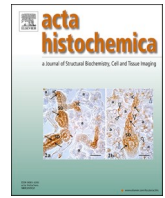




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## Molecular signaling pathways, pathophysiological features in various organs, and treatment strategies in SARS-CoV2 infection

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### ARTICLE INFO

#### Keywords:

SARS-CoV-2

COVID-19

Signaling pathways

ACE2

### ABSTRACT

Cytokine storms and extra-activated cytokine signaling pathways can lead to severe tissue damage and patient death. Activation of inflammatory signaling pathways during Cytokine storms are an important factor in the development of acute respiratory syndrome (SARS-CoV-2), which is the major health problem today, causing systemic and local inflammation. Cytokine storms attract many inflammatory cells that attack the lungs and other organs and cause tissue damage. Angiotensin-converting enzyme 2 (ACE2) are expressed in a different type of tissues. Inhibition of ACE2 activity impairs renin-angiotensin (RAS) function, which is related to the severity of symptoms and mortality rate in COVID-19 patients. Different signaling cascades are activated, affecting various organs during SARS-CoV-2 infection. Nowadays, there is no specific treatment for COVID-19, but scientists have recognized and proposed several treatment alternatives, including applying cytokine inhibitors, immunomodulators, and plasma therapy. Herein, we have provided the detailed mechanism of SARS-CoV-2 induced cytokine signaling and its connection with pathophysiological features in different organs. Possible treatment options to cope with the severe clinical manifestations of COVID-19 are also discussed.

### 1. Introduction

SARS-CoV-2 (COVID-19) infection is accompanied by an invasive inflammatory response that releases large amounts of pro-inflammatory cytokines. The host immune response to the SARS-CoV-2 virus is overactive, which leads to an excessive inflammatory response (Chen, G. et al., 2020; Huang, Chaolin et al., 2020; Ragab et al., 2020 Ruan, Qiurong et al., 2020). When the SARS-CoV-2 virus attacks, the immune

system is activated to clear the virus from the body, but the immune system cannot overwhelm the virus leading to immune system dysregulation and finally initiating the hyper-inflammatory stage of COVID-19 infection, entitled the cytokine storm (CRS) (Huang, Chaolin et al., 2020).

At a more fundamental level, the biochemistry of cytokine activity has become a pattern for understanding evolutionarily conserved membrane-to-nucleus signal transduction, suggesting important

**Abbreviations:** RAS, renin-angiotensin system; JAK/STAT, Janus kinase/STAT; TCR, T-cell receptor; TLR, toll-like receptor; AT1R, angiotensin II receptor 1; CSR, cytokine storm; ARDS, acute respiratory distress syndrome; TMPRSS2, transmembrane serine protease 2; DPP4, dipeptidyl peptidase-4; ANPEP, alanyl aminopeptidase; PRRs, Pattern recognition receptors; AT2, pulmonary alveolar type 2; ECs, enterocytes; IFABP, fatty acid-binding molecule; CRS, cytokine release syndrome; CVD, cardiovascular disease.

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<https://doi.org/10.1016/j.acthis.2022.151908>

Received 4 May 2022; Accepted 19 May 2022

Available online 25 May 2022

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opportunities for understanding how extracellular signals are detected and translated into gene expression control (O'Shea et al., 2011). Excessive secretion of pro-inflammatory cytokines and chemokines causes uncontrolled systemic inflammation. Especially inflammatory signaling pathways such as interleukin-6/Janus kinase/ STAT (IL -6/ JAK /STAT), tumor necrosis factor- $\alpha$  (TNF $\alpha$ ), nuclear factor-kappa (NF- $\kappa$ B) (Feldmann et al., 2020), interferon (IFN) (Prokunina-Olsson et al., 2020; Ritchie and Singanayagam, 2020), T-cell receptor (TCR) signaling pathway, toll-like receptor (TLR) pathway (Golonka et al., 2020), JAK-STAT pathway (Goker Bagca and Biray Avci, 2020; Luo et al., 2020), etc., are activated during SARS-CoV-2 infection. In summary, a low amount of antiviral cytokines such as IFNs and a high amount of pro-inflammatory cytokines such as IL - 1 $\beta$ , IL - 2R, IL - 6, IL - 7, IL - 8, IL - 17, and TNF- $\alpha$  are secreted by a variety of immunological cells (Battagello et al., 2020). These secretions of pro-inflammatory cells lead to an unrestricted inflammatory response playing a key role in the pathogenesis of COVID - 19 infection leading to damage of various types of tissues (Battagello et al., 2020). High amounts of TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 are predominantly correlated with the severity of the disease. Activated immune cells in the inflammatory process can accelerate the inflammatory response, leading to a cytokine storm. Cytokine storm deteriorates the infection and can cause ARDS accompanied by multi-organ damage. (Chen, G. et al., 2020; Tay et al., 2020). Several complications associated with COVID-19 infection have been reported by scientists, including cardiovascular, thrombotic, neurological, rhabdomyolysis, and hematological complications that may be associated with immune system dysfunction (Filatov et al., 2020; Jin and Tong, 2020; Klok et al., 2020; Long, Brit et al., 2020). In addition, the malfunction of RAS system also plays an important role in the pathogenesis of SARS-CoV-2. Decreased systemic blood pressure, hypokalemia, and lung damage worsen the disease by decreasing ACE2 and increasing angiotensin II receptor 1 (AT1R) stimulation (Silhol et al., 2020). The cytokines biology is now recognized as an essential building block in immunology, and the cytokines' actions are considered the basic mechanisms of host defense, immune regulation, and auto-immunity. Furthermore, cytokines and cytokine antagonists have become some of the most successful emerging drugs (O'Shea et al., 2011). Scientists are trying to find new and higher-quality vaccines or specific treatments for COVID-19. A variety of drugs are made to provide the proper treatment. The general guidelines for the treatment of COVID-19 include cytokine inhibitors, antivirals, Janus kin Janus kinase (JAK) inhibitors, immunomodulators, chloroquine, hydroxychloroquine, and corticosteroids (Silhol et al., 2020). The current review provides details on the cytokine signaling pathways in various organs, pathophysiological features, therapeutic options, especially those that may act as potential treatments for the inflammatory damage associated with COVID-19.

## 2. Cytokine storm and cellular signaling pathways induced by the coronavirus

In COVID-19 infection, cytokine storm (CSR) is an overstimulated inflammatory response triggered by elevated levels of cytokines such as IL-6, IL-1, IFN-, and TNF- $\alpha$  (1). CRS is an inflammatory process with two step in which the initial response to viral infection is recognized by activated innate immunity in epithelial cells. Several inflammatory cytokines are released by epithelial and endothelial cells to prevent viral replication. The secondary cytokine cascade is triggered by the permanent release of the initial cytokines and activation of immune cell signaling during viral infection (Xi-zhi and Thomas, 2017). Following SARS-CoV-2 binding to the ACE-2 receptors, an inflammatory cascade in the lower respiratory tract is triggered (Murakami et al., 2019b). Infected macrophages release interleukin-12 (IL-12) in response to the viral antigen presentation to T-helper cells (CD4 and Th1). Activated Th1 cells stimulate CD8 and T-killer cells (Tk) to attack cells carrying viral antigens. The antiviral activity and cytotoxic effects of CD8T cells

can be induced directly or indirectly through the production of cytokines. T cells trigger the NF- $\kappa$ B signaling pathway, causing the formation of pro-inflammatory cytokines. The cytokine storm can insult various organs by the elevated level of particular cytokines and chemokines such as IL-21, IL-8, TNF- $\alpha$ , IL-6, IL-1, and CCL-2, 3, and 5 (Catanzaro et al., 2020b). During the COVID-9 infection, inflammation ensues due to decreased CD4 and CD8 cell counts and increased cytokine levels. Excessive cytokine formation resulting from acute respiratory distress syndrome (ARDS) determines the outcome and severity of COVID-19. The cytokine storm-induced hyper-inflammatory response in the SARS-CoV2 infection is responsible for illness progression and damage to various body organs (Catanzaro et al., 2020b).

### 2.1. Mechanism of cellular interaction by angiotensin-converting enzyme2

SARS-CoV-2 consists essentially of four structural components: membrane glycoprotein (M), envelope (E), nucleocapsid (N), and spike protein (S) (Chen, Y. et al., 2020; Thomas, 2020). Furthermore, SARS-CoV-2 exhibits biological properties similar to those of other coronavirus family members, such as genomic sequences, protein structure, and interactions with angiotensin-converting enzyme 2 (ACE2) receptors (Corman et al., 2018; Ni et al., 2020). ACE2 has been identified as a functional cell receptor for SARS-CoV-2, which plays a key role in the pathogenesis of COVID - 19 infection. ACE2 is a main regulatory enzyme of the renin-angiotensin system, which plays an important role in regulating innate immunity, the cardiovascular system, and renal function (De Cauwer, 2020). Angiotensinogen has been known as an angiotensin precursor that can be transformed into angiotensin-1 (Ang-I) by the enzyme renin. ACE then converts Ang-I to Ang-II, attaching to their specific receptors ( AT1R and AT2R) (Noe and Noe-Letschnig, 2021). ACE2 can convert Ang II to Ang 1,2,3,4,5,6 and 7 in endothelial cells that binds to Mas receptors and have anti-fibrotic and anti-inflammatory actions. ACE2 is widely expressed in different organs, including the respiratory system, especially in the alveolar epithelial cells and endothelium of the pulmonary capillaries, the cardiovascular system, the renal system, the lymphoid tissue, the central nervous system, and the gastrointestinal tract (small intestinal epithelial cells) (Albini et al., 2020). Since SARS-CoV2 and SARS-CoV are so similar in terms of glycoprotein sequence and structure, it's been suggested that ACE2 could be an efficient host cell receptor for SARS-CoV-2 (Zhou, P. et al., 2020). In addition, the spike (S) protein was found to bind to ACE2 with a ten-fold higher affinity compared to SARS-CoV, possibly promoting virus entry into target cells and dissemination into various cell and tissue types (Wrapp et al., 2020). Primarily, SARS-CoV-2 enters target cells via the binding of the spike (S) protein to ACE2 receptors. Proteinases, such as transmembrane serine protease 2 (TMPRSS2), can facilitate viral entry by cleaving the spike S protein and promoting viral endocytosis (Hoffmann et al., 2020). Interestingly, unicellular transcriptomic studies have also illustrated that ACE2 expression is related to the expression of recognized receptors for SARS-CoV-2, including dipeptidyl peptidase-4 (DPP4) and alanyl aminopeptidase (ANPEP) (Raj et al., 2013). This finding shows that these two peptidases may function as SARS-CoV-2 accessory receptors. Moreover, the existence of furin-like cleavage positions in the spike (S) protein and the transmembrane glycoprotein CD147 may be involved in the viral entry mechanism and pathogenicity of SARS-CoV2 in various types of tissue (Coutard et al., 2020; Wang et al., 2020). SARS-CoV-2 can suppress the expression of ACE2 in a variety of tissues (Coutard et al., 2020; Wang et al., 2020). ACE2 inhibition may appear to be favorable, but it may increase Ang-II accumulation, which can bind to their receptors (ATR1) and induce pro-inflammatory gene expression via the JAK/STAT signaling cascade. Furthermore, several cytokines, such as IL-1, IL-6, and IFN - $\alpha$ , have been shown to suppress ACE2 production, which can disturb the Ang-2/Ang (1-7) balance in favor of an inflammatory response. Ang-II signaling leads to the pathogenic effects on different types of tissues in COVID-19 patients since ACE2-mediated

