



COVID-19 and the role of cytokines in this disease

Amin Hasanvand¹

Received: 2 April 2022 / Accepted: 5 April 2022

© The Author(s), under exclusive licence to Springer Nature Switzerland AG 2022

Abstract

Studies have shown that SARS-CoV-2 has the ability to activate and mature proinflammatory cytokines in the body. Cytokine markers are a group of polypeptide signalling molecules that can induce and regulate many cellular biological processes by stimulating cell receptors at the surface. SARS-CoV-2 has been shown to be associated with activation of innate immunity, and an increase in neutrophils, mononuclear phagocytes, and natural killer cells has been observed, as well as a decrease in T cells including CD4+ and CD8. It is noteworthy that during the SARS-CoV-2 infection, an increase in the secretion or production of IL-6 and IL-8 is seen in COVID-19 patients along with a decrease in CD4+ and CD8+ and T cells in general. SARS-CoV-2 has been shown to significantly increase Th2, Th1/Th17 cells and antibody production in the body of patients with COVID-19. Specific immune profiles of SARS-CoV-2 infection can lead to secondary infections and dysfunction of various organs in the body. It has been shown that Interleukins (such as IL-1, IL-4, IL-6, IL-7, IL-10, IL-12, IL-17, and IL-18), IFN- γ , TNF- α , TGF- β and NF- κ B play major roles in the body's inflammatory response to SARS-CoV-2 infection. The most important goal of this review is to study the role of inflammatory cytokines in COVID-19.

Keywords COVID-19 · Cytokines · Inflammatory response

History of COVID-19

Huang et al. (2020) and Fajgenbaum and June (2020) examined and analysed the clinical manifestations of patients with SARS-CoV-2 and found in their studies that the prognosis for individuals with COVID-19 is associated with high concentrations of inflammatory agents. Another similar study found that serious patients with COVID-19 had high levels of neutrophils and low lymphocyte concentrations, which caused a cytokine storm in these patients. This inverse correlation between the numbers of neutrophils versus the number of lymphocytes may be characteristic of an acute systemic inflammation in patients (Qin et al. 2020). Cytokine markers are a group of polypeptide signalling molecules that can induce and regulate many cellular biological processes by stimulating cell receptors at the surface (Bartee and McFadden 2013). Primary and important cytokines include those that can play an important role in the types of adaptive

immunity, proinflammatory cytokines, and interleukins and anti-inflammatory cytokines. However, host cells may secrete cytokines that can induce processes in the body as a defence response to cell metabolism (O'Neill 2015; Vabret et al. 2020). Studies have shown that SARS-CoV-2 infection has the ability to induce specific and disparate inflammatory responses in the body. Research has shown that an inappropriate immune response most often occurs in patients with certain diseases or other diseases such as diabetes, heart, and kidney disease. This condition increases the virus' ability to multiply and, in turn, increases its associated side effects (Blanco-Melo et al. 2020).

IL-1

Interleukin-1 has been shown to play a major role in the body's inflammatory response to infection (Turner et al. 2014), while active macrophages and monocytes are its main sources (Borne et al. 1997). The IL-1 family, which includes IL-1 α , IL-1 β , and IL-18, plays an important and central role in the regulation of immune or inflammatory responses, including infectious or non-infectious inflammations in the body. It has been shown that upon initiation of inflammation, the enzyme caspase-1 can convert pro-interleukin-1 beta to

✉ Amin Hasanvand
dr.hasanvand@yahoo.com

¹ Department of Physiology and Pharmacology, Faculty of Medicine, Lorestan University of Medical Sciences, Khorramabad, Iran

IL-1 β and also to pro-interleukin-18 to IL-18 (Dinarello and Meer 2013). Studies have shown to some extent that SARS-CoV-2 has the ability to activate and mature IL-1 β , which in turn can trigger the activation of other proinflammatory cytokines in the body (Siu et al. 2019; Nieto-Torres et al. 2014; DeDiego et al. 2014). Hence, IL-1 β forms part of the cytokine storm produced by coronavirus infections (Chu et al. 2016; Conti et al. 2020). SARS-CoV-2, in addition to activating the cytokine storm, can cause pyroptosis, which is a form of cell death associated with inflammation. This type of cell death is associated with activation of proinflammatory signals. Interestingly, one of the main characteristics of pyroptosis is the need to activate caspase-1, and cells with this type of cell death are also able to release more IL-1 β and IL-18 (Ferreira et al. 2021). Studies have shown that patients with COVID-19 are associated with high levels of SARS-induced interleukin-1 beta, complications of intravascular coagulation, or excessive coagulation in their body with levels of 1-beta interleukin (Zhang et al. 2020b). In diseases such as rheumatoid arthritis, Anakinra is used as an interleukin-1 receptor antagonist to treat and prevent cytokine storms caused by it (Miettunen et al. 2011; Ye et al. 2020). Anakinra has been shown to inhibit the activity of IL-1 α and IL-1 β by antagonising the receptor (Cavalli and Dinarello 2015). In patients with COVID-19 who showed severe inflammation, mortality was significantly reduced by inhibiting the activity of interleukin-1 (Cavalli et al. 2021). Studies have shown that taking a high dose of Anakinra in a completely safe manner can increase the efficiency of respiratory function in COVID-19 patients (Cavalli et al. 2020). On the other hand, another study showed that taking Anakinra with complete safety and without side effects reduces mortality in COVID-19 patients or requires mechanical ventilation (Huet et al. 2020). Canakinumab, like Anakinra, is an interleukin-1 antagonist shown to have anti-inflammatory effects with long-lasting effects (Dinarello and Meer 2013).

IL-4

Another proinflammatory cytokine that activates its receptor, causing cellular interactions, is interleukin-4 IL-4, which has been shown to utilise Janus kinase (JAKs). It is important to note that different signalling pathways that play an important role in regulating cell proliferation have been shown to be activated by IL-4 (Jiang et al. 2000). Various important cytokines that may be secreted by proinflammatory monocytes, inhibiting the cytotoxic activity of macrophages and even producing nitric oxide are inhibited by activation of interleukin (Renu et al. 2020a; Opal and DePalo 2000). The secretion and activation of IL-4, and ultimately the stimulation of the IL-4 receptor, inhibits the secretion of other inflammatory cytokines, including TNF- α , IL-1, and PGE 2, as well as increasing LDL oxidation and ultimately reducing

inflammation (Bhattacharjee et al. 2013). On the other hand, IL-4 can well activate JAK-STAT, one of the side effects of which is induction of infertility disorders in men, and it has also been shown that this interleukin is activated by Th2 cells and induces apoptosis by stimulating the STAT signalling pathway (Renu et al. 2020a). Studies and evidence at the time of SARS-CoV-2 has been shown to significantly increase Th2, Th1/Th17 cells and antibody production in the body of patients with COVID-19 and however, if Th2 levels were elevated, patients should receive intensive care (Renu et al. 2020b). In summary, during COVID-19 disease, one of the pathways of inflammation in the body is that the virus increases apoptotic activity by inducing the activity of the JAK-STAT6 signalling pathway by increasing Th2 and IL-4 cells, and this can justify one of the complications of this disease, which is infertility in men (Renu et al. 2020a).

