did not [17]. Th17 cells produce GM-CSF, and high Th17 counts have been associated with elevated GM-CSF levels [163]. It has also been observed that the activation of Th1 cells by pathogens generate GM-CSF, among other cytokines [93].

IP-10

IP-10 was initially identified as a chemokine whose secretion is induced by IFN-γ. IP-10 is secreted by neutrophils, endothelial cells, keratinocytes, fibroblasts, dendritic cells, astrocytes, and hepatocytes. Through its binding to chemokine receptor 3 (CXCR3), it regulates immune system responses by activating and recruiting leukocytes, including T cells, monocytes, and NK cells. Therefore, IP-10 and CXCR3 play a key role in recruiting leukocytes to inflamed tissues and in perpetuating inflammation, thereby making a major contribution to tissue damage [179]. Elevated IP-10 concentrations have been found in numerous infections, mainly viral infections [180].

Serum IP-10 levels were found to be elevated in patients with COVID-19 and even higher in those who required ICU admission, suggesting their relationship with lung damage and disease severity [17]. High levels of this biomolecule were previously found in patients with SARS-CoV [77], and the levels are even higher in those with SARS-CoV-2 [81]. Thus, the hyperproduction of IP-10, among others, is considered to contribute to disease progression [17]. Liu et al. associated elevated serum IP-10 levels with a higher viral load and greater lung damage in patients with SARS-CoV-2 [56]. Yang et al. also found especially high levels of this cytokine in the most severe cases of COVID-

19, and they associated IP-10 expression with disease progression and mortality, alongside the expressions of monocyte chemotactic protein-3 (MCP-3) and IL-1Ra [55].

IFN-γ

IFN-γ is a type-II IFN produced by a wide variety of lymphocyte cells, including $CD4^+$ and $CD8^+$ T cells, Treg cells, $FoxP3^+$ $CD8^-$ T cells, B cells, and NK cells. Monocytes, macrophages, dendritic cells, and neutrophil granulocytes can also produce this cytokine. Although numerous cells can be the source of IFN-γ, it is mainly produced by T and NK cells. MSCs can also secrete low IFN-γ levels to regulate hematopoiesis [181]. IFN-γ participates in numerous immune and adaptive immunological functions and in inflammatory processes. It promotes macrophage activation and antigen presentation and is highly involved in anti-bacteria and anti-virus immunity and in signal transduction. It is difficult to classify IFN-γ as a pro- or anti-inflammatory cytokine, given its complex and varied roles [182].

Huang et al. found that serum IFN-γ levels were higher in patients with COVID-19 than in healthy individuals and proposed that the elevation of this and other cytokines might result from the activation of Th1 and Th2 cells. Also, elevated serum IFN-γ levels were previously reported in patients with SARS-CoV or MERS [17,77,183]. Liu *et al.* (2020) observed that elevated IFN-γ levels were associated with greater viral load and lung damage [56]. Sun et al. found that IFN-γ, IL-6, and IL-10 levels were higher in patients with infection by SARS-CoV-2 but did not differ between patients who required ICU admission and those who did not [88]. In fact, these authors found that levels of this cytokine were lower in $CD4^+$ T-cells from patients with *severe* versus mild symptoms and suggested that the infection may initially affect $CD4^+$ and $CD8^+$ T-cells, reducing the production of IFN-γ [64].

MCP-1

This protein belongs the C-C chemokine family and is a powerful monocyte chemotactic factor that is constitutively produced or induced by oxidative stress, cytokines, or growth factors. It can be expressed by endothelial cells, fibroblasts, epithelial cells, smooth muscle cells, mesangial cells, astrocytes, monocytes, and

microglial cells, which play an important role in the antiviral response in the peripheral circulation and tissues. Monocytes and macrophages are the main source of MCP-1, which regulates the migration and infiltration of monocytes, memory T cells, and NK cells [184].