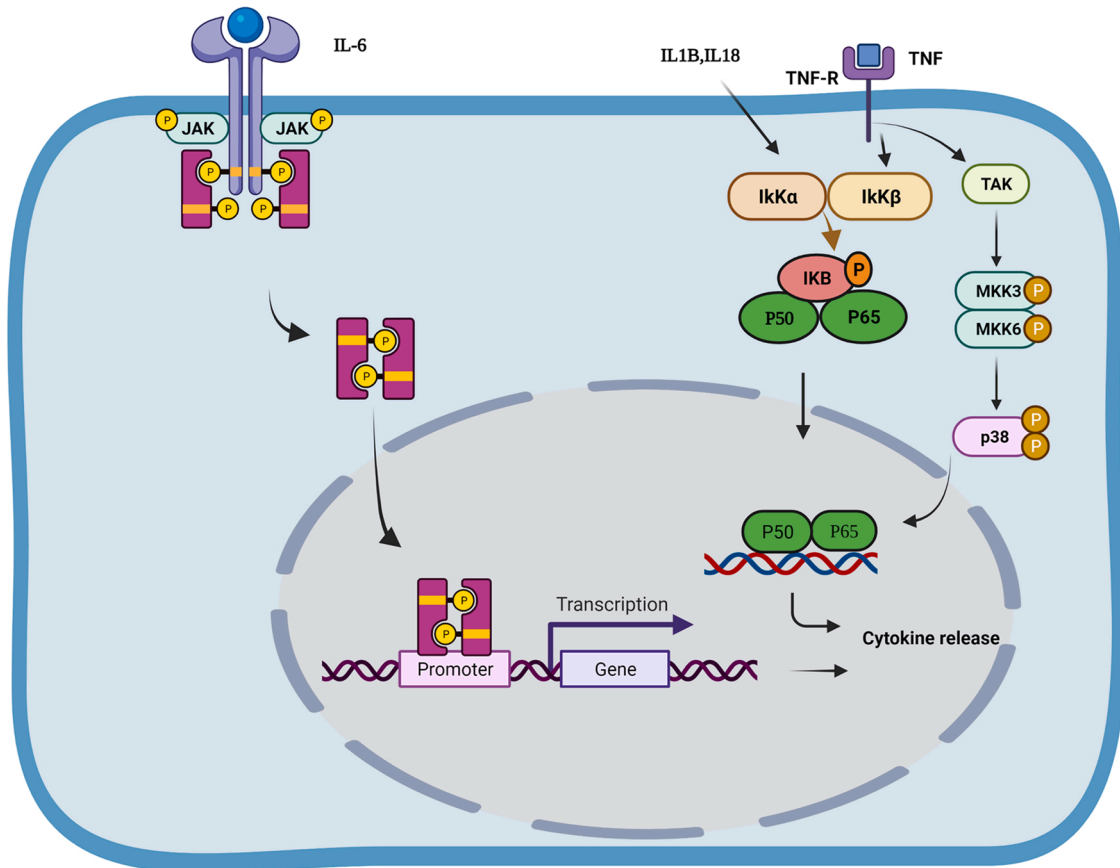
protection is reduced in SARS-CoV-2 infection (Battagello et al., 2020).

## 2.2. Activation of signaling cytokine pathways after SARS-COV2 infection

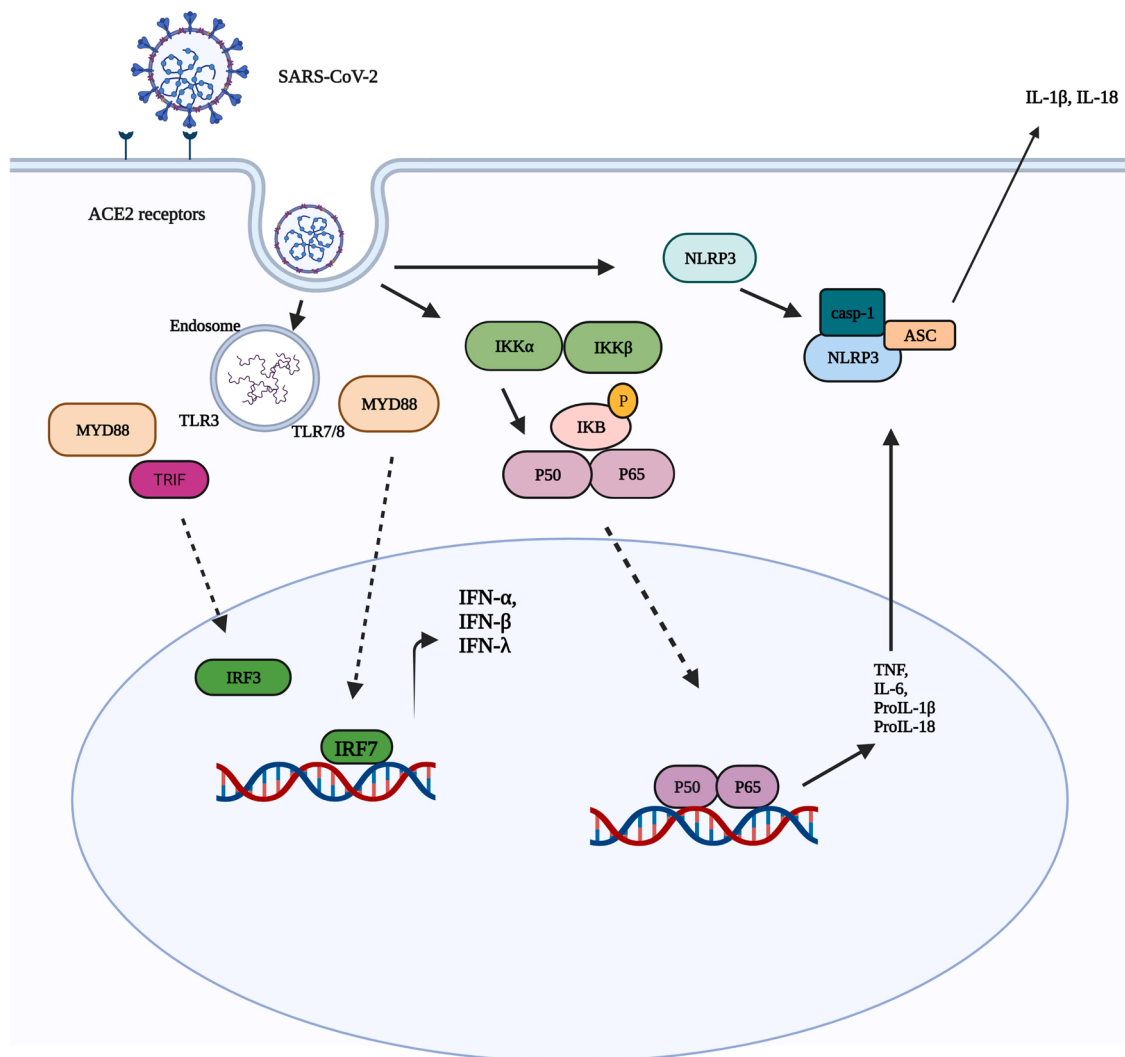
The cytokine storm is an inflammatory response caused by cytokines released by a large number of activated B cells, T cells, NK cells, monocytes, dendritic cells, and macrophages. (Ye et al., 2020). TLRs are the most important Pattern recognition receptors (PRRs) in host cells, which can identify pathogens primarily through pathogen-associated molecular patterns (PAMPs). PRRs identifying PAMPs lead to the expression of pro-inflammatory mediators, resulting in various inflammatory responses (Ye et al., 2020). Pro-inflammatory cytokines are known to be associated with the immunopathology of SARS-CoV2 infection. Since the rapid innate immune response is the primary line of protection, severe immune responses can cause immunological damage to various host cells and tissues. Recent clinical studies suggest that extensive changes in pro-inflammatory cytokine concentrations and activation of various signaling pathways play a pivotal role in SARS-CoV2 pathogenesis (Ye et al., 2020). A rise in the production of specific cytokines such as IL-6, IL-1, and IFN- $\gamma$  as a result of SARS-COV2 infection may activate the JAK/STAT pathway (25). IL-6 is the key cytokine that triggers CRS and has been found to be elevated in the serum of COVID-19 patients with severe clinical symptoms and ARDS. IL-6 binds to IL-6R and gp130 receptors to stimulate the JAK/STAT-3 pathway and is then involved in the CRS (Fig. 1) (Farahani et al., 2022). Essentially, IL-6 has been shown to upregulate Ang-II expression, which in turn triggers increased production of IL-6 via the JAK/STAT

pathway, creating a harmful feedback loop that ultimately leads to progressive tissue damage (Murakami et al., 2019a). IL-6 can also induce the expression of SOCS-1 via STAT3, which inhibits the phosphorylation of STAT1 and, as a result, lowers IFN- $\gamma$  levels (Velazquez-Salinas et al., 2019). IL-6 binds to IL-6R and gp130 in both Th1 CD4 + lymphocytes and NK cells in lung tissue. In addition, IL-6 acts non-canonically by moderating numerous signaling pathways, from JAK/STAT-3 to Notch pathways (Velazquez-Salinas et al., 2019). In addition, various cytokines such as colony-stimulating factors and IFNs can activate the JAK/STAT pathway, resulting in changes in specific gene expression. (O'Shea et al., 2015).

