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Virus-Induced Host Chemokine CCL2 in COVID-19 Pathogenesis: Potential Prognostic Marker and Target of Anti-Inflammatory Strategy

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ABSTRACT

A wide variety of inflammatory mediators, mainly cytokines and chemokines, are induced during SARS CoV-2 infection. Among these proinflammatory mediators, chemokines tend to play a pivotal role in virus-mediated immunopathology. The C-C chemokine ligand 2 (CCL2), also known as monocyte chemoattractant protein-1 (MCP-1) is a potent proinflammatory cytokine and strong chemoattractant of monocytes, macrophages and CD4+ T cells bearing C-C chemokine receptor type-2 (CCR2). Besides controlling immune cell trafficking, CCL2 is also involved in multiple pathophysiological processes including systemic hyperinflammation associated cytokine release syndrome (CRS), organ fibrosis and blood coagulation. These pathological features are commonly manifested in severe and fatal cases of COVID-19. Given the crucial role of CCL2 in COVID-19 pathogenesis, the CCL2:CCR2 axis may constitute a potential therapeutic target to control virus-induced hyperinflammation and multi-organ dysfunction. Herein we describe recent advances on elucidating the role of CCL2 in COVID-19 pathogenesis, prognosis, and a potential target of anti-inflammatory interventions.

1 | Introduction

Coronavirus disease 19 (COVID-19) led to a global pandemic responsible for over 7 million deaths worldwide (https://data.who.int/dashboards/covid19/deaths?n=c). The disease is caused by severe acute respiratory syndrome coronavirus 2 (SARS CoV-2), a newly identified highly pathogenic enveloped virus belonging to the family of beta coronaviruses [1, 2]. The virus enters the body via nasal route and invades the cells following binding of spike (S) protein with host angiotensin-

Abbreviations: ACE2, angiotensin converting enzyme 2; ARDS, acute respiratory distress syndrome; BALF, bronchoalveolar lavage fluid; CCL2, chemokine (C-C motif) ligand 2; CCR2, C-C chemokine receptor 2; CCR5, C-C chemokine receptor 5; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CRS, cytokine release syndrome; CXCL10, chemokine (C-X-C motif) ligand 10; DIC, disseminated intravascular coagulation; GPCR, G-protein coupled receptor; IFN-γ, interferon gamma; IL-1, interleukin 1; IL-6, interleukin 6; MCP-1, monocyte chemoattractant protein 1; MERS CoV, middle east respiratory, syndrome coronavirus; MIS-C, multi-system inflammatory syndrome in children; PBMCs, peripheral blood mononuclear cells; RSV, respiratory syncytial virus; SARS CoV-2, severe acute respiratory syndrome coronavirus 2; TMPRSS2, transmembrane serine protease 2; TNF-α, tumour necrosis factor alpha.

converting enzyme 2 (ACE2) receptor on target cells [3]. This triggers release of numerous inflammatory mediators mainly cytokines and chemokines [4] leading to hyperinflammation, also known as 'cytokine storm' [5] that later manifests as cytokine release syndrome (CRS)-associated multi-organ dysfunction [4]. Major clinical characteristics include hypoxia and pneumonia that progressively develop to acute respiratory distress syndrome (ARDS), multi-organ failure and death [6].

Chemokines belong to a large family of small molecular weight proteins that play a key role in various pathophysiological processes including cell trafficking, inflammation, and immune regulation [7, 8]. Chemokines primarily interact with their seven transmembrane G-protein-coupled receptors (GPCRs) expressed on cell surfaces [9]. Structurally, depending on cysteine residues at the N-terminal, chemokines are broadly categorised into four subfamilies: C, C-C, C-X-C, and C-X3-C [9]. Functionally they can be of two major types; homoeostatic or inflammatory, however, a third type of chemokine with overlapping functions is also described. Two of the most common homoeostatic chemokines CCL19 and CCL21 are known to control lymphocytes and dendritic cells trafficking in the secondary lymphoid organs for initiation of effective immune reactions. While inflammatory chemokines such as CCL2, CCL7, CXCL8, interferon-induced CXCL9, CXCL10, and CXCL11 are involved in infection, inflammation, and malignancies [9]. One of the striking features of chemokines is functional dichotomy exerted by various members of the same family. For example, C-C family member, CCL2 reported to support HIV replication [10, 11] while CCL3, CCL4 and CCL5 mediated resistance is reviewed elsewhere [12]. During acute viral infections, several inflammatory chemokines are overexpressed by the infected and activated cells to facilitate effector leucocyte recruitment, immune cell activation to promote inflammation, virus clearance and/or inducing immunopathology in severe cases [13].