Huang et al. found that MCP-1 levels were higher in patients with COVID-19 and even higher among those admitted to ICU [17]. It has been reported that MCP-1 increases rapidly in the early acute phase of infection and then progressively decreases with the advance of the disease [185]. Xiong et al. detected elevated levels of MCP-1 and other cytokines in the bronchoalveolar lavage fluid of patients with COVID-19 and associated the pathogeny of the virus with these cytokines [186]. Elevated levels of this protein have also been detected in the lung tissue of patients infected with SARS-CoV-2 [81].

TNF-α

TNF-α is produced by various cell types, such as monocytes, macrophages, and T cells, among others. This cytokine has been related to proinflammatory responses mediated by IL-1β and IL-6. Alongside other cytokines, TNF-α is involved in the regulation of inflammatory processes, infectious diseases, and malignant tumors [187].

It has been observed that serum TNF-α levels are elevated in patients with COVID-19 and are higher with more severe disease [17,57,64]. Diao et al. reported similar results in a sample of 522 patients with COVID-19 and found an inverse relationship between TNF-α levels and T-cell counts [82]. In contrast, Wan et al. described normal TNF-α levels in patients with COVID-19 [54]. TNF-α was one of the cytokines whose overproduction was related to a poor prognosis in patients with SARS-CoV and MERS [48–50,183]. Zhang et al. proposed that the administration of certolizumab, an anti-TNF-α antibody, might have beneficial effects on patients with COVID-19 [188]. Another possible therapeutic approach is to use MSCs to inhibit TNF-α and IL-1α, among other cytokines [145].

SARS-CoV-2 and other biomolecules

Other biomolecules besides cytokines have shown increased expression in patients with COVID-19, including growth factors.

VEGF

VEGF is essential for vascular endothelial homeostasis and is present in numerous cells and tissues. It has also been found to participate in the pathogenesis of tumor growth and metastasis. VEGF plays an essential role in endothelial cell activation by binding to cell surface receptors (VEGFR). The integrity of the endothelial barrier in lung tissue is crucial for alveolar immune regulation. Severe inflammation and the associated immune responses induce the apoptosis of epithelial and endothelial cells, increasing the production of VEGF and exacerbating edema and the extravasation of immune cells [188]. The pathogenic effects of this factor are related to its action on vascular permeability and neoangiogenesis [189,190]. VEGF hyper-regulation is observed in various viral infections, and attempts have been made to stimulate this factor by using VEGF homologs present in some viruses or by activating inflammatory mediators that trigger the overexpression of VEGF [189].

Serum VEGF levels were found to be higher in patients with SARS-CoV-2, although they did not differ between those who were admitted to ICU and those who were not [17]. As noted above, the therapeutic application of MSCs is under consideration due to their regenerative and immunomodulatory potential. Besides VEGF, MSCs can also secrete VEGF, among others, which would be useful in the approach to respiratory distress syndrome and in the regeneration of lung tissue and treatment of lung fibrosis induced by infections [145].

HGF

Hepatocyte growth factor (HGF) is synthesized by fibroblasts and by endothelial and hepatic cells, among other cell populations. The active form is produced by the action of a serine protease enzyme released by damaged tissues. In the lungs, HGF is sequested by pulmonary fibroblasts, and its secretion is increased when the tissue is damaged [191].

Serum HGF and MIP 1-α levels were found to be elevated in patients with COVID-19, and even higher MIP 1-α levels were found in those requiring ICU admission [17].

Conclusions

The immunological reaction triggered by infection with SARS-CoV-2 mobilizes numerous cytokines, mainly of proinflammatory character. Changes in their levels are associated with the presence of the disease and a more severe prognosis. This study summarizes findings on the role of these cytokines in the onset and outcomes of SARS-CoV-2 infection and on possible therapeutic approaches involving the inhibition of their activity.

Conflict of interest

The authors declare no competing or financial interests.

Acknowledgements

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