The binding of ligands to the receptors triggers auto- and trans-phosphorylation of JAK proteins, which leads to the phosphorylation and dimerization of STATs, followed by their translocation to the nucleus, where they bind to specific DNA sequences and affect the expression of genes responsive to inflammatory cytokines (Fig. 1) (O'Shea et al., 2015). TLRs stimulate innate immune responses against numerous pathogens via recognition of PAMPs on the pathogens. TLRs are expressed in immune cells, fibroblasts, and epithelial cells. Activation of TLRs induces recruitment of adaptor molecules such as MyD88 and TRIF, which leads to the subsequent production of type I IFNs and inflammatory cytokines via activation of NF- $\kappa$ B and IFN-regulatory factors (IRFs) (Fig. 2) (Lawrence, 2009). According to recent studies, TLRs and TLR 7/8 are involved in identifying SARS-CoV2 PAMPs (Jung and Lee, 2021). NF- $\kappa$ B is an important transcription factor that can be stimulated by SARS-CoV-2 infection and plays an important role in the pathogenesis of COVID-19 (Hariharan et al., 2020). In the NF- $\kappa$ B pathway, successive phosphorylation events lead to phosphorylation of



**Fig. 1.** Cytokine signaling pathways related to pathogenesis of COVID-19. The binding of ligands to receptors causes auto- and trans-phosphorylation of JAK proteins, which causes STATs to be phosphorylated and dimerized, followed by their translocation to the nucleus, and exert their effect by binding to related DNA sequences and affect the expression of genes responsive to inflammatory cytokines (O'Shea et al., 2015). IL-6 can involve in the CRS by activating JAK/STAT-3 pathway. Furthermore, IL-1, IL-18, and TNF- $\alpha$  can bind to specific receptors and cause more nuclear NF- $\kappa$ B translocation and phosphorylation of p38 MAPK, leading to an increased expression of chemokines and pro-inflammatory cytokines (Grimes and Grimes, 2020). (created with biorender.com).



**Fig. 2.** SARS-COV2 induced signaling pathways in host cells. Toll-like receptors (TLR3 and TLR 7/8) can recognize RNA, initiating the inflammatory cascade in SARS-CoV2 infection. TLR3 and TLR7/8 exert their effects via the recruitment of adaptor proteins MyD88 and TRIF, causing translocation of NF- $\kappa$ B and IFNs gene expression (Frieman and Baric, 2008). NF- $\kappa$ B, expression initiates the production of various pro-inflammatory cytokines, including pro-IL-1 $\beta$ , IL-6, IL-18, and TNF  $\alpha$  (Giraldez et al., 2005). In addition, cytoplasmic NLRP3 can recognize the virus forming the inflammasome complex, with caspase-1 (Casp-1) and ASC, cleaving and releasing matured IL-1 $\beta$  and IL-18 (Zhao and Zhao, 2020). (created with biorender.com).

IKK $\alpha$  and IKK $\beta$ , which induces phosphorylation of I $\kappa$ Bs protein that binds to NF- $\kappa$ B subunits such as p50 and p65 (Akira and Takeda, 2004). Phosphorylation of I $\kappa$ B can lead to ubiquitination and proteasomal degradation of these proteins and then to translocation of the released p50/p65 dimers into the nucleus and binding to the specific regions that regulate the expression of  $\kappa$ B-related genes (Hariharan et al., 2020). The NF- $\kappa$ B pathway can stimulate the expression of numerous pro-inflammatory genes, including pro-IL-1 $\beta$ , pro-IL-18, TNF- $\alpha$ , and IL-6 (Li and Verma, 2002). In addition, IL-1 $\beta$ , IL-18, and TNF- $\alpha$  can bind to specific receptors and stimulate greater translocation of nuclear NF- $\kappa$ B and phosphorylation of p38 MAPK, leading to high expression of chemokines and pro-inflammatory cytokines (Fig. 1) (Grimes and Grimes, 2020).

Several studies have shown that TNF- $\alpha$  is the most important factor in the pathogenesis of COVID-19 infection. TNF- $\alpha$ , an important pro-inflammatory cytokine, can regulate various cellular biological processes, such as differentiation, proliferation, and immune response (Patel and Wadhwa, 2021). Several mechanisms have been proposed to describe the molecular mechanism of TNF- $\alpha$  in COVID-19 infection. One possible mechanism is related to SARS-CoV2's S protein, which moderates ADAM17/TACE and causes the rapid recall of the ACE2

ectodomain to the cell surface for virus entry, which is linked to TNF- $\alpha$  production. Another mechanism is the activating the cells of the innate immune system and macrophages as the main producers of TNF- $\alpha$ , which is predominantly elevated in the serum of COVID-19 infected patients. TNF- $\alpha$ , produced by macrophages in viral infections, can regulate innate immune system activity, stimulate other macrophages, natural killer cells, dendritic cells, and neutrophils, and inhibit viral replication (Patel and Wadhwa, 2021). TNF- $\alpha$  can cause leukocyte chemotaxis by activating endothelial cells and inducing them to secrete chemokines. Members of the TNF- $\alpha$  family act through two specific cell surface receptors, including TNF-R1 and TNF-R2. TNF-R1 is found in all cell types, whereas TNF-R2 is only found in immune system cells (Mackay et al., 1993). TNF-R1 has a protein-protein interaction domain known as the death domain (DD), which can link to another DD-containing protein and connects the death receptors to activate the caspase cascade and cause cell apoptosis (Mackay et al., 1993).

TNF-R2 activation can induce gene expression via the TRAF-2-dependent pathway and may also interact with TNF-R1. The multiple effects of TNF may be associated with its ability to trigger various signaling pathways simultaneously in cells. The binding of TNF $\alpha$  to TNF-R1 can change receptor configuration and lead to inhibitory protein

release, exposing the intracellular domain of TNF-R1. This intracellular domain recruits an adaptor protein encompassing the death domain, TRADD, through homophilic interactions. TRADD, as a platform protein, recruits TRAF2 and RIPK1 to form a complex known as complex 1, which is critical for the activation of JNK and NF- $\kappa$ B signaling (Wajant and Siegmund, 2019). TNF-activated NF- $\kappa$ B induces the expression of pro-inflammatory IL – 6 and anti-apoptotic genes such as BCL-2, BIRC2, and BIRC3 (Farahani et al., 2022).

IFNs play a key role in protection against COVID-19 disease, and they are a type of cytokine that links cells against pathogens, playing a critical role in the immune system (Bakadia et al., 2021). For example, they can stimulate NK cells and macrophages, which have immunomodulatory and antiviral effects (Mosaddeghi et al., 2020). IFNs are classified into type I (IFN- $\alpha$ / IFN- $\beta$ ) and type II (IFN- $\gamma$ ) by sequence homology and receptor specificity (Mosaddeghi et al., 2020). IFN- $\gamma$  is the most important factor in innate and adaptive immunity communication. Furthermore, IFN- $\gamma$  has been identified primarily as a mediator that inhibits viral replication (Mosaddeghi et al., 2020).

When the viral genome enters the host cell, IFN-s are secreted to mediate communication between cells against pathogens. Subsequently, macrophages activated by IFN- $\gamma$  cause activation of antiviral mechanisms and increase NK cell activity and leukocyte attraction (Li and De Clercq, 2020). IL-12 and IL-18 are the cytokines secreted by antigen-presenting cells (APCs) that can control IFN secretion. These cytokines mediate strong communication between viral infection and IFN-s production in the innate immune system (Otani et al., 1999). IFN- $\gamma$  can trigger the JAK/STAT pathway, one of the identified signaling pathways in COVID-19 infections (Schroder et al., 2004). Increases in the levels of IL-1, IL-2, IL-7, IL-8, IL-9, IL-10, IL-17, granulocyte-macrophage colony-stimulating factor (GM-CSF), TNF $\alpha$ , and IFN $\gamma$  are associated with inflammatory responses and the severity of COVID-19 symptoms. TNF $\alpha$  and IL-1 are two important cytokines that play a critical role in increasing TH17 cell activity and vascular permeability (Wu and Yang, 2020). TH17 cells can secrete GM-CSF and IL-17, as GM-CSF is related to human TH17 cells. IL – 17 is a pro-inflammatory cytokine that can be produced in response to IL – 23 stimulation (Xu, Zhe et al., 2020). Thus, the IL-17/IL-23 axis has a possible function in the production of inflammatory cytokines such as IL 1 $\beta$ , IL-6, and TNF $\alpha$  (Teunissen et al., 1998). In addition, the IL – 17/IL-23 axis is thought to mediate communication between the innate and adaptive immune responses (Wu and Yang, 2020). In this regard, recent studies have demonstrated the crucial role of IL-17 and GM-CSF in triggering autoimmune inflammation in patients with COVID-19 infection (Zenewicz, 2018).

The p38 mitogen-activated protein kinase (MAPK) pathway plays a critical role in the COVID-19 cytokine storm and has been proposed as a recognized therapeutic target (Asiedu et al., 2021; Grimes and Grimes, 2020). The p38 MAPK signaling pathway can be triggered by environmental factors and pro-inflammatory stimuli that significantly influence a range of physiological activities, such as immune and inflammatory responses (Cuadrado and Nebreda, 2010). Several extracellular stimuli such as inflammatory cytokines, IL-1, TGF $\beta$ , and G-coupled protein receptors (GPCRs) can stimulate the p38 MAPK pathway (Morrison, 2012). The p38 MAPK pathway contains multiple protein kinases that is activated successively, allowing specificity and variety of signaling pathway (Cargnello and Roux, 2011). Apoptosis signal-regulating kinase (ASK), MAPK/ERK kinase (MEKK), dual-leucine zipper-bearing kinase (DLK), TGF-activated kinase 1 (TAK1), and mixed-lineage kinase 3 (MLK3) are the most stimulatory factors for MAP3K (Cuadrado and Nebreda, 2010). Subsequently, phosphorylation of MAP3Ks can activate MAP2Ks such as MKK3 and MKK6, the most abundant MAP2Ks responsible for stimulating p38 MAPKs (Alonso et al., 2000; Cuevas et al., 2007). P38 induce phosphorylation of protein kinases such as MAP kinase-activated protein kinase 2 (MK2), transcription factors (ATF1/2/6) and p53 (Battagello et al., 2020). Furthermore, p38 can mediate the regulation of transcription of the genes encoding various

inflammatory cytokines and cell surface receptors (Battagello et al., 2020; Xu et al., 2017). It has also been demonstrated that, activating the p38 pathway increases the production of pro-inflammatory cytokines such as IL-6, TNF- $\alpha$ , and IL-1 $\beta$ , which appear to play a key role in the cytokine storm triggered by SARS-CoV-2 infection (Catanzaro et al., 2020a). Notably, p38 MAPKs may mediate interaction with NF- $\kappa$ B signaling, which could increase pro-inflammatory cytokines (Saccani et al., 2002). Taken together, it is thought that understanding the numerous signaling pathways activated by SARS-COV2 in a cell/tissue-specific manner may be required to understand the pathogenesis and treatments for COVID-19.