CCL2 is one of the early discovered chemokines belonging to C-C (b) family [14, 15] that binds to its cognate receptor CCR2 [16]. CCL2 confers a strong chemotactic behaviour towards CCR2+ monocytes, macrophages, and CD4+ T cells [17]. Apart from its chemotactic activity, CCL2 plays multiple immunoregulatory roles including systemic inflammation, angiogenesis and organ fibrosis [18]. CCL2 is considered as one of the major players in the recruitment of monocytes, macrophages and CD4+ T cells into the lung, thus can effectively contribute to CRS, a hallmark of COVID-19. Recent studies on clinical specimens including bronchoalveolar lavage fluid (BALF) and biopsies have shed light on the involvement of CCL2 in COVID-19 [6, 19–21]. This review highlights the recent advances in the role of CCL2 in COVID-19 pathogenesis, prognosis, and a potential target of anti-inflammatory interventions. As the role of CCL2 in COVID-19 pathogenesis is evolving, certainly, there are gaps that need to be seriously addressed. For example, whether CCL2 has a direct or indirect role on COVID-19 replication? What are the mechanisms of CCL2-mediated tissue injury? Therefore, further studies are warranted to have a deeper mechanistic insight to precisely understand the role of CCL2 in COVID-19 pathogenesis.

2 | The CCL2:CCR2 Biology

CCL2 was identified decades back in human glioma cells and peripheral blood mononuclear cell cultures [14, 15]. CCL2 is predominantly expressed by immune cells of myeloid lineages including monocytes, macrophages and dendritic cells [22] and primarily regulates monocytes, macrophages, memory T lymphocytes, and natural killer (NK) cell trafficking [17, 23]. Migration of cells involves a series of dynamic changes in the activated integrins leading to rolling, adhesion and translocalisation through the vascular endothelium [24]. In brief, binding of CCL2 to its cognate receptor CCR2 instigates an amplification cascade involving multiple signalling pathways. Human CCR2 exists in two spliced forms, CCR2A and CCR2B requiring different signalling pathways [16]. CCR2B is the most common isoform present on cell surface while CCR2A is mostly cytoplasmic. Ligation of CCL2 to CCR2 triggers dissociation of the α subunit from the α, β and γ complex of an intracellular G-protein to block adenylyl cyclase (AC) resulting in decreased adenosine 3′,5′-cyclic monophosphate (cAMP). Release of a subunit results in formation of a β−γ heterodimer that activates PI3K-Akt-NFκB [25, 26], JAK-STAT [27], Ras-MEK-JNK/p38/ERK [25] pathways (Figure 1). Mobilisation of NFκB, AP-1 and STAT transcription factors induce expression of genes involved in inflammation, migration, and angiogenesis. For example, CCL2 activation of macrophages results in the release of cytokines IL-1, IL-6, CCL2, TNF-α and growth factors such as platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF) and transforming growth factor (TGF-β) [28], thereby, contributing to various biological processes.

2.1 | CCL2 in Inflammation and Tissue Injury

Several structural cells such as epithelial cells [29], endothelial cells [30], fibroblast [30] and astrocytes [31] have been described to secrete CCL2 (Figure 1). Apart from controlling cell migration, CCL2 induces expression of other inflammatory cytokines and chemokines that lead to tissue injury and organ damage. For example, CCL2 promotes fibrosis of several organs including lung, liver and heart (reviewed in detail elsewhere) [32]. Fibrosis or scarring is an immunopathological event triggered by inflammatory mediators like CCL2 [33]. Recruitment of inflammatory cells, fibroblasts proliferation and accumulation of extra cellular matrix (ECM) proteins are the key features of tissue fibrosis [32]. CCL2 is considered as one of the potent pulmonary fibrogenic factors by controlling macrophage infiltration into the lung, activating CCR2+ fibroblasts to initiate remodelling, survival [34], and fibroblast procollagen production [35]. These events consequently lead to fibroproliferative disorders in ARDS [36]. Association of elevated levels of CCL2 in chronic hepatitis patients with hepatic fibrogenesis indicates their involvement in fibrosis [32]. Fibrotic role of CCL2 can also be extended to diabetic nephropathy [37] and lupus nephritis patients [38] where urine CCL2 levels and macrophage infiltration correlate with disease severity. Importantly, CCL2 seems to play a pivotal role in cardiovascular diseases, with overexpression of CCL2 found in myocardial samples of heart failure patients [39]. Furthermore,