IL-6

SARS-CoV-2 has been shown to be associated with activation of innate immunity, and an increase in neutrophils, mononuclear phagocytes, and natural killer cells has been observed, as well as a decrease in T cells including CD4+ and CD8. It is noteworthy that during the SARS-CoV-2 infection, an increase in the secretion or production of IL-6 and IL-8 is seen in COVID-19 patients along with a decrease in CD4+ and CD8+ and T cells in general (Zhang et al. 2020a; Rabaan et al. 2021). Studies by Ruan et al. have shown that IL-6 and ferritin levels were higher in patients who lost their lives due to COVID-19 than in patients who recovered (Ruan et al. 2020). Studies have shown that increasing the secretion and activity of IL-6 in the bloodstream can increase blood pressure and subsequent complications (Furuya et al. 2010). Studies show that people with high blood pressure as well as high levels of interleukin-6 and COVID-19 have a very high risk of developing severe respiratory failure (Zheng et al. 2020). In addition to the previous study, it was found that severe lung damage can be caused by an overproduction of IL-6 production (Zhang et al. 2004). However, one of the most exciting tasks in treating cytokine storms in patients with COVID-19 can be to inhibit the IL-6 receptor using tocilizumab to prevent serious complications from SARS-CoV-2 (Pelaia et al. 2021). The administration of IL-6 receptor blockers is one of the best-suggested treatments for COVID-19, which can be very promising (Zhang et al. 2020c). Various studies have shown that tocilizumab can be effective in treating SARS-CoV-2 patients and reducing its complications by inhibiting interleukin-6 receptors in patients with COVID-19 (Colaneri et al. 2020; Ramaswamy et al. 2020; Morena et al. 2020). In clinical trials of a large number of patients with COVID-19, which were associated with severe pneumonia with severe inflammatory effects, it was found that tocilizumab

administration accelerated the recovery of patients with a rapid and significant response (Toniatì et al. 2020). Another study in Italy found that tocilizumab reduced mortality compared to expectations in COVID-19 patients (Perrone et al. 2020). By collecting various data from clinical trials, promising reports of reduced mortality or reduced side effects of COVID-19 have been published in various patients. This showed that inhibition of interleukin 6 receptor can play an effective role in the treatment of these patients (Luo et al. 2020; Gupta et al. 2021). Considering that tocilizumab can be one of the most important treatment options in critically ill patients with high levels of interleukin 6, it can be used to treat these patients effectively (Luo et al. 2020). Finally, interleukin-6 antagonist drugs can be used either as a single drug or in combination with other drugs such as antiviral drugs, and the effects of these combination therapies can be investigated (Ascierto et al. 2021).

IL-7

Interleukin-7 (IL-7) is a cytokine produced by stromal cells that plays an important role in the survival or maintenance of T cells in the body (ElKassar and Gress 2010; Al-Rawi et al. 2003). By stimulating its specific receptors, interleukin 7 can increase the amount of proteins that are anti-apoptotic and prevent memory CD4 + T cell apoptosis (Chetoui et al. 2010). In some diseases, including chronic HIV-1, interleukin-7 levels rise and IL-7Ra expression and activity decrease, which is due to the high activity of interleukin-7 (Huet et al. 2020). However, the progression of the disease is associated with an increase in the plasma level of interleukin-7 (Park et al. 2004). However, by increasing and strengthening IL-7-dependent lymphocytes, the activity of antiviral factors in the body can be increased (Francois et al. 2018). But in Corona, a study in Switzerland found that patients with SARS-CoV-2 lost their T cells and had impaired antiviral activity in their bodies (Adamo et al. 2021). Serum IL-7 levels were also shown to be significantly increased in patients with severe COVID-19, whereas in patients with milder symptoms this was not the case (Adamo et al. 2021). Importantly, IL-7 production is usually constant and controlled by T cells, and when the number of T cells decreases, serum IL-7 levels increase (Kim et al. 2011; Martin et al. 2017). On the other hand, patients with SARS-CoV-2 have been identified with innate lymphoid cell abnormalities (García et al. 2020), which can be associated with interleukin-7 signalling pathway disorders and its receptor (Sheikh and Abraham 2019). Researchers have shown experimentally that a vaccine combined with interleukin-7 can produce more antibody levels in the body by activating and spreading T and B cells. Interestingly, administration of anti-IL-7 drugs significantly reduces B cells and ultimately reduces

antibody production in the body (Seo et al. 2014). The use of IL-7 as an adjunct drug in the treatment of various diseases has been shown to have many benefits and minimal side effects. It has been suggested that IL-7 can be used as a drug, vaccine, or even a biomarker in the treatment of patients with COVID-19, and that future studies may clarify this therapeutic role for IL-7 (Bekele et al. 2021). Laterre PF et al. showed that IL-7 administration in patients with severe COVID-19 deficiency can be associated with increased lymphocytes and increased recovery without increasing the rate of inflammation, infection, or lung damage (Laterre et al. 2020).

IL-10

Studies have shown that serum levels of interleukin-10 (IL-10) in the cytokine storm in patients with COVID-19 infection increase significantly (Huang et al. 2020; Zhao et al. 2020; Wang et al. 2020). It has also been shown that COVID-19 patients admitted to the intensive care unit (ICU) have significantly more elevated serum levels of interleukin-10 than other non-ICU patients (Huang et al. 2020; Diao et al. 2020). A study of 2157 patients in various studies found that interleukin-10 is one of the most important criteria for identifying the severity of the disease and predicting the course of the disease in people with COVID-19 (Dhar et al. 2020). Importantly, elevated serum interleukin-10 levels in patients with COVID-19 infection can be both an anti-inflammatory mechanism and an immunosuppressive biomarker (Zhao et al. 2020; Diao et al. 2020). Studies have shown that recombinant IL-10 can be used with anti-fibrotic activity as well as modulating immune-regulating functions in patients with COVID-19 (Lu et al. 2021). Several studies have shown that the production and increase of IL-10 during COVID-19 can play a detrimental pathological role in this period (Lu et al. 2021). Evidence has shown that in the early stages of COVID-19 and before the increase in other cytokines, the amount of interleukin-10 increases (Zhao et al. 2020). On the other hand, in patients with severe COVID-19, the expression of bacterial DNA and LPS, which are important pathological markers and activators of inflammation, have been shown to increase (Arunachalam et al. 2020). On the one hand, increased gene expression in macrophages, which may be due to LPS, is inhibited by IL-10 (Murray 2006). On the other, the increase in the efficiency of inflammatory responses induced by LPS occurs with increasing IL-10 concentration (Lauw et al. 2000), and finally, these are the cases can support the hypothesis that a combination of high concentrations of IL-10 and bacterial derivatives ultimately increases inflammation in patients with SARS-CoV-2.

IL-12

Another important cytokine secreted mainly by macrophages and dendritic cells is interleukin-12, which has two important subunits, including IL-12p35 and IL-12p40. Interleukin-12 can activate IFN- γ secretion in the body through CD4 T cells (King and Segal 2005). IL-12 has been shown to inhibit the replication of viruses by increasing and inducing IFN- γ activity, and can increase the quality of the CD8 + T cell response (Costela-Ruiz et al. 2020). This type of interleukin acts on its receptor (IL-12R) after being secreted against stimuli such as microbial or viral derivatives. One thing to keep in mind is that it has been shown that these receptors are usually expressed by certain cells, including T and NK cells, and it has also been shown to increase the serum concentration of this interleukin in patients with high COVID-19 infection (Young et al. 2021; Liu et al. 2021). The p35 and p40 subunits incorporate the structure of IL-12 and the induction of IL-12 production, and secretion is associated with virus entry into the cell and it rapidly induces the gene expression of IL-12. In addition, the next important point, this interleukin has the ability to establish links between innate and adaptive immune responses (Coutelier et al. 1995; Barna et al. 1996; Kanangat et al. 1996; Guo et al. 2019). Studies in patients with COVID-19 have shown that serum titers of interleukin-12 are increased (Huang et al. 2020; Chen et al. 2020a, 2020b) and in other infections similar to the coronavirus, such as SARS-CoV, this increase in serum interleukin-12 has been observed (Wong et al. 2004). It has been suggested that due to its inhibitory effect on mesenchymal stem cells against IL-12, IFN- γ and TNF- α , it can be used to treat COVID-19 infections (Costela-Ruiz et al. 2020).