### 3. Potential molecular signaling pathways activated by SARS-CoV2 in different organs and pathophysiological features

The cytokine storm and activated signaling routes are main indicators in the understanding of the clinical and pathophysiological features of various tissue types and organ damage. As confirmed cases of COV-SARS2 increase along with clinical data, it has become increasingly clear that this virus causes neurological, cardiopulmonary, respiratory, gastroenterological, and thromboembolic damage (Table 1). (Battagello et al., 2020).

#### 3.1. Respiratory system damage

##### 3.1.1. COVID-19 and respiratory system clinical features

COVID-19 symptoms include fever and chills, sore throat, exhaustion, bruises, and loss of smell and taste. Shortness of breath, cough, pneumonia, and hypoxia, a low level of blood oxygen or a decline in oxygen saturation (SAO<sub>2</sub>), are respiratory signs of COVID-19 infection in severe cases of COVID-19 infection (Assiri et al., 2013) ARDS is underdiagnosed in severe care situations. ARDS manifests in 42% of patients presenting with COVID-19 infection, and 61–81% of those requiring intensive care. Monitoring of patients is critical for the progress of ARDS during COVID-19 infection. Respiratory rate and SpO<sub>2</sub> are two critical for evaluating patients' clinical situation and permitting timely diagnosis of ARDS. A patient who present any one of the following symptoms may need further assessment and intensive care: respiratory rate higher than 30 breaths per min; SpO<sub>2</sub> lower than 92% (Gibson et al., 2020).

##### 3.1.2. Pathophysiological effects of SARS-COV2 on respiratory system

According to histopathology, COVID-19 pneumonia is characterized by an alveolar lesion with alveolar edema (Danzi et al., 2020). CT scans of the lungs typically reveal bilateral and scattered ground-glass opacities (GGO) that become consolidated as the disease progresses (Torkian et al., 2020). CT lung scans may show diffuse bilateral infiltration, mainly observed in the lower lobes with peripheral distribution. Other less common findings include pleural effusion and lymphadenopathy (Marini and Gattinoni, 2020). The infections they cause range from mild respiratory illness to acute pneumonia and, in severe cases, respiratory failure (Zhang, Q. et al., 2020).

##### 3.1.3. Cellular signaling pathways induced by COVID-19 on respiratory system

symptoms of ARDS show the surface expression of the ACE2 protein on the lungs and enterocytes. Infection, production, and transmission of viruses begin in the nasal epithelium within the upper airway. Nasal swabs have yielded higher levels of CoV-SARS-2 viral loads than throat swabs for both asymptomatic and symptomatic patients. It was not possible to detect ACE2 expression on the surface of epithelial cells lining the oral cavity, nasal mucosa, or nasopharynx (Yu et al., 2020). Inflammatory infectious diseases, such as COVID-19, can cause the distal lung to fail to function properly. Mouse alveolar type II (AT2) epithelial cells produce AT1 and AT2 cells during homeostasis, and additional progenitors are selected following severe injury (Salahudeen et al.,

**Table 1**  
SARS- COV2 activated signaling pathways and Pathophysiological effects in various organs.

Affected organ	Clinical features	Involved receptors or signaling pathways or cytokine	Pathophysiological effects
Respiratory system	cough, pneumonia, hypoxia low level of blood oxygen Shortness of breath	CD4 cytokine receptors, TLRs, and T-cell receptors IKKa and IKKb, p50 and p65, NF-κB subunits MAPK/ERK, GPCRs DLK, ASK, MKK3 and MKK6, ATF1/2/6, p53, SOCS-1 JAKs	alveolar lesion, alveolar edema, ground-glass opacities, diffuse bilateral infiltration, respiratory failure
gastrointestinal (GI) symptoms	stomach discomfort, anorexia, lack of appetite, vomiting, nausea, diarrhea, melena, constipation, haematochezia, upper GI bleeding, and acid reflux (Zhong et al., 2020).	TMPRSS2, ACE2 and RAS NF-κB and p38 mitogen kinase, pathways. IL-8, IL-6, IL-1, TNF-α MIP1α, MCP1, IP10, GM-CSF, IL-10, IL-7, and IL-2.	primary GI damage and Secondary GI damage. Disruption of the intestinal barrier integrity, The gut microbiota alteration, Systemic immune reaction and inflammation
Cardiovascular system	myocarditis, acute coronary syndrome (ACS), hypertension, cardiac arrhythmia, cardiac arrest, acute myocardial infarction (AMI), elevated serum creatinine, venous thromboembolic disease, increase in cardiac troponin I, decreased systolic function, decreased cardiac contractility strength, producing inotropic deficit, increased filling pressures, ventricular dysfunction, myocardial edema, reduced ventricular ejection fraction, ST-segment elevation, depression of ST segment and inverted T wave in V1 and a VR lead	ACE2 and its receptors in heart, MiRNAs, IL-4, IL-10, IL-6	diffuse edema in myocardium and interstitial space, hypokinesia, myocardial thickening, macrophage infiltration, coronary vasospasm, microthrombi, activated macrophages, collagen degradation, Endotheliitis, infiltration of inflammatory cells, apoptotic bodies, imbalance of oxygen supply
Kidney	AKI, renal infarction proteinuria, hematuria	ACE2 and its receptors in kidney epithelial, IL6, IL-1, and TNF- alpha	Cytokine storm acute tubular necrosis (ATN), tubulointerstitial necrosis (TIN), collapsing

**Table 1 (continued)**

Affected organ	Clinical features	Involved receptors or signaling pathways or cytokine	Pathophysiological effects
Nervous system	Headache	Inflammatory cytokines that are involved in the fever process and ACE2 receptor	glomerulopathy Glomerular lesions Increase in cytokine storms
Nervous system	Impaired Consciousness	viral encephalitis, septic encephalopathy, metabolic perturbations, stroke	reflect the disease severity
Nervous system specially the brain stem	Agitation and Delirium	Activation of CNS inflammatory mediators	secondary effect of other organ system failure
Nervous system specially olfactory dysfunction and gustatory dysfunction	Hypogeusia/ Dysgeusia and Hyposmia/ Anosmia	viral attachment to ACE2 receptors in endothelium causing widespread endotheliitis that is associated to the cytokine storm	Loss of smell may be caused by axonal movement of SARS-CoV-2 into the brain via the cribriform plate
Nervous system	Seizures	electrolyte derangements, hypoxia, organ failure	rhythmic discharges or arrhythmies
Nervous system	meningitis	Increase in inflammatory cytokine activation	Lethargy and unconsciousness
Nervous system	Encephalopathy	Associated with cytokine-mediated brain injury	high inflammatory response
Nervous system	mood disorders	RAS mechanisms	Unknown exact mechanism
Nervous system	cerebrovascular diseases	RAS mechanisms	Decrease in blood pressure

Signaling pathways activated by SARS-CoV2, clinical features, pathophysiological effects in various organs. **Abbreviations:** (RAS, renin-angiotensin systems; NF-κB, nuclear factor-κB, AMI, acute myocardial infarction; TNF-α, tumor necrosis factor -α)

2020).

When applied to the apical surface, SARS-CoV2 efficiently infected ciliated cells. The virus replicated in polarized epithelia and preferred to exit via the apical surface. Also, it would be interesting to test if mucociliary clearance is affected. In another study, ACE2 expression was positively correlated with epithelial differentiation. The ACE2 protein was more abundant on the apical surface than on the basolateral surface of the polarized airway. SARS-CoV2 principally targets Oct4 + pulmonary stem cells expressing ACE2 in addition to Type II pneumocystis. Loss of lung repair capacity was observed in SARS patients (Yu et al., 2020). There were increased levels of phosphatidylinositol, abnormal glucose metabolism, and a greater likelihood of lung infections in patients with COVID-19 compared with healthy controls (Becker, 2020). Monocytes and macrophages are the major inflammatory cells that infiltrate the lungs. A moderate number of multinucleated giant cells and monocytes were present in the alveolar tissue as well as diffuse alveolar injury. A few lymphocytes infiltrated the lungs, though they were mostly CD4 positive. Patients with COVID-19 have elevated D-dimer levels, which is important and persists through disease. A thrombotic tendency is likely caused by ACE-2 receptor binding by the virus in COVID-19 patients, which activates or damages endothelial cells. Patients with COVID-19 had a high prevalence of traditional

venous thromboembolism risk factors (Asrani and Hassan, 2021). Lung resident epithelial cells are the first cells to contact SARS-CoV-2, initiating replication of the virus and triggering the inflammatory cytokine cascade. These cells express molecules such as TLR 3 and TLR 7/8, which are able to identify PAMPs, recognize the nucleic acid of the virus, and induce a signal that initiates the expression of type I IFN genes (Vareille et al., 2011). The key role of NF- $\kappa$ B in activating pro-inflammatory gene expression, particularly in the lung, has been confirmed in several studies investigating coronavirus infection (Yoshikawa et al., 2010). The function of TLRs in promoting inflammation in the lung has been confirmed in several studies (Yoshikawa et al., 2010). In acute lung injury, TLR4 in macrophages is a key factor causing the severity of inflammation and tissue damage (Imai et al., 2008). Poor ARDS prognosis has also been associated with TLR4 polymorphisms. Although TLRs are critical for proper viral clearance, constitutive TLR signaling, particularly by TLR4, may contribute to excessive inflammation in COVID-19-associated ARDS (Olejnik et al., 2018). Bronchial epithelial cells and alveolar macrophages may respond to SARS-CoV2 infection through NF- $\kappa$ B-mediated production of pro-inflammatory cytokines such as TNF, IL-6, and IL-8 (Chang et al., 2004; Wang et al., 2007). Cytokines such as TNF and IL-1 $\beta$  that are increased in COVID-19 can trigger NF- $\kappa$ B-mediated gene expression in immune and lung epithelial cells (Kelley, 1990).

IL-1 $\beta$  can induce the secretion of IFNs and several antiviral factors via activating the IRF1/STAT1 signaling pathways in endothelial cells, thus accounting for a major factor in the antiviral effect in the lung tissue (Orzalli et al., 2018). Several recent studies have also indicated a key role of MAPKs in the regulation of SARS-CoV2 infection and the pro-inflammatory effects of p38 in lung tissue cells. In this regard, p38 phosphorylation may induce downstream signaling and gene expression that mediate cell apoptosis but also the persistence of pathogens (Feng et al., 2019; Grimes and Grimes, 2020).

### 3.2. Gastrointestinal system

Although SARS-CoV2 infection is primarily a lung disorder, gastrointestinal (GI) symptoms are prevalent in patients with SARS-CoV2 infection. Critically, these patients had a greater risk for GI problems than critically non-COVID-19 ill patients (74 vs. 37%) (Zhong et al., 2020). According to a 2020 cohort study, 17.6% of COVID-19 patients have GI complications, and 48.1% of fecal specimens of COVID-19 participants tested positive for virus-RNA. Potential GI problems and fecal-oral transmission of the disease need to be carefully considered (Zhong et al., 2020).