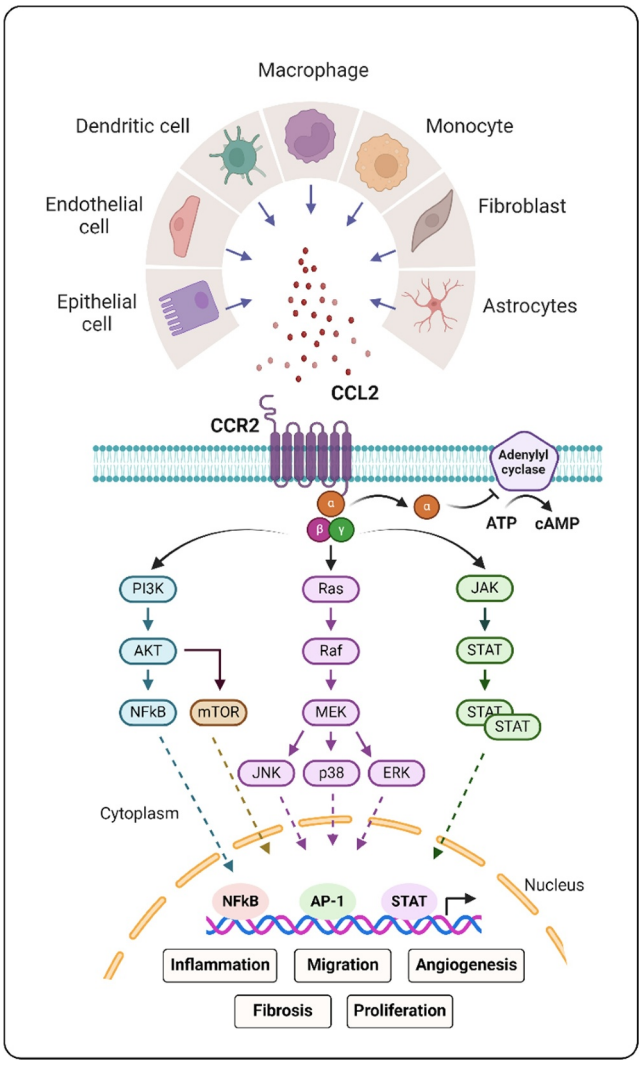

FIGURE 1 | Major CCL2 producing cell types and signalling cascade. Illustrated view depicting major human cells such as monocyte/macrophages, dendritic, epithelial, endothelial cells, and fibroblasts known to produce CCL2 following viral infections or activation by inflammatory mediators. Binding of CCL2 to CCR2, a GPCR receptor triggers dissociation of the α subunit from the α, β and γ complex of the intracellular G-protein. The α subunit then inhibits adenylyl cyclase (AC) function resulting in decreased adenosine 3′,5′-cyclic monophosphate (cAMP). Dissociation of the α subunit subsequently results in the formation of β−γ heterodimer that eventually leads to activation of NFkB, AP-1 and STAT transcription factors downstream to PI3K-Akt, JAK-STAT, and Ras-MEK-JNK/p38/ERK pathways. Activation of transcription factors induce expression of genes involved in various biological processes such as inflammation, migration, fibrosis and angiogenesis. (Created with Biorender.com.)

CCL2 significantly contributes to cardiac fibrosis by recruiting CCR2+ monocytes and macrophages enriched in fibrogenic mediators such as TGF-β and osteopontin [40, 41].

2.2 | CCL2 During Viral Infections

Several human viruses including human immunodeficiency virus (HIV), hepatitis-C virus (HCV), human cytomegalovirus

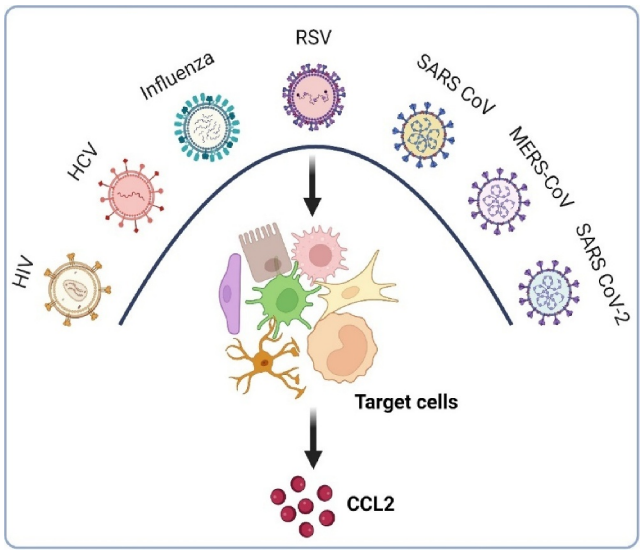

FIGURE 2 | CCL2 induction by various human viruses. Several human viruses including those causing acute or chronic infections, are known to induce chemokine CCL2. Some of the common respiratory viruses such