IL-17

Another important interleukin, which plays a key role in adaptive immunity and inflammatory responses in the body during infection and is produced by Th17 cells, is IL-17 (Robins et al. 2021). IL-17A and IL-17F are important components of the IL-17 cytokine family that, as mentioned, can be expressed by Th17 cells (Brevi et al. 2020). Studies have shown that IL-17 can have protective and pathological effects in the body (Amatya et al. 2017). Studies in patients have shown that IL-17 can be a therapeutic indicator for reducing complications, especially pulmonary complications in patients with COVID-19 (Pacha et al. 2020). Several studies have shown that increased neutrophil infiltration into the lungs is associated with increased IL-17 titers and ultimately pathological complications (Wiche Salinas et al. 2020; Mikacenic et al. 2016; Muir et al. 2016). Researchers have found that activation of the IL-17A signalling pathway is closely related to an increase in the severity of viral

respiratory infections and ultimately inflammatory side effects (Mangodt et al. 2015). Studies have shown that baricitinib has the potential to inhibit the release of viral specific cytokines in blood samples taken from patients with SARS-CoV-2 (Petrone et al. 2021). Baricitinib, under the brand name Olumiant, is a drug used to treat autoimmune and inflammatory diseases and its mechanism of action is a Janus kinase (JAK) 1/2 inhibitor (Assadiasl et al. 2021). Fedratinib is another drug that, by inhibiting the Janus kinase 2 pathway and ultimately reducing Th17 pathway activity, has the ability to control cytokine storms as well as improve COVID-19 side effects and ultimately increase survival in patients with SARS-CoV-2 infection (Wu and Yang 2020). Other drugs, including ruxolitinib, have been shown to have the potential to reduce cytokine storm activity, increase oxygen delivery, and reduce COVID-19 complications in patients with SARS-CoV-2 infection (Goker Bagca and Biray 2020; Yeleswaram et al. 2020; Avdeev et al. 2021).

IL-18

Another large family of interleukins is interleukin-18, which has been shown to have an important ability in the body against infections (Yasuda et al. 2019). Various cells of the gastrointestinal tract, including cells of the intestinal nervous system or intestinal epithelium, are able to make and secrete interleukin (IL)-18 in the body (Stadnyk 2002; Edgar 2010), and However, studies have shown that IL-18 titers in patients with SARS-CoV-2 infection are elevated and are associated with the severity of COVID-19 (Rognes et al. 2016; Lucas et al. 2020). The researchers found that there was a specific link between IL-18 and NK cells, $\gamma\delta$ T cells, and CD4+ and CD8+ T cells, which could induce and activate innate and adaptive T cells and This ability may be due to increased IL-18 receptor response and signalling pathway (Cox et al. 2013; Nakanishi 2018; Tsai et al. 2015). The findings indicate that an increase in IL-18 levels as well as a response to its signalling pathway and an increase in T cells during SARS-CoV-2 infection may indicate the occurrence or increase in COVID-19 side effects and according to what has been said, the role of anti-interleukin-18 therapies for this disease can be considered (Yasuda et al. 2019; McKie et al. 2016). It should be noted that when a viral infection occurs in the body, the secretion of IL-18 triggers the production of ferritin, which well justifies hyperferritinemia during viral infections with these explanations, it is possible to understand the relationship between interleukin-18 and hyperferritinemia and cytokine storms during patients with COVID-19 infection (Slaats et al. 2016). Anakinra is one of the most important drugs that can indirectly inhibit the production of IL-18 by inhibiting the expression of caspase-1 (Slaats et al. 2016). Studies have shown that Anakinra can safely reduce severe respiratory failure, acute hypoxemia and

ultimately reduce mortality in COVID-19 patients (Kyriazopoulou et al. 2021a, 2021b; King et al. 2020; Navarro-Millán et al. 2020).

IFN- γ

IFN- γ is another important cytokine that can be made and secreted by NK cells and T lymphocytes and plays an important role in the body's immunity (Robinson et al. 2010). The cytokine IFN- γ is one of the important cytokines that is important and vital for the body's defence against viruses. It has been shown that this cytokine, when the virus enters the body, inhibits the replication of the virus on the one hand and increases the cytotoxic T lymphocyte killing activity in the body on the other hand (Levy and García-Sastre 2001). Various studies have shown that T and NK cells reduce IFN- γ expression in the body when the patient has immunodeficiency disorders (Chen et al. 2020c). During SARS-CoV-2 infection and in various studies of patients, it was found that the level of T cells was lower than normal. But another study found the opposite, showing that IFN- γ -producing T cell levels were higher than in healthy people (Biasi et al. 2020). Studies in patients have shown that the level of IFN- γ has increased in children with COVID-19, which has not been high compared to adults with COVID-19, this indicates that COVID-19 infection is not severe in children with the disease (Xiong et al. 2020). During SARS-CoV-2 infection-related cytokine storms, IFN- γ irregularities are visible and cell transcripts are seen with overexpression of the COVID-19-related gene (Gadotti et al. 2020).

TNF- α

TNF- α is one of the most important cytokines in the body, which can be made or secreted by different types of immune cells, including monocytes, lymphocytes, fibroblasts, etc. (Grivennikov et al. 2005; Tay et al. 2020). TNF- α has been shown to have different receptors, and TNF1 receptors are expressed and scattered almost throughout the body, indicating different functions. However, TNF2 receptor expression is restricted in T cells or other lymphocytes and can signal NF- κ B, and it has also been shown to lack inducing inherent cell death in the body (Ware et al. 1991; Wicovsky et al. 2009). During the course of SARS-CoV-2 infection, studies have shown that sTNFR1 expression is increased in patients with COVID-19 (McElvaney et al. 2020) and, on the other hand, studies have shown that serum TNF- α levels in these patients are increased and associated with increased disease severity (Qin et al. 2020; Huang et al. 2020; Chen et al. 2020c). Zhang et al. proposed that the administration of certolizumab, an anti-TNF- α antibody, might have beneficial effects on patients with COVID-19 (Zhang et al. 2020d). A recent study in a clinical trial showed that umbilical

cord mesenchymal stem cells reduced their inflammation in patients with COVID-19 with acute respiratory distress syndrome by acting on the sTNF2 receptor (Kouroupis et al. 2021) and it has also been shown that TNFR2 has strong anti-inflammatory and protective effects on the skin and nerves (Medler and Wajant 2019).