#### 3.2.1. COVID-19 and Gastrointestinal clinical features

Clinical features of COVID-19 and GI problems have been observed in individuals with COVID-19 in many studies. Most studies cite stomach discomfort, anorexia, loss of appetite, vomiting, nausea, and diarrhea as the most common symptoms of GI. However, other GI symptoms and signs have also been observed in a few patients, including melena, constipation, hematochezia, upper GI bleeding, and acid reflux (Zhong et al., 2020). In addition, a meta-analysis of 10,890 individuals found that stomach pain (2.7%), vomiting or nausea (7.8%), and diarrhea (7.7%) were the most common GI symptoms (Sultan et al., 2020).

#### 3.2.2. Pathophysiological effects of SARS-COV2 on Gastrointestinal injury

COVID-19 pathophysiology is complicated and multifaceted; it is known that gastrointestinal symptoms are often accompanied by GI injury or inflammation. GI injuries in COVID-19 individuals are likely a combination of etiologic causes. Pathologically, these injuries could be classified into two types: primary GI injuries, in which the COVID-19 virus enters GI systems via the digestive system, and secondary GI injuries, which occur when SARS-CoV-2 enters the lungs via the pulmonary system. Primary GI damage is produced by direct cytotoxic injury, the RAS deregulation, or intestinal epithelial tryptophan-malabsorption.

Secondary GI damage is induced by endothelial injury and thromboinflammation of blood vessels or deregulation of immune cells. Primary or secondary GI damage may be caused by intestinal dysbiosis. These variables may interact to exacerbate gastrointestinal damage. Greater viral load and/or extended viral excretion would likely result from GI damage, allowing SARS-CoV-2 viruses to spread to other human organs (Mitsuyama et al., 2020). Moreover, intact intestinal epithelial cells and tight junctions form an intestinal mucosal barrier that can restrict intestinal flora and resist external damage by controlling intestinal permeability (de Punder and Pruimboom, 2015). Intestinal bacteria could stimulate innate/adaptive immune cells and secrete pro-inflammatory factors into the bloodstream when the integrity of the intestinal mechanical barrier is compromised, ultimately leading to systemic inflammation (Xu et al., 2021).

#### 3.2.3. Cellular signaling pathways induced by COVID-19 on Gastrointestinal injury

Currently, the pulmonary system is the most common dissemination route for SARS-CoV2. However, the presence of SARS-COV2 RNA in the digestive tract and feces suggests that the SARS-CoV2 virus has infected the intestinal system and can be spread fecal-orally (Stanifer, Megan L et al., 2020). As shown by human transcriptome data, TMPRSS2 and ACE2 are co-expressed in absorptive enterocytes (ECs) from the colon and ileum, glandular cells, upper epithelia of the esophagus, and pulmonary alveolar type 2 (AT2) cells (Zhang, H. et al., 2020). In particular, the greatest ACE2 expression was reported in the absorptive ECs of the small intestine (Guo et al., 2021). At the same time, ACE2 was moderately expressed in a small fraction of colonic epithelial cells (Stanifer, M. L. et al., 2020). According to immune-histochemical studies of ACE2, ACE2 expression is high in the ileum enterocytes' brush border. In the submucosa of the ileum, ACE2 is detected in vascular smooth muscle/endothelial cells. In the intestine and colon, ACE2 is expressed mostly in the muscle layers and blood vessels, which is associated with the single-cell transcriptome data showing that only a small number of colonic epithelial cells show ACE2. Overall, the TMPRSS2 and ACE2 expressional patterns indicate the possibility of SARS-CoV-2 infection in the colon and intestine (Guo et al., 2021).

In addition, COVID-19 viruses mostly infect enterocyte cells rather than goblet cells. Infected human cells have a double membrane structure created by viral replication, and the viral particles could be found in the cell's endoplasmic reticulum (ER). Newly formed viral proteins mainly were discharged from the apical side lumen. The presence of sub-genomic mRNA (sg mRNA) might indicate ongoing virus replication in the patient's intestine. In the human organoids, COVID-19 infection induces interferon-mediated immunity (Wölfel et al., 2020; Xu et al., 2021). ACE2 breaks down angiotensin (Ang) in the RAS into Ang (1–7) that bind to Mas receptors and induce anti-fibrotic and anti-inflammatory effects in vivo (Xu et al., 2021). SARS-CoV2 viruses interact with resident lymphocyte cells in the intestinal lamina propria and epithelium to stimulate the immune cells (Azkur, A.K. et al., 2020).

The phosphorylation of p38-mitogen kinase or NF- $\kappa$ B signaling cascade occurs as a result of the intestinal immune cells' activation and the RAS-ACE2 imbalance, resulting in the production of inflammation factors such as interleukin-1 (IL-1), IL-8, IL-6, and TNF- $\alpha$  (Beacon et al., 2020). Consequently, intestinal epithelial cells shed and undergo apoptosis, eventually increasing the permeability of the intestinal mucosa. Normal flora is also involved in the decomposition and provision of nutrients to the intestinal mucosa, the defense against bacteria and viruses, and intestinal barrier formation. The permeability of the intestinal mucosa is increased by epithelial cell death. Intestinal pathogens may cause a long-term condition of systemic inflammation with bacterial toxins entering the lymphatic and blood systems via a compromised intestinal barrier, further impairing the host's immune responses (Ferreira et al., 2020; Xu et al., 2021).

Hoel et al. (2021) measured markers of intestinal epithelial cell damage or fatty acid-binding molecule (IFABP),



lipopolysaccharide-binding protein (LBP) or leakage marker, C-C chemokine motif ligand 25 (CCL25) or intestinal homing, and IL-18 or inflammasome activation marker in plasma from 16 healthy individuals as controls and 39 cases with SARS-CoV-2 disease. Compared to the control group, SARS-CoV-2 patients had higher levels of CCL25 and LBP, indicating the impaired function of the gut barrier and enhanced T cell homing without significant ECs injury. Inflammatory factors such as TNF, MIP1 $\alpha$ , MCP1, IP10, GM-CSF, IL-10, IL-7, IL-6, and IL-2 are elevated in individuals with severe illness (Azkur, Ahmet Kursat et al., 2020). Furthermore, levels of IL-18 have been shown to rise in severe SARS-CoV-2 patients. However, the involvement of inflammatory cytokines induced by intestinal infections and their role in cytokine release syndrome (CRS) is unknown, and additional inquiry is needed. According to histological analysis, inflammatory and lymphocyte cells penetrated the intestinal lamina propria. Diarrhea patients had higher fecal calprotectin levels, mostly produced by infiltrating neutrophil cells. However, it is not yet known whether intestinal infiltrations of neutrophil, macrophage, B, and T cells and their IgA and cytokine secretion are connected with COVID-19 severity. Also, the structure of the gut microbiota community changes due to COVID-19 infection. In COVID-19 individuals, there was an increase in opportunistic infections and a reduction in helpful commensals. These alterations were linked to inflammation substances in these patients' blood. Nevertheless, further research is needed to see whether the microbiome profiles may predict the incidence of CRS and if modulating the microbiome might assist in resolving CRS (Guo et al., 2021).

### 3.3. Cardiovascular system

Although respiratory system infections are the most common general manifestation of COVID-19, myocardial injury may be involved directly or indirectly as an adverse effect of SARS-CoV-2. Increasing age, male sex, obese people, comorbidities, all cancers, and ICU admission are the most important factors for increasing the risk of cardiovascular disease (CVD) in COVID-19 (Khan et al., 2020; Vakili et al., 2020). In a study, among the confirmed individuals of COVID-19, CVD was universally identified in cases who died (13 of 68) than in cases who recovered from COVID-19 (0 of 82) (Ruan, Q. et al., 2020).

#### 3.3.1. COVID-19 and cardiovascular clinical features

Interestingly, some of the patients with COVID-19 had CVD manifestations before respiratory presentations for COVID-19. Accordingly, 11.8% of them without any history of heart disease had significant heart injury and even cardiac arrest, with a simultaneous increase in cardiac troponin I level during hospitalization (Zheng et al., 2020). Also, decreased systolic function, decreased cardiac contractility strength, producing inotropic deficit, increased filling pressures, ventricular dysfunction, myocardial edema, and acute heart failure in severe myocarditis have been observed in individuals with COVID-19 (Hua et al., 2020; Madjid et al., 2020). SARS-CoV2 attacks the cardiovascular system and manifests several clinical characteristics, including myocardial insult, myocarditis, acute coronary syndrome or ACS, acute myocardial infarction or AMI, hypertension, cardiac arrhythmia, cardiac arrest, elevated serum creatinine, venous thromboembolic disturbances, and heart failure (Chen, C. et al., 2020; Driggin et al., 2020). Interestingly, it was emphasized that myocardial dysfunction can occur even in the absence of upper respiratory tract infection symptoms (Inciardi et al., 2020). Serum troponin I (hs-cTnI) and creatine kinase (CK)-MB (Huang, C. et al., 2020), as well as C-reactive protein and natriuretic peptide, were higher in patients with severe COVID-19 than in those with mild COVID-19 (Inciardi et al., 2020; Lippi et al., 2020). Accordingly, in a meta-analysis of 341 patients, it was found that severe COVID-19 disease had a markedly higher troponin I concentration than mild one (Lippi et al., 2020). A minimal diffuse ST-segment elevation was observed in electrocardiogram (ECG) analysis of COVID-19 patients, and also, a depression of the ST segment was detected, which is

followed by an inverted T wave in V1 and a VR lead of infected patients (Inciardi et al., 2020). In view of the above, COVID-19 infected patients are more likely to have cardiovascular manifestations in addition to systemic inflammatory reactions and immune system disorders (Zheng et al., 2020).

#### 3.3.2. Pathophysiological effects of SARS-COV2 on cardiovascular injury

In a prospective cohort study, the autopsy showed deep venous thrombosis in 58% of patients whose SARS-CoV-2 RNA test was positive for high coronavirus infection rates. However, they had no venous thromboembolism diagnosis before death (Wichmann et al., 2020). Among 700 patients due to COVID-19 at the Hospital of the University of Pennsylvania, 9 cardiac arrests, 25 incident atrial fibrillation events, 9 Brady arrhythmias, and 10 non-sustained ventricular tachycardia were identified over 9 weeks. It was deduced that cardiac arrests and arrhythmias are due to the direct effect of COVID-19 illness and linked to systemic illness (Manolis et al., 2020). In the largest cohort study, 3011 COVID-19 infected patients from 13 countries registered to ascertain the cardiac complications following COVID-19 infection. The most common cardiac complication in this study was atrial fibrillation, Heart failure, acute coronary syndrome, ventricular arrhythmia, bacterial endocarditis and myocarditis, and pericarditis respectively (Linschoten et al., 2020). An echocardiogram is the most common approach to distinguish myocarditis. Accordingly, providers of reduced ejection fraction or dilated cardiomyopathy should assume concurrent myocarditis (Olimulder et al., 2009). In MRI, cardiac hyperemia and elevated capillary permeability were found, contributing to acute inflammatory pathology (Olimulder et al., 2009). Therefore, myocardial injury, thrombotic disorders, and heart failure are assumed to be secondary to severe COVID infection linked to increased inflammatory response or thrombotic events in the cardiopulmonary vasculature (Long, B. et al., 2020). According to this viewpoint, this evidence should prompt providers to consider concurrent myocarditis and better manage its complications. Following an acute infection, increased inflammatory cytokines, platelet activation, thromboxane synthesis, and fibrinolytic dysfunction can cause myocardial damage (Musher et al., 2019). An important event that leads to a cytokine storm is an imbalance in the T-helper 1 (Th1) and Th2 responses in COVID-19. As a result, the elevation of IL-4, IL-10, and IL-6 in tissue samples may result in hypoxemia, shock, or hypotension (Huang, C. et al., 2020; Wong et al., 2004; Zheng et al., 2020). In one study, 123 patients with a COVID-19 positive test had higher plasma levels of IL-6 and IL-10 than controls, probably associated with developing heart failure (Liu et al., 2020; Mann, 2002; Wang et al., 2020). As a result of the hyperactivity of the inflammatory immune system, hypercytokinaemia may cause myocardial damage (Tajbakhsh et al., 2021). Myocarditis in SARS-CoV-2 has been defined as an important acute ventricular dysfunction with diffuse edema in the myocardium (Xu, Zhe et al., 2020). Transthoracic echocardiography can also detect diffuse hypokinesia with myocardial thickening and reduced ventricular ejection fraction, and cardiac magnetic resonance imaging can distinguish diffuse interstitial edema (Inciardi et al., 2020). Heart autopsy has also demonstrated the presence of mild inflammation, and viral RNA in COVID-19 confirmed patients (Wichmann et al., 2020). Macrophages and some CD4 + T cells, were found in the myocardium of death patients with COVID-19 (Xu, Z. et al., 2020). In a study of 10 Canadian patients with COVID-19 infection, autopsy samples from the heart revealed the viral RNA of SARS-CoV2 in 35% of the samples. In addition, there was a significant increase in macrophage infiltration in heart samples, implying that SARS-CoV2 caused direct myocardial damage (Oudit et al., 2009). Myocardial infarction in patients with COVID-19 might occur in infected patients. It might be because of plaque rupture, coronary vasospasm, or micro-thrombi due to hyper-cytokemia (Bentzon et al., 2014; Libby et al., 2014). Activated macrophages can degrade collagen in atherosclerotic plaques by producing collagenases, resulting in plaque rupture. Following the activation of macrophages, tissue factors are secreted to trigger thrombus

formation when the plaque ruptures (Libby et al., 2014). Former histological results from three patients with COVID-19 have shown that endothelial tissue might be a direct goal of SARS-CoV-2 (Varga et al., 2020). On histological analysis, Endotheliitis with infiltration of inflammatory cells was revealed in corporations with apoptotic bodies in various organs such as the lungs, small intestine, and heart (Varga et al., 2020). Similarly, SARS-CoV-2 can attack endothelial cells directly, which can trigger inflammation in the endothelium (Varga et al., 2020). On the other hand, an imbalance in oxygen supply caused by acute respiratory illness plays a key role in impairing myocardial demand-supply ratio and results in acute myocardial injury (Tajbakhsh et al., 2021). It is important to keep in mind that myocardial injury is a detrimental event with a poor prognosis and is directly responsible for higher mortality in COVID-19. Thus, it is urgent to develop advanced therapies or preventive strategies against future complications, especially in the severe form of COVID-19 illness (Inciardi et al., 2020).

### 3.3.3. Cellular signaling pathways induced by COVID-19 on cardiovascular organ

COVID-19 might infect the cardiovascular system directly or indirectly. ACE2 is a type of membrane-bound aminopeptidase highly expressed in the CV system and can bind to ACE2 receptors found on infected myocardial cells (Alexander et al., 1993; Alhoghani, 2016; Tan et al., 2020). ACE2 is widely expressed in venous and arterial smooth muscle cells and endothelial cells (Zhou, F. et al., 2020). Interaction between SARS-CoV-2 and ACE-2 receptors can lead to alteration of ACE2 signaling pathways (Li, B. et al., 2020) and directly damage cardio myocytes through several inflammatory responses (Oudit et al., 2009). ACE2 is a pivotal contributor to immune and cardiovascular mechanisms related to myocardial injury (Turner et al., 2004). It has been reported that the binding of the SARS-Cov-2 virus spike protein to ACE2 is required for the disease to occur (Turner et al., 2004). This might lead to cardiovascular dysfunction, coagulation abnormalities, and MI (Guzik et al., 2020). Notably, the disease symptoms can be more severe in CVD individuals with a greater expression of ACE2 (Zheng et al., 2020).

Hence, microRNAs (miRNAs) can be detected in the circulatory system. They have been considered potential biomarkers in various diseases, especially in cardiovascular disturbances (Garg, A. et al., 2021). Interestingly, as evidenced by many reports, miRNA-virus interactions are widespread and complex and can promote or suppress viral replication (Hum et al., 2021). Twenty mechanically-ventilated COVID-19 patients and 32 healthy individuals were involved in a cohort study to detect circulating cardiovascular and inflammatory miRNAs. miRNAs -specific TaqMan PCR analyses demonstrate that serum levels of miR-21, miR-155, miR-208a, and miR-499 were markedly increased in COVID-19 confirmed patients compared to the healthy group, which may be valuable markers of myocardial disarrangement in COVID-19 (Garg, A. et al., 2021).

### 3.4. Renal system

There is evidence that the kidneys are the primary entry point for SARS-CoV-2. Obesity, diabetes, hypertension, cardiovascular disease, a low baseline estimated glomerular filtration rate (eGFR), a higher level of IL-6, and the need for vasopressor medications or mechanical ventilation were assumed to be independent AKI predictors (Bowe et al., 2020; Xia et al., 2020).

#### 3.4.1. COVID-19 and renal system clinical features

Renal disease in COVID-19 individuals can usually present as acute kidney injury (AKI), proteinuria, or hematuria. It is associated with more severe diseases and a high mortality rate (Cheng et al., 2020; Hirsch et al., 2020). In a large prospective study of 701 COVID-19 cases, kidney dysfunction was mainly found as mild to moderate proteinuria in nearly half of the patients (43.9%), likely related to glomerular filtration disturbances. In contrast, nearly two-thirds of them (26.7%) experienced

hematuria. These patients had a lower platelet and lymphocyte count, a higher leukocyte count, a greater prevalence of comorbidities, and a requirement for intensive care than individuals with normal kidney function (Cheng et al., 2020). Some studies demonstrated renal parenchymal involvement in COVID-19 (Chen, T. et al., 2020; Cheng et al., 2020; Diao et al., 2020; Larsen et al., 2020). Hematuria and proteinuria are prevalent in COVID-19 individuals and are independent predictors of inpatient COVID-19 non-survivors, implying a more severe illness with early viral invasion and hyper-inflammation (Cheng et al., 2020). Glomerular lesions and renal infarction have been noted in some patients with COVID-19 (Guillet et al., 2021; Murray et al., 2021; Webb et al., 2021).

#### 3.4.2. Pathophysiological effects of SARS-COV2 on renal injury

Histological findings revealed a wide range of renal pathologies, including acute tubular necrosis (ATN), tubulointerstitial necrosis (TIN), and collapsing glomerulopathy with or without podocytopathies (Ahmed et al., 2020; Braun et al., 2020). Most likely, sepsis-related hemodynamic and blood coagulation abnormalities, and enhanced effects of IL-6 and TNF on kidney epithelial cells, are responsible for ATN and TIN (Thaunat et al., 2006). COVID-19 Hyper-inflammation can also lead to hypercoagulability that induces fibrin thrombi occlusions in renal capillaries (Panigada et al., 2020). Hypovolemia (Mao, R. et al., 2020; Ronco et al., 2020), cytokine storm syndrome-related AKI, ARDS-related AKI, and direct viral attack have been proposed as primary probable mechanisms for kidney damage in patients with COVID-19 (Ahmed et al., 2020). In addition, the consequences of hypercapnic gaseous exchange impairment on the hypoxia-inducible factor system are increased proximal tubule oxygen utilization, reduced renal vasodilation, and altered diuresis. The release of vasopressin is also triggered by sympathetic nervous system activation (Ahmed et al., 2020). The cytokine storm can insult various organs by the elevated level of particular cytokines and chemokines such as IL-21, IL-8, TNF $\alpha$ , IL-6, and IL-1 (Catanzaro et al., 2020b). The cytokine storm and hyper-inflammatory response elicited by SARS-CoV2 are responsible for illness progression, the development of AKI, and mortality. Kidney endothelial cells release pro-inflammatory chemokines and cytokines, leading to microcirculatory dysfunction (Desai et al., 2002). capillary leak syndrome, and thrombosis, which can progress to disseminated intravascular coagulation (Henderson et al., 2020). Erythrophagocytosis and anemia are found due to cytokine-induced damage to macrophages. The induced haemophagocytosis is also causing damage to kidney cells. Infection with a virus causes CD68 macrophages to infiltrate the tubulointerstitium. As a result, natural killer cells and CD4-positive T cells produce pro-inflammatory cytokines in the tubular interstitium. Accordingly, overactive immune cells exacerbate fibrosis, apoptosis, and microvascular changes (Ahmadian et al., 2021; Battagello et al., 2020) may reduce vascular perfusion and lower the kidneys' glomerular filtration rate (Battagello et al., 2020). Cytokine storms cause epithelial, endothelial, and macrophage cells to migrate to mesenchymal cells, activating the mesenchyme, podocyte cell apoptosis, and severe proteinuria (Srivastava et al., 2021). Endothelial cell damage is a consequence of a cytokine storm. The fibroblasts derived from endothelial-to-mesenchymal cell transition interacted with platelets, neutrophils, and other immune cells that produce thrombosis (Srivastava et al., 2021).

#### 3.4.3. Cellular signaling pathways induced by COVID-19 in renal system

It is still unclear if SARS-CoV-2 causes a direct kidney infection (Lite et al., 2021). The viral sequences were discovered in the distal renal tubule epithelial cells of 18 non-survivors of COVID-19 (Gu et al., 2005). Alternatively, these could be misidentified as endosomal subcellular structures (Ahmed et al., 2020; Goldsmith et al., 2020). The SARS-CoV-2 virus was found in the cytoplasm of distal, proximal, and podocyte cells, with a considerable increase in ACE2 expression in proximal tubular cells (Jansen et al., 2022).