TGF- β

TGF- β , another family of cytokines that has a wide range of activities in the body, including the induction of low-grade fever (Matsumura et al. 2007). Complications of TGF- β secretion in patients with SARS-CoV-2 infection can include induction of interstitial lung change, increased pulmonary secretion, sputum, dry cough, bronchial asthma and finally inhibition of normal respiration (Costela-Ruiz et al. 2020; Shen et al. 2021). In addition, based on analyses performed, it has been seen that this cytokine can reduce the recovery of the disease in the body by suppressing and inhibiting immunity in the body (Sheng et al. 2015). During the outbreak of SARS-CoV-2 infection, examination of TGF β titer showed that the serum level of this cytokine increased in patients and in turn, inhibited the activity of the immune system of these patients (Ferreira-Gomes et al. 2020). Researchers have shown that activating the bone morphogenetic protein signalling pathway can counteract the effects or complications of TGF- β in patients with COVID-19, such as inflammatory processes, pulmonary fibrosis, and apoptosis (Carlson et al. 2020; Chen 2020).

NF-kappa B

The cytokine NF- κ B is another important cytokine that can induce transcription of various genes associated with inflammation (Lawrence 2009). High levels of TNF- α and TNF1 receptor activation have been shown to increase abnormal NF- κ B activity, which can lead to pulmonary oedema and pneumonia in patients (Mozafari et al. 2020; Quickelberghe et al. 2018; Kircheis et al. 2020). Cytokines such as TNF- α and IL1 β have also been shown to activate granulocyte colony-stimulating factor (G-CSF) via the NF- κ B signalling pathway and, studies have shown that G-CSF administration may have dangerous pulmonary side effects for patients with COVID (Cao et al. 2014; Nawar et al. 2020; Taha et al. 2020). Studies show that the progression of inflammation in COVID-19 patients may be related to the amount of G-CSF and GM-CSF (Huang et al. 2020; Zhu et al. 2020). Considering the role of NF- κ B signalling pathway and its inflammatory processes, by inhibiting NF- κ B, beneficial and therapeutic effects can be considered in patients with SARS-CoV-2 infection (Davies et al. 2021). By inhibiting the NF- κ B signalling pathway in laboratory animals with SARS-CoV infection, it was determined that this cytokine

could play an important role in inducing inflammation and infection (DeDiego et al. 2014). Studies have shown that modulating immunity at the level of NF- κ B activation and NF- κ B degradation inhibitors (I κ B) can well reduce the level of cytokine storm and its effects and established a potential and effective therapeutic role in patients with SARS-CoV-2 infection (Hariharan et al. 2021). Studies have shown that taking cromolyn, an NF- κ B inhibitor, can reduce inflammation in patients with SARS-CoV-2 infection (Mahase 2020; Yousefi et al. 2021). Various studies have shown that cromolyn has high anti-tumour and anti-inflammatory effects and can attenuate the production of inflammatory cytokines mediated by NF- κ B (Sinniah et al. 2017). Viroporins are ion channels in viruses, which have been shown to depend on the level of viral infections and their proliferation in coronaviruses, and cromolyn and nonsteroidal anti-inflammatory drugs (such as diclofenac) can show their anti-inflammatory effects by blocking this canal (Prasher et al. 2021; Wang et al. 2011; Ramalingam et al. 2018; Castaño-Rodríguez et al. 2018). In addition to the above, several experiments have shown that salicylates can also inhibit the NF- κ B signalling pathway and ultimately reduce inflammation (Goldfine et al. 2008). In addition, in another study, researchers examined the anti-inflammatory role of salicylates and the progression of coronary plaque and its volume (Hauser et al. 2016). Studies have shown that acetylsalicylic acid attenuates the activation of inflammatory cytokines dependent on the NF- κ B signalling pathway and, on the other hand, can improve respiratory function in patients with SARS-CoV-2 infection (Taha et al. 2020; Alegbeleye et al. 2020). Considering the effects of salicylates in various studies, in a large clinical trial, its effects in reducing various inflammatory cytokines caused by cytokine storm and therapeutic effects in COVID-19 can be investigated. Finally, various drugs, including Kaletra, have been shown to be able to treat patients with SARS-CoV-2 infection by inhibiting the NF- κ B signalling pathway (Kariya et al. 2014; Dewan et al. 2009).

Conclusion

Patients with SARS-CoV-2 infection have high levels of various cytokines that can be identified as an indicator of disease progression and a therapeutic goal. Specific immune profiles of SARS-CoV-2 infection can lead to secondary infections and dysfunction of various organs in the body. Therefore, understanding the role of different cytokines in inducing infection and inflammation in patients with COVID-19 may reveal effective treatment strategies. In addition to the above, in the field of drug and treatment, more activities should be done to find a solution to control

and replicate the COVID-19 virus and ultimately reduce its side effects.

Funding The authors have not disclosed any funding.

Data availability Enquiries about data availability should be directed to the authors.

Declarations

Conflict of interest The authors have not disclosed any competing interests.

References

- Adamo S, Chevrier S, Cervia C, Zurbuchen Y, Raebler ME, Yang L et al (2021) Profound dysregulation of T cell homeostasis and function in patients with severe COVID-19. *Allergy* 76(9):2866–2881
- Alegbeleye BJ, Akpoveso O-OP, Alegbeleye AJ, Mohammed RK, Esteban-Zubero E (2020) The novel aspirin as breakthrough drug for COVID-19: a narrative review. *Iberoam J Med* 2(4):335–350
- Al-Rawi MA, Mansel RE, Jiang WG (2003) Interleukin-7 (IL-7) and IL-7 receptor (IL-7R) signalling complex in human solid tumours. *Histol Histopathol* 18(3):911–923
- Amatya N, Garg AV, Gaffen SL (2017) IL-17 signaling: the Yin and the Yang. *Trends Immunol* 38(5):310–322
- Arunachalam PS, Wimmers F, Mok CKP, Perera R, Scott M, Hagan T et al (2020) Systems biological assessment of immunity to mild versus severe COVID-19 infection in humans. *Science* 369(6508):1210–1220
- Ascierto PA, Fu B, Wei H (2021) IL-6 modulation for COVID-19: the right patients at the right time? *J Immunother Cancer* 9(4):e002285
- Assadiasl S, Fatahi Y, Mosharmovahed B, Mohebbi B, Nicknam MH (2021) Baricitinib: from rheumatoid arthritis to COVID-19. *J Clin Pharmacol* 61(10):1274–1285
- Avdeev SN, Trushenko NV, Tsareva NA, Yaroshetskiy AI, Merzhoeva ZM, Nuralieva GS et al (2021) Anti-IL-17 monoclonal antibodies in hospitalized patients with severe COVID-19: a pilot study. *Cytokine* 146:155627
- Barna M, Komatsu T, Reiss CS (1996) Activation of type III nitric oxide synthase in astrocytes following a neurotropic viral infection. *Virology* 223(2):331–343
- Bartee E, McFadden G (2013) Cytokine synergy: an underappreciated contributor to innate anti-viral immunity. *Cytokine* 63(3):237–240
- Bekele Y, Sui Y, Berzofsky JA (2021) IL-7 in SARS-CoV-2 infection and as a potential vaccine adjuvant. *Front Immunol* 12:737406
- Bhattacharjee A, Shukla M, Yakubenko VP, Mulya A, Kundu S, Cathcart MK (2013) IL-4 and IL-13 employ discrete signaling pathways for target gene expression in alternatively activated monocytes/macrophages. *Free Radic Biol Med* 54:1–16
- Blanco-Melo D, Nilsson-Payant BE, Liu WC, Uhl S, Hoagland D, Möller R et al (2020) Imbalanced host response to SARS-CoV-2 drives development of COVID-19. *Cell* 181(5):1036–45.e9
- Brevi A, Cogrossi LL, Grazia G, Masciovecchio D, Impellizzieri D, Lacanfora L et al (2020) Much more than IL-17A: cytokines of the IL-17 family between microbiota and cancer. *Front Immunol* 11:565470
- Cao Y, Slaney CY, Bidwell BN, Parker BS, Johnstone CN, Rautela J et al (2014) BMP4 inhibits breast cancer metastasis by