Similarly, SARS-CoV-2 antigen and RNA were found in the epithelial cells of distal convoluted renal tubules using a murine monoclonal antibody specific for SARS-CoV-2 nucleoprotein (Ding et al., 2004). MERS data suggested viruses in proximal tubular epithelial cells (Alsaad et al., 2018). These findings cast doubt on the various mechanisms underlying AKI in patients with COVID-19. ACE2 coreceptors allow SARS-CoV-2 entry into cells (Zhang, X. et al., 2020). A large amount of ACE is detected in the kidney's epithelial cells, but only modest levels are present in the parietal epithelial cells. ACE2 is missing in the endothelial cells of the kidney's glomerulus or mesangium (Hamming et al., 2004). While hypertension is linked to a poor outcome in COVID-19 infection, data does not support claims that it is caused by ACE inhibitors or angiotensin receptor blockers (Vaduganathan et al., 2020). Plasma ACE2 activity is higher in individuals who take ACE inhibitors or ARBs than in non-users, but there is no evidence that ACE inhibitors or ARBs facilitate SARS-CoV-2 viral entry into cells (Ramchand et al., 2018; Vaduganathan et al., 2020). Patients with ACE2 dysregulation or a genetic variation that allows SARS-CoV-2 infection to occur quickly may develop new-onset proteinuria and hematuria (Ahmed et al., 2020; Li, Z. et al., 2020).

The direct renal damage caused by multiple organ dysfunction syndrome results from an increase in pro-inflammatory cytokines such as IL-6, IL-1, and TNF-alpha and consequently widespread malfunction in endothelial cells as well as disseminated intravascular coagulation. Direct TNF- $\alpha$  binding to its receptor-1 in tubular cells of the kidneys has been shown to induce apoptosis (Cunningham et al., 2002). The role of IL-6 has been implicated in the development and severity of AKI in human and animal models, including ischemia AKI, nephrotoxin-induced AKI, and sepsis-induced AKI, via binding to the sIL6R and signaling downstream by STAT3 in tubular epithelial cells (Nechemia-Arbely et al., 2008). IL-6 impairs microcirculation and increases the permeability of renal arteries while stimulating the Protein Kinase C pathway, signaling chemokines renal endothelial cells to secrete additional cytokines (IL-6, IL-8, and MCP-1) The bioavailability of has a substantial impact on AKI. In the pathogenesis of AKI, chemokines such as CCL14 and CCL2 interact with atypical chemokine receptors (ACKR2). The two most potent pro-inflammatory mediators, CCR5 and CCR7, may be stifled by ACKR2. ACKR2 prevents AKI progression via limiting leukocyte infiltration, inflammation, and fibrous tissue remodeling. As a result, ACKR2 is assumed as a possible therapeutic target for AKI-associated renal inflammation and fibrosis (Ahmadian et al., 2021; Lux et al., 2019). SARS-CoV-2 infects kidney podocytes, resulting in proteinuria and the spread of pro-inflammatory cytokines such as transforming growth factor (TGF), platelet-derived growth factor (PDGF), interferon-gamma, interleukin, vascular endothelial growth factors (VEGF), and chemokine ligand 1 (CXCL1). Sclerosis, hyalinosis, and the deposition of mesangial matrix and fibrosis may develop due to the action of these mediators' in the glomeruli (Srivastava et al., 2021). Glomerular hyperfiltration leads to oxidative stress, which exacerbates glomerular injury by depositing the mesangial matrix and fibrosis. Hypertension, acid-base abnormalities, and other fluid and electrolyte imbalances, as well as edema and glomerular necrosis (AKI), are common symptoms in patients with COVID-19-associated chronic kidney disease (Srivastava et al., 2021).

Many clinical renal disorders, such as diabetic nephropathy and chronic kidney disease, may be caused by changes in miRNA expression (Fan et al., 2020). Additionally, miRNA may be used as a diagnostic and monitoring indicator for renal illnesses such as DN and CKD (Paul et al., 2022). miRNA can inhibit viral DNA implication to strengthen the immune system and reduce the risk of SARS-CoV-2 infection (Srivastava et al., 2021). The mechanism by which miRNAs in kidney cells regulate the expression of the SARS-CoV-2 gene in order to limit viral DNA amplification is yet unknown (Srivastava et al., 2021).

### 3.5. Nervous system

As evidence accumulates, SARS-CoV-2 may not be constrained only to the respiratory tract but may also invade the central nervous system (CNS) and the peripheral nervous system (PNS), resulting in some fatal neurological diseases (Lahiri et al., 2020). In a study carried out in Wuhan by Mao et al., 36.4% of the target population infected with COVID-19 presented neurologic manifestations (Mao, L. et al., 2020).

#### 3.5.1. COVID-19 and neural clinical features

There has been a wide range of CNS manifestations in patients with COVID-19, including headaches, delirium, mental impairment, impaired taste and smell, encephalitis, strokes, seizures, myelitis, acute disseminated encephalomyelitis, encephalopathy, neurogenic respiratory failure, silent hypoxia, and neuroleptic malignant syndromes (Divani et al., 2020a). SARS-CoV-2 can cause headaches like any other systemic viral infection. Headaches are usually accompanied by fever in COVID-19 (Guan et al., 2020; Mao, L. et al., 2020). COVID-19 patients experience impairments in consciousness, which may indicate the severity of the disease. Impairment of consciousness can be caused by septic encephalopathy, viral encephalitis, metabolic perturbations, strokes, and seizures with post-ictal misunderstanding (Lahiri and Ardila, 2020). Also, agitation and delirium were discontinued in patients after neuromuscular blockade treatment (Kremer et al., 2020). The primary neurological manifestations and the predominant neurological clinical outcome of COVID-19 are hypogeusia (hypogeusia/dysgeusia) and hyposmia (hyposmia/anosmia). SARS-CoV-2 may be involved in the absence of smell caused by atonal transport from the brain to the olfactory bulb via the cribriform plate (Dahm et al., 2016). Patients with COVID-19 are at risk of seizures due to electrolyte derangements, hypoxia, organ damage, and cerebral injury. Seizures have been reported in patients without any medical history of mesial temporal sclerosis or seizures and normal MRI and CSF studies (Karimi et al., 2020; Lu et al., 2020; Moriguchi et al., 2020).

#### 3.5.2. Pathophysiological effects of SARS-COV2 in neural injury

SARS-CoV-2 pathogenicity and its manifestations are determined by cytokines, chemokines, and other immune-modulating genes' expression and, consequently, the activities of these molecules (Singh et al., 2021). An intracranial cytokine storm commences with abnormally enhanced immune cells, leading to a breakdown of the blood-brain barrier as well as multi-focal, symmetrical lesions (Ellul et al., 2020). Hypoxic/metabolic changes triggered by a high inflammatory response that causes cytokine storms lead to ARDS and multiple organ damage, including brain damage (Garg, R.K. et al., 2021). Also, COVID-19 has been associated with a few cases of meningitis and encephalitis. Still, it is unclear whether these are or whether they are not immune-mediated infections secondary to direct or parainfectious conditions (Gao et al., 2020; Moriguchi et al., 2020; Sarma and Bilello, 2020). Some case reports have demonstrated Acute Disseminated Encephalomyelitis as a neurological disorder and that patients' CT and MRI showed multifocal patchy areas of white matter hypodensities (Zhang, T. et al., 2020). The most common finding for EEG in patients with COVID was encephalopathy (Galanopoulou et al., 2020).

#### 3.5.3. Cellular signaling pathways induced by COVID-19 on GI organ

SARS-CoV-2 is internalized by host cells through their ACE2 receptors. ACE2 is expressed in the endothelial cells of the brain (Nath, 2020). Furthermore, ACE2 is expressed in neurons, astrocytes, and oligodendrocytes (Chen et al., 2021). The SARS-CoV-2 spike glycoprotein has been activated by TMPRSS2, which allows the pathogen to interact with ACE2 (Divani et al., 2020b). As a result, the virus affects the nervous system via a variety of mechanisms, including disturbances of the renin and angiotensin systems (Simmons et al., 2005). Cytokines (IL-1 $\beta$ , IFN- $\gamma$ , IL-12, IL-33, IL-6, IL-18, IFN- $\alpha$ ), TGF- $\beta$ , and chemokines (CCL2, CCL3, CCL5, CXCL9, CXCL10) are inflammatory mediators secreted by

immune effector cells which were stimulated by SARS-CoV-2 through the ACE2 receptor. This stimulates excessive expression of inflammation-related proteins, a process that causes an atypical immune response and alters immune cells' function (Coperchini et al., 2020). Among these cytokines, IL-6 induces numerous proteins associated with acute inflammation in the brain (Uciechowski and Dempke, 2020).

#### 4. Interventions

For treatment of COVID-19, various drugs are currently approved by the U.S. FDA and have received emergency use authorization (EUA). Remdesivir is the first COVID-19 drug authorized by the FDA that strongly inhibits coronavirus RNA-dependent RNA polymerase (RdRp) (Niknam et al., 2022). According to the CDC's guidelines, remdesivir alone or combined with dexamethasone is recommended for COVID-19 patients who are hospitalized and need supplemental oxygen, not any device or ventilator (Rezagholizadeh et al., 2021). Dexamethasone is a corticosteroid drug with a strong anti-inflammatory effect in COVID-19 patients. Corticosteroids are used to inhibit and modulate inflammation through non-genomic and genomic impacts. In accordance with the CDC guidelines, the prescription dose of dexamethasone is 6 mg per day for a maximum of 10 days or until the patient is discharged. Other alternative drugs to dexamethasone are glucocorticoids such as methylprednisolone (32 mg), hydrocortisone (160 mg), or prednisone (40 mg) (Annane, 2021).

##### 4.1. Cytokine-based intervention in COVID-19

###### 4.1.1. IL-1 $\beta$ blockers

IL-1 $\beta$  plays an essential role in the pathogenesis of the CSR that often occurs in SARS-CoV-2 infection [4]. Many drugs against IL-1 $\beta$  signaling, such as IL-1 $\beta$  antagonist canakinumab and IL-1 receptor antagonist anakinra, may have beneficial effects on the improvement of COVID-19 patients (Yang et al., 2021). A meta-analysis study on the therapeutic effect of anakinra in COVID-19 patients illustrated that anakinra could reduce the need for ventilation and decrease the mortality of non-intubated patients without enhancing the serious side effects (Barkas et al., 2021). Nonetheless, more studies are required to approve anakinra as a promising agent for COVID-19 treatment.

###### 4.1.2. IL-6 blockers

One of the inducers of several biological processes involved in COVID-19 is the over-activation of IL-6 related signaling pathways that lead to organ damage. At present, many monoclonal antibodies against IL-6 signaling, including IL-6 blockers (sirukumab, clazakizumab, siltuximab, olokizumab) and IL-6R blockers (tocilizumab, levilimab, sarilumab) are suggested for combating COVID-19 (Yang et al., 2021). Several studies have investigated the pharmacodynamics, efficacy, and safety of tocilizumab to reduce the inflammatory reactions in severe COVID-19 patients. The FDA approves this drug to cure the coronavirus induced cytokine storm (Santos et al., 2020). One meta-analysis of randomized clinical trials demonstrated that tocilizumab could lead to a lower mortality risk for COVID-19 in prospective studies. According to the COVID-19 treatment guidelines, tocilizumab (single IV dose of 8 up to 800 mg/kg) in combination with dexamethasone (6 mg/day for up to 10 days) is recommended for the treatment of certain hospitalized COVID-19 patients with rapid respiratory decompensation (Khan et al., 2021). In one systematic review, the role of sarilumab as a potential regimen has been investigated for the treatment of COVID-19 patients, and it has been concluded that sarilumab is a safe and efficient drug with good clinical outcomes (Chamlagain et al., 2021). Also, a network meta-analysis demonstrated that sarilumab and tocilizumab alone or in combination with standard care such as corticosteroids might have similar effects and probably decrease the mortality rate in severe COVID-19 patients (Zeraatkar et al., 2021). In one double-blind and placebo-controlled phase III clinical trial, the efficacy and safety of

levilimab have been investigated in severe COVID-19 patients who do not need mechanical ventilation, and it was shown that administration of levilimab combined with standard treatment leads to an enhanced sustained clinical improvement rate (Lomakin et al., 2021). An observational cohort study demonstrated that siltuximab has beneficial effects in rapidly progressing COVID-19 patients requiring ventilatory support for decreasing cytokine-drive hyper-inflammation and mortality. Several clinical trials have been registered to evaluate the potential of various IL-6 or IL-6R antagonists for treatment or to improve the condition of COVID-19 patients (Gritti et al., 2020).

###### 4.1.3. IL-17 blockers

IL-17 functions upstream of both IL-6 and IL-1 therefore it has a central role in the COVID-19 related hyper-inflammatory syndrome. One clinical trial (NCT04403243) is currently ongoing on secukinumab, as a monoclonal antibody against IL-17. A retrospective case-control study reported that the prescription of netakimab (an anti-IL-17 monoclonal antibody) to severe COVID-19 patients might mitigate the inflammatory biomarkers and improve oxygenation without significant side effects. But netakimab does not affect the need for a ventilator and the mortality rate of coronavirus (Avdeev et al., 2021).

###### 4.1.4. TNF- $\alpha$ blockers

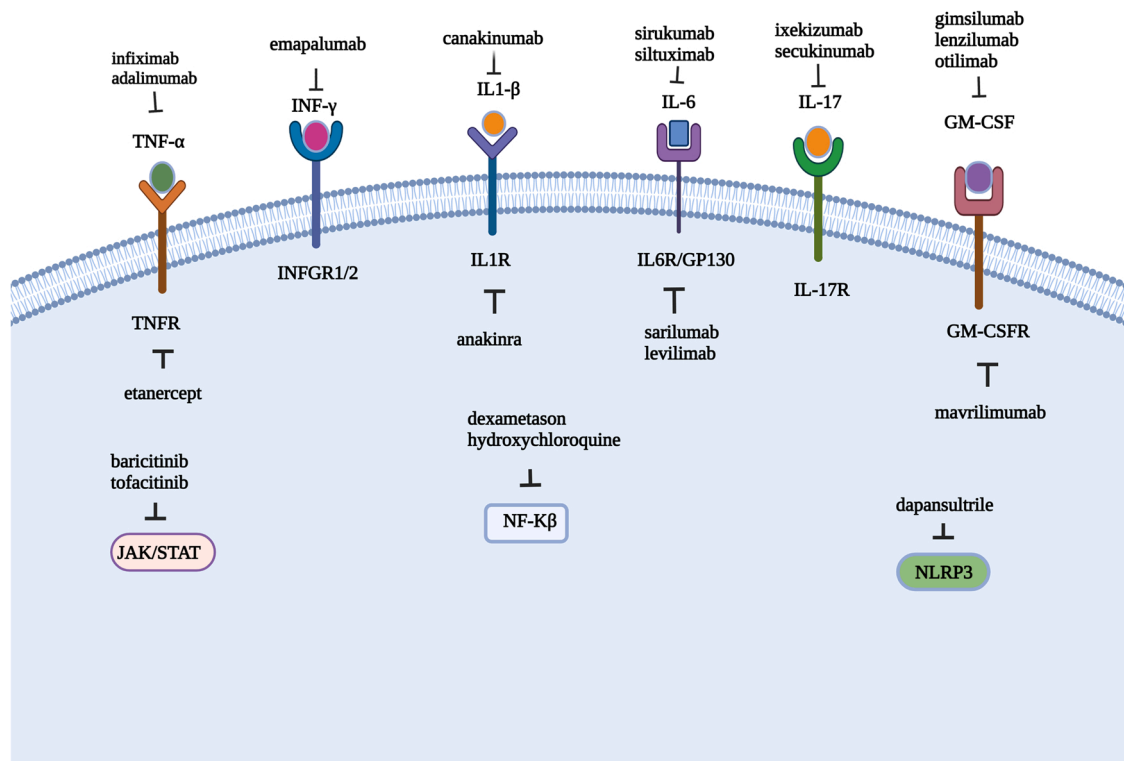
It is hypothesized that blockade of TNF- $\alpha$  can inhibit severe symptoms of COVID-19 or its incidence. TNF-blockers (adalimumab, etanercept, and infliximab) have a direct and positive relationship with a decrease in COVID-19 incidence and may have prophylactic effects in inhibiting COVID-19 in patients with rheumatoid arthritis and seronegative spondyloarthropathies, according to a case-control study (Salesi et al., 2021). A cohort study of 6077 patients with immune-mediated inflammatory diseases and COVID-19 demonstrated that TNF inhibitor monotherapy reduces adverse outcomes for COVID-19 compared to other commonly used immunomodulatory therapies (Fig. 3) (Izadi et al., 2021).

###### 4.1.5. GM-CSF blockers

GM-CSF is an important immune modulator cytokine that helps to regulate the pro-inflammatory processes in COVID-19 (Bonaventura et al., 2020). Several clinical trials have demonstrated the efficacy of GM-CSF blockade in the treatment of COVID-19. The blocking of the GM-CSF signaling pathway can also be done by the GM-CSF receptor blockers or through direct binding of them to the circulating GM-CSF. Some GM-CSF monoclonal antibodies such as lenzilumab, mavrilimumab and gimsilumab have been used in the announced clinical trials for COVID-19 treatment. One randomized clinical trial phase III assessed the safety and efficacy of lenzilumab in treating COVID-19 beyond available treatments and concluded that Lenzilumab significantly improved the survival of hospitalized COVID-19 patients with a safety profile and no need for invasive mechanical ventilation (Temesgen et al., 2021). Another randomized clinical trial investigated the use of gimsilumab for hyperinflammatory COVID-19 pneumonia (Gottlieb et al., 2021). According to this trial, gimsilumab improved ventilated patients compared with placebo. Also, gimsilumab received patients did not experience a sharp rise in NT-proBNP, a marker of heart failure. It has been suggested that a neurohormonal mechanism may be involved in the therapeutic effects of GM-CSF inhibition (Gottlieb et al., 2021). Whereas the efficacy and safety of GM-CSF monoclonal antibodies in the treatment of COVID-19 patients is a controversial issue, more randomized clinical trials are needed to evaluate these therapeutic agents against coronavirus (Fig. 3).

###### 4.1.6. IFN-I

Type 1 interferons (IFN-1) are cytokines that have anti-coronavirus properties. Due to their antiviral activity and high efficacy against diseases with excessive cytokine release, recombinant IFN-1 proteins (both IFN- $\alpha$  and IFN- $\beta$ ) are currently under evaluation for the treatment of



**Fig. 3.** The potential therapeutics for COVID19 induced-CRS. various drugs have been used or has been considered to treat COVID 19 induced -CRS, including those targeting pro-inflammatory cytokines, their receptors or related signaling pathways (created with biorender.com).

COVID-19 patients (Rana, 2020). A recent randomized trial on severe COVID-19 patients showed that IFN $\beta$ 1a has an excellent safety profile and possible benefits (Darazam et al., 2021). However, additional randomized controlled clinical trials are required to approve of this therapeutic option for COVID-19.

## 5. Conclusions

COVID-19 is a rapidly spreading pandemic disease that has triggered a global health emergency, impacting a large portion of the global population, particularly those with a history of health issues. People with chronic inflammatory illnesses, primarily asthma, lung disease, cardiovascular disease, etc., have a higher risk of being affected by SARS-CoV-2 infection when compared to the normal population. COVID-19 infection is an inflammatory, autoimmune disease in which the body's immune system becomes overexcited and attacks healthy cells rather than pathogens. Naturally, immune responses serve as a defense mechanism against invasive infections, but uncontrolled immune responses result in excess of inflammatory cells and immune cell recruitment. These cellular events in various tissues can activate inflammatory signaling pathways such as the IL-6/JAK/STAT, the IFN cell, the NF- $\kappa$ B, the TLRs, and many others. Cytokine storm and also activated signaling pathways in different cells or tissue types are associated with the severity of illness and damage to various tissues and organs. It is critical to detect and treat it by inhibiting related cytokine, receptors, and signaling pathways involved in organs as soon as possible. In this way, researchers are investigating different treatment options such as IL inhibitors, kinase inhibitors, IFN therapy, immunomodulatory agents, immunoglobulins, TLR-7 agonists, plasma therapy, etc., that can control the activated signaling pathway in involved organs and improve the damage in COVID-19 patients (Choudhary et al., 2021).

## Funding source

This research did not receive any specific grant from funding

agencies in the public, commercial, or not-for-profit sectors.

## CRediT authorship contribution statement

"Y. R, Sh. H, R.N, A.S, V.N, F.H, Y. F wrote the main manuscript text and Y. R performed the review and editing of the manuscript and L. J performed conceptualization, resources, and Supervision, prepared Figs. 1–3 and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript."

## Data Availability

Data will be made available on request.

## Acknowledgments

The authors are thankful to Department of biochemistry, cellular and Molecular Medicine Institute, Urmia University of Medical Sciences, Urmia, Iran.

## Conflict of interest

The authors declare no conflict of interests.

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