- blocking myeloid-derived suppressor cell activity. *Cancer Res* 74(18):5091–5102
- Carlson FR Jr, Bosukonda D, Keck PC, Carlson WD (2020) Multiorgan damage in patients with COVID-19: is the TGF- β /BMP pathway the missing link? *Basic Transl Sci* 5(11):1145–1148
- Castaño-Rodríguez C, Honrubia JM, Gutiérrez-Álvarez J, DeDiego ML, Nieto-Torres JL, Jimenez-Guardeño JM et al (2018) Role of severe acute respiratory syndrome coronavirus viroporins E, 3a, and 8a in replication and pathogenesis. *Mbio* 9(3):e02325–e2417
- Cavalli G, Dinarello CA (2015) Treating rheumatological diseases and co-morbidities with interleukin-1 blocking therapies. *Rheumatology* 54(12):2134–2144
- Cavalli G, De Luca G, Campochiaro C, Della-Torre E, Ripa M, Canetti D et al (2020) Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *Lancet Rheumatol* 2(6):e325–e331
- Cavalli G, Larcher A, Tomelleri A, Campochiaro C, Della-Torre E, De Luca G et al (2021) Interleukin-1 and interleukin-6 inhibition compared with standard management in patients with COVID-19 and hyperinflammation: a cohort study. *Lancet Rheumatol* 3(4):e253–e261
- Chen W (2020) A potential treatment of COVID-19 with TGF- β blockade. *Int J Biol Sci* 16(11):1954–1955
- Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y et al (2020a) Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 395(10223):507–513
- Chen C, Zhang XR, Ju ZY, He WF (2020b) Advances in the research of mechanism and related immunotherapy on the cytokine storm induced by coronavirus disease 2019. *Zhonghua Shao Shang Za Zhi* 36(6):471–475
- Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H et al (2020c) Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest* 130(5):2620–2629
- Chetoui N, Boisvert M, Gendron S, Aoudjit F (2010) Interleukin-7 promotes the survival of human CD4+ effector/memory T cells by up-regulating Bcl-2 proteins and activating the JAK/STAT signalling pathway. *Immunology* 130(3):418–426
- Chu H, Zhou J, Wong BH-Y, Li C, Chan JF-W, Cheng Z-S et al (2016) Middle East respiratory syndrome coronavirus efficiently infects human primary T lymphocytes and activates the extrinsic and intrinsic apoptosis pathways. *J Infect Dis* 213(6):904–914
- Colaneri M, Bogliolo L, Valsecchi P, Sacchi P, Zuccaro V, Brandolino F et al (2020) Tocilizumab for treatment of severe COVID-19 patients: preliminary results from SMAtteo COvid19 Registry (SMACORE). *Microorganisms* 8(5):695
- Conti P, Ronconi G, Caraffa A, Gallenga C, Ross R, Frydas I et al (2020) Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. *J Biol Regul Homeost Agents* 34(2):327–331
- Costela-Ruiz VJ, Illescas-Montes R, Puerta-Puerta JM, Ruiz C, Melguizo-Rodríguez L (2020) SARS-CoV-2 infection: the role of cytokines in COVID-19 disease. *Cytokine Growth Factor Rev* 54:62–75
- Coutelier JP, Van Broeck J, Wolf SF (1995) Interleukin-12 gene expression after viral infection in the mouse. *J Virol* 69(3):1955–1958
- Cox MA, Kahan SM, Zajac AJ (2013) Anti-viral CD8 T cells and the cytokines that they love. *Virology* 435(1):157–169
- Davies DA, Adlimoghaddam A, Albensi BC (2021) The effect of COVID-19 on NF- κ B and neurological manifestations of disease. *Mol Neurobiol* 58(8):4178–4187
- De Biasi S, Meschiari M, Gibellini L, Bellinazzi C, Borella R, Fidanza L et al (2020) Marked T cell activation, senescence, exhaustion and skewing towards TH17 in patients with COVID-19 pneumonia. *Nat Commun* 11(1):3434
- DeDiego ML, Nieto-Torres JL, Regla-Nava JA, Jimenez-Guardeño JM, Fernandez-Delgado R, Fett C et al (2014) Inhibition of NF- κ B-mediated inflammation in severe acute respiratory syndrome coronavirus-infected mice increases survival. *J Virol* 88(2):913–924
- Dewan MZ, Tomita M, Katano H, Yamamoto N, Ahmed S, Yamamoto M et al (2009) An HIV protease inhibitor, ritonavir targets the nuclear factor-kappaB and inhibits the tumor growth and infiltration of EBV-positive lymphoblastoid B cells. *Int J Cancer* 124(3):622–629
- Dhar SK, Vishnupriyan K, Damodar S, Gujar S, Das M (2020) IL-6 and IL-10 as predictors of disease severity in COVID-19 patients: results from meta-analysis and regression. *medRxiv* 1843:2563
- Diao B, Wang C, Tan Y, Chen X, Liu Y, Ning L et al (2020) Reduction and functional exhaustion of T cells in patients with coronavirus disease 2019 (COVID-19). *Front Immunol* 11:827
- Dinarello CA, van der Meer JW (eds) (2013) Treating inflammation by blocking interleukin-1 in humans. *Seminars in immunology*. Elsevier, Amsterdam
- Edgar RC (2010) Search and clustering orders of magnitude faster than BLAST. *Bioinformatics* 26(19):2460–2461
- ElKassar N, Gress RE (2010) An overview of IL-7 biology and its use in immunotherapy. *J Immunotoxicol* 7(1):1–7
- Fajgenbaum DC, June CH (2020) Cytokine storm. *N Engl J Med* 383(23):2255–2273
- Ferreira AC, Soares VC, de Azevedo-Quintanilha IG, Dias SDSG, Fintelman-Rodrigues N, Sacramento CQ et al (2021) SARS-CoV-2 engages inflammasome and pyroptosis in human primary monocytes. *Cell Death Discov* 7(1):1–12
- Ferreira-Gomes M, Kruglov A, Durek P, Heinrich F, Tizian C, Anne Heinz G et al (2020) In severe COVID-19, SARS-CoV-2 induces a chronic TGF- β -dominated adaptive immune response. *medRxiv* 11:36
- Francois B, Jeannet R, Daix T, Walton AH, Shotwell MS, Unsinger J et al (2018) Interleukin-7 restores lymphocytes in septic shock: the IRIS-7 randomized clinical trial. *JCI Insight*. <https://doi.org/10.1172/jci.insight.98960>
- Furuya Y, Satoh T, Kuwana M (2010) Interleukin-6 as a potential therapeutic target for pulmonary arterial hypertension. *Int J Rheumatol* 2010:720305
- Gadotti AC, de Castro DM, Telles JP, Wind R, Goes M, Garcia Charello-Ossoski R et al (2020) IFN- γ is an independent risk factor associated with mortality in patients with moderate and severe COVID-19 infection. *Virus Res* 289:191
- García M, Kokkinou E, Carrasco García A, Parrot T, Palma Medina LM, Maleki KT et al (2020) Innate lymphoid cell composition associates with COVID-19 disease severity. *Clin Transl Immunol* 9(12):e1224
- Goker Bagca B, Biray AC (2020) The potential of JAK/STAT pathway inhibition by ruxolitinib in the treatment of COVID-19. *Cytokine Growth Factor Rev* 54:51–62
- Goldfine AB, Silver R, Aldhahi W, Cai D, Tatro E, Lee J et al (2008) Use of salsalate to target inflammation in the treatment of insulin resistance and type 2 diabetes. *Clin Transl Sci* 1(1):36–43
- Grivnenkov SI, Tumanov AV, Liepinsh DJ, Kruglov AA, Marakusha BI, Shakhov AN et al (2005) Distinct and nonredundant in vivo functions of TNF produced by t cells and macrophages/neutrophils: protective and deleterious effects. *Immunity* 22(1):93–104
- Guo Y, Cao W, Zhu Y (2019) Immunoregulatory functions of the IL-12 family of cytokines in antiviral systems. *Viruses* 11(9):772
- Gupta S, Wang W, Hayek SS, Chan L, Mathews KS, Melamed ML et al (2021) Association between early treatment with tocilizumab and mortality among critically ill patients with COVID-19. *JAMA Intern Med* 181(1):41–51

- Hariharan A, Hakeem AR, Radhakrishnan S, Reddy MS, Rela M (2021) The role and therapeutic potential of NF-kappa-B pathway in severe COVID-19 patients. *Inflammopharmacology* 29(1):91–100
- Hauser TH, Salastekar N, Schaefer EJ, Desai T, Goldfine HL, Fowler KM et al (2016) Effect of targeting inflammation with salsalate: the TINSAL-CVD randomized clinical trial on progression of coronary plaque in overweight and obese patients using statins. *JAMA Cardiol* 1(4):413–423
- Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y et al (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 395(10223):497–506
- Huet T, Beaussier H, Voisin O, Jouvesshomme S, Dauriat G, Lazareth I et al (2020) Anakinra for severe forms of COVID-19: a cohort study. *Lancet Rheumatol* 2(7):e393–e400
- Jiang H, Harris MB, Rothman P (2000) IL-4/IL-13 signaling beyond JAK/STAT. *J Allergy Clin Immunol* 105(6 Pt 1):1063–1070
- Kanangat S, Thomas J, Gangappa S, Babu JS, Rouse BT (1996) Herpes simplex virus type 1-mediated up-regulation of IL-12 (p40) mRNA expression. Implications in immunopathogenesis and protection. *J Immunol* 156(3):1110–1116
- Kariya R, Taura M, Suzu S, Kai H, Katano H, Okada S (2014) HIV protease inhibitor Lopinavir induces apoptosis of primary effusion lymphoma cells via suppression of NF- κ B pathway. *Cancer Lett* 342(1):52–59
- Kim GY, Hong C, Park JH (2011) Seeing is believing: illuminating the source of in vivo interleukin-7. *Immune Netw* 11(1):1–10
- King IL, Segal BM (2005) Cutting edge: IL-12 induces CD4+CD25- T cell activation in the presence of T regulatory cells. *J Immunol* 175(2):641–645
- King A, Vail A, O'Leary C, Hannan C, Brough D, Patel H et al (2020) Anakinra in COVID-19: important considerations for clinical trials. *Lancet Rheumatol* 2(7):e379–e381
- Kircheis R, Haasbach E, Lueftenegger D, Heyken WT, Ocker M, Planz O (2020) NF- κ B pathway as a potential target for treatment of critical stage COVID-19 patients. *Front Immunol* 11:3446
- Kouroupis D, Lanzoni G, Linetsky E, Messinger Cayetano S, Wishnek Metalonis S, Leñero C (2021) Umbilical cord-derived mesenchymal stem cells modulate TNF and soluble TNF receptor 2 (sTNFR2) in COVID-19 ARDS patients. *Eur Rev Med Pharmacol Sci* 25(12):4435–4438
- Kyriazopoulou E, Huet T, Cavalli G, Gori A, Kyprianou M, Pickkers P et al (2021a) Effect of anakinra on mortality in patients with COVID-19: a systematic review and patient-level meta-analysis. *Lancet Rheumatol* 3(10):e690–e697
- Kyriazopoulou E, Panagopoulos P, Metallidis S, Dalekos GN, Poulakou G, Gatselis N et al (2021b) An open label trial of anakinra to prevent respiratory failure in COVID-19. *Elife* 10:e66125
- Latterre PF, François B, Collienne C, Hantson P, Jeannet R, Remy KE et al (2020) Association of interleukin 7 immunotherapy with lymphocyte counts among patients with severe coronavirus disease 2019 (COVID-19). *JAMA Netw Open* 3(7):e2016485
- Lauw FN, Pajkrt D, Hack CE, Kurimoto M, van Deventer SJ, van der Poll T (2000) Proinflammatory effects of IL-10 during human endotoxemia. *J Immunol* 165(5):2783–2789
- Lawrence T (2009) The nuclear factor NF-kappaB pathway in inflammation. *Cold Spring Harb Perspect Biol* 1(6):a001651
- Levy DE, García-Sastre A (2001) The virus battles: IFN induction of the antiviral state and mechanisms of viral evasion. *Cytokine Growth Factor Rev* 12(2–3):143–156
- Liu Y, Chen D, Hou J, Li H, Cao D, Guo M et al (2021) An inter-correlated cytokine network identified at the center of cytokine storm predicted COVID-19 prognosis. *Cytokine* 138:155365
- Lu L, Zhang H, Dauphars DJ, He YW (2021) A Potential Role of Interleukin 10 in COVID-19 Pathogenesis. *Trends Immunol* 42(1):3–5
- Lucas C, Wong P, Klein J, Castro TB, Silva J, Sundaram M et al (2020) Longitudinal analyses reveal immunological misfiring in severe COVID-19. *Nature* 584(7821):463–469
- Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J (2020) Tocilizumab treatment in COVID-19: a single center experience. *J Med Virol* 92(7):814–818
- Mahase E (2020) Covid-19: what treatments are being investigated? *BMJ* 368:m1252
- Mangold TC, Van Herck MA, Nullens S, Ramet J, De Dooy JJ, Jorens PG et al (2015) The role of Th17 and Treg responses in the pathogenesis of RSV infection. *Pediatr Res* 78(5):483–491
- Martin CE, Spasova DS, Frimpong-Boateng K, Kim HO, Lee M, Kim KS et al (2017) Interleukin-7 availability is maintained by a hematopoietic cytokine sink comprising innate lymphoid cells and T cells. *Immunity* 47(1):171–82.e4
- Matsumura S, Shibakusa T, Fujikawa T, Yamada H, Inoue K, Fushiki T (2007) Increase in transforming growth factor-beta in the brain during infection is related to fever, not depression of spontaneous motor activity. *Neuroscience* 144(3):1133–1140
- McElvaney OJ, McEvoy NL, McElvaney OF, Carroll TP, Murphy MP, Dunlea DM et al (2020) Characterization of the inflammatory response to severe COVID-19 illness. *Am J Respir Crit Care Med* 202(6):812–821
- McKie EA, Reid JL, Mistry PC, DeWall SL, Abberley L, Ambery PD et al (2016) A study to investigate the efficacy and safety of an anti-interleukin-18 monoclonal antibody in the treatment of type 2 diabetes mellitus. *PLoS ONE* 11(3):e0150018
- Medler J, Wajant H (2019) Tumor necrosis factor receptor-2 (TNFR2): an overview of an emerging drug target. *Expert Opin Ther Targets* 23(4):295–307
- Miettunen PM, Narendran A, Jayanthan A, Behrens EM, Cron RQ (2011) Successful treatment of severe paediatric rheumatic disease-associated macrophage activation syndrome with interleukin-1 inhibition following conventional immunosuppressive therapy: case series with 12 patients. *Rheumatology (oxford)* 50(2):417–419
- Mikacenic C, Hansen EE, Radella F, Gharib SA, Stapleton RD, Wurfel MM (2016) Interleukin-17A is associated with alveolar inflammation and poor outcomes in acute respiratory distress syndrome. *Crit Care Med* 44(3):496–502
- Morena V, Milazzo L, Oreni L, Bestetti G, Fossali T, Bassoli C et al (2020) Off-label use of tocilizumab for the treatment of SARS-CoV-2 pneumonia in Milan, Italy. *Eur J Intern Med* 76:36–42
- Mozafari N, Azadi S, Mehdi-Alamdarlou S, Ashrafi H, Azadi A (2020) Inflammation: a bridge between diabetes and COVID-19, and possible management with sitagliptin. *Med Hypotheses* 143:110111
- Muir R, Osbourn M, Dubois AV, Doran E, Small DM, Monahan A et al (2016) Innate lymphoid cells are the predominant source of IL-17A during the early pathogenesis of acute respiratory distress syndrome. *Am J Respir Crit Care Med* 193(4):407–416
- Murray PJ (2006) Understanding and exploiting the endogenous interleukin-10/STAT3-mediated anti-inflammatory response. *Curr Opin Pharmacol* 6(4):379–386
- Nakanishi K (2018) Unique action of interleukin-18 on T cells and other immune cells. *Front Immunol* 9:763
- Navarro-Millán I, Sattui SE, Lakhnpal A, Zisa D, Siegel CH, Crow MK (2020) Use of anakinra to prevent mechanical ventilation in severe COVID-19: a case series. *Arthritis Rheumatol* 72(12):1990–1997
- Nawar T, Morjaria S, Kaltsas A, Patel D, Perez-Johnston R, Daniyan AF et al (2020) Granulocyte-colony stimulating factor in COVID-19: is it stimulating more than just the bone marrow? *Am J Hematol*. <https://doi.org/10.1002/ajh.25870>
- Nieto-Torres JL, DeDiego ML, Verdía-Báguena C, Jimenez-Guardeño JM, Regla-Nava JA, Fernandez-Delgado R et al (2014) Severe

- acute respiratory syndrome coronavirus envelope protein ion channel activity promotes virus fitness and pathogenesis. *PLoS Pathog* 10(5):e1004077
- O'Neill LA (2015) How low cholesterol is good for anti-viral immunity. *Cell* 163(7):1572–1574
- Opal SM, DePalo VA (2000) Anti-inflammatory cytokines. *Chest* 117(4):1162–1172
- Pacha O, Sallman MA, Evans SE (2020) COVID-19: a case for inhibiting IL-17? *Nat Rev Immunol* 20(6):345–346
- Park JH, Yu Q, Erman B, Appelbaum JS, Montoya-Durango D, Grimes HL et al (2004) Suppression of IL7R α transcription by IL-7 and other prosurvival cytokines: a novel mechanism for maximizing IL-7-dependent T cell survival. *Immunity* 21(2):289–302
- Pelaia C, Calabrese C, Garofalo E, Bruni A, Vatrella A, Pelaia G (2021) Therapeutic role of tocilizumab in SARS-CoV-2-induced cytokine storm: rationale and current evidence. *Int J Mol Sci* 22(6):3059
- Perrone F, Piccirillo MC, Ascierto PA, Salvarani C, Parrella R, Marata AM et al (2020) Tocilizumab for patients with COVID-19 pneumonia. The single-arm TOCIVID-19 prospective trial. *J Transl Med* 18(1):405
- Petrone L, Petruccioli E, Alonzi T, Vanini V, Cuzzi G, Najafi Fard S et al (2021) In-vitro evaluation of the immunomodulatory effects of baricitinib: implication for COVID-19 therapy. *J Infect* 82(4):58–66
- Prasher P, Sharma M, Gunupuru R (2021) Targeting cyclooxygenase enzyme for the adjuvant COVID-19 therapy. *Drug Dev Res* 82(4):469–473
- Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y et al (2020) Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan, China. *Clin Infect Dis* 71(15):762–768
- Rabaan AA, Al-Ahmed SH, Muhammad J, Khan A, Sule AA, Tirupathi R et al (2021) Role of inflammatory cytokines in COVID-19 patients: a review on molecular mechanisms, immune functions, immunopathology and immunomodulatory drugs to counter cytokine storm. *Vaccines (basel)* 9(5):436
- Ramalingam S, Cai B, Wong J, Twomey M, Chen R, Fu RM et al (2018) Antiviral innate immune response in non-myeloid cells is augmented by chloride ions via an increase in intracellular hypochlorous acid levels. *Sci Rep* 8(1):1–11
- Ramaswamy M, Mannam P, Comer R, Sinclair E, McQuaid DB, Schmidt ML (2020) Off-label real world experience using tocilizumab for patients hospitalized with COVID-19 disease in a regional community health system: a case-control study. *Medrxiv*. <https://doi.org/10.1101/2020.05.14.20099234>
- Renu K, Subramaniam MD, Chakraborty R, Myakala H, Iyer M, Bharathi G et al (2020a) The role of Interleukin-4 in COVID-19 associated male infertility: a hypothesis. *J Reprod Immunol* 142:103213
- Renu K, Prasanna PL, Valsala GA (2020b) Coronaviruses pathogenesis, comorbidities and multi-organ damage: a review. *Life Sci* 255:117839
- Robins E, Zheng M, Ni Q, Liu S, Liang C, Zhang B et al (2021) Conversion of effector CD4(+) T cells to a CD8(+) MHC II-recognizing lineage. *Cell Mol Immunol* 18(1):150–161
- Robinson CM, O'Dee D, Hamilton T, Nau GJ (2010) Cytokines involved in interferon-gamma production by human macrophages. *J Innate Immun* 2(1):56–65
- Rognes T, Flouri T, Nichols B, Quince C, Mahé F (2016) VSEARCH: a versatile open source tool for metagenomics. *PeerJ* 4:e2584
- Ruan Q, Yang K, Wang W, Jiang L, Song J (2020) Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan. *China Intensive Care Med* 46(5):846–848
- Seo YB, Im SJ, Namkoong H, Kim SW, Choi YW, Kang MC et al (2014) Crucial roles of interleukin-7 in the development of T follicular helper cells and in the induction of humoral immunity. *J Virol* 88(16):8998–9009
- Sheikh A, Abraham N (2019) Interleukin-7 receptor alpha in innate lymphoid cells: more than a marker. *Front Immunol* 10:2897
- Shen WX, Luo RC, Wang JQ, Chen ZS (2021) Features of cytokine storm identified by distinguishing clinical manifestations in COVID-19. *Front Public Health* 9:671788
- Sheng J, Chen W, Zhu HJ (2015) The immune suppressive function of transforming growth factor- β (TGF- β) in human diseases. *Growth Factors* 33(2):92–101
- Sinniah A, Yazid S, Flower RJ (2017) The anti-allergic cromones: past, present, and future. *Front Pharmacol* 8:827
- Siu KL, Yuen KS, Castano-Rodriguez C, Ye ZW, Yeung ML, Fung SY et al (2019) Severe acute respiratory syndrome Coronavirus ORF3a protein activates the NLRP3 inflammasome by promoting TRAF3-dependent ubiquitination of ASC. *FASEB J* 33(8):8865–8877
- Slaats J, Ten Oever J, van de Veerdonk FL, Netea MG (2016) IL-1 β /IL-6/CRP and IL-18/ferritin: distinct inflammatory programs in infections. *PLoS Pathog* 12(12):e1005973
- Stadnyk AW (2002) Intestinal epithelial cells as a source of inflammatory cytokines and chemokines. *Can J Gastroenterol* 16(4):241–246
- Taha M, Sharma A, Soubani A (2020) Clinical deterioration during neutropenia recovery after G-CSF therapy in patient with COVID-19. *Respir Med Case Rep* 31:101231
- Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP (2020) The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol* 20(6):363–374
- Toniati P, Piva S, Cattalini M, Garrafa E, Regola F, Castelli F et al (2020) Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: a single center study of 100 patients in Brescia, Italy. *Autoimmun Rev* 19(7):102568
- Tsai CY, Liong KH, Gunalan MG, Li N, Lim DS, Fisher DA et al (2015) Type I IFNs and IL-18 regulate the antiviral response of primary human $\gamma\delta$ T cells against dendritic cells infected with Dengue virus. *J Immunol* 194(8):3890–3900
- Turner MD, Nedjai B, Hurst T, Pennington DJ (1843) Cytokines and chemokines: at the crossroads of cell signalling and inflammatory disease. *Biochimica Et Biophysica Acta (BBA)* 11:2563–2582
- Vabret N, Britton GJ, Gruber C, Hegde S, Kim J, Kuksin M et al (2020) Immunology of COVID-19: current state of the science. *Immunity* 52(6):910–941
- Van den Borne B, Dijkmans B, De Rooij H, Le Cessie S, Verweij C (1997) Chloroquine and hydroxychloroquine equally affect tumor necrosis factor-alpha, interleukin 6, and interferon-gamma production by peripheral blood mononuclear cells. *J Rheumatol* 24(1):55–60
- Van Quickenberghe E, De Sutter D, van Loo G, Eyckerman S, Gevaert K (2018) A protein-protein interaction map of the TNF-induced NF- κ B signal transduction pathway. *Sci Data* 5(1):180289
- Wang K, Xie S, Sun B (2011) Viral proteins function as ion channels. *Biochimica Et Biophysica Acta (BBA)* 2:510–515
- Wang F, Hou H, Luo Y, Tang G, Wu S, Huang M et al (2020) The laboratory tests and host immunity of COVID-19 patients with different severity of illness. *JCI Insight*. <https://doi.org/10.1172/jci.insight.137799>
- Ware CF, Crowe PD, Vanarsdale TL, Andrews JL, Grayson MH, Jerzy R et al (1991) Tumor necrosis factor (TNF) receptor expression in T lymphocytes. Differential regulation of the type I TNF receptor during activation of resting and effector T cells. *J Immunol* 147(12):4229–4238
- Wiche Salinas TR, Zheng B, Routy JP, Ancuta P (2020) Targeting the interleukin-17 pathway to prevent acute respiratory distress

- syndrome associated with SARS-CoV-2 infection. *Respirology* 25(8):797–799
- Wicovsky A, Henkler F, Salzmann S, Scheurich P, Kneitz C, Wajant H (2009) Tumor necrosis factor receptor-associated factor-1 enhances proinflammatory TNF receptor-2 signaling and modifies TNFR1–TNFR2 cooperation. *Oncogene* 28(15):1769–1781
- Wong CK, Lam CW, Wu AK, Ip WK, Lee NL, Chan IH et al (2004) Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. *Clin Exp Immunol* 136(1):95–103
- Wu D, Yang XO (2020) TH17 responses in cytokine storm of COVID-19: an emerging target of JAK2 inhibitor fedratinib. *J Microbiol Immunol Infect* 53(3):368–370
- Xiong X, Chua GT, Chi S, Kwan MYW, Wong WHS, Zhou A et al (2020) Haematological and immunological data of Chinese children infected with coronavirus disease 2019. *Data Brief* 31:105953
- Yasuda K, Nakanishi K, Tsutsui H (2019) Interleukin-18 in health and disease. *Int J Mol Sci* 20(3):649
- Ye Q, Wang B, Mao J (2020) The pathogenesis and treatment of the ‘Cytokine Storm’ in COVID-19. *J Infect* 80(6):607–613
- Yeleswaram S, Smith P, Burn T, Covington M, Juvekar A, Li Y et al (2020) Inhibition of cytokine signaling by ruxolitinib and implications for COVID-19 treatment. *Clin Immunol* 218:108517
- Young BE, Ong SWX, Ng LFP, Anderson DE, Chia WN, Chia PY et al (2021) Viral dynamics and immune correlates of coronavirus disease 2019 (COVID-19) severity. *Clin Infect Dis* 73(9):e2932–e2942
- Yousefi H, Mashouri L, Okpechi SC, Alahari N, Alahari SK (2021) Repurposing existing drugs for the treatment of COVID-19/SARS-CoV-2 infection: a review describing drug mechanisms of action. *Biochem Pharmacol* 183:114296
- Zhang Y, Li J, Zhan Y, Wu L, Yu X, Zhang W et al (2004) Analysis of serum cytokines in patients with severe acute respiratory syndrome. *Infect Immun* 72(8):4410–4415
- Zhang Q, Bastard P, Liu Z, Le Pen J, Moncada-Velez M, Chen J et al (2020a) Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. *Science* 370(6515):eabd4570
- Zhang W, Zhao Y, Zhang F, Wang Q, Li T, Liu Z et al (2020b) The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): the perspectives of clinical immunologists from China. *Clin Immunol* 214:108393
- Zhang S, Li L, Shen A, Chen Y, Qi Z (2020c) Rational use of tocilizumab in the treatment of novel coronavirus pneumonia. *Clin Drug Investig* 40(6):511–518
- Zhang R, Wang X, Ni L, Di X, Ma B, Niu S et al (2020d) COVID-19: melatonin as a potential adjuvant treatment. *Life Sci* 250:117583
- Zhao Y, Qin L, Zhang P, Li K, Liang L, Sun J et al (2020) Longitudinal COVID-19 profiling associates IL-1RA and IL-10 with disease severity and RANTES with mild disease. *JCI Insight*. <https://doi.org/10.1172/jci.insight.139834>
- Zheng YY, Ma YT, Zhang JY, Xie X (2020) COVID-19 and the cardiovascular system. *Nat Rev Cardiol* 17(5):259–260
- Zhu Z, Lian X, Su X, Wu W, Marraro GA, Zeng Y (2020) From SARS and MERS to COVID-19: a brief summary and comparison of severe acute respiratory infections caused by three highly pathogenic human coronaviruses. *Respir Res* 21(1):224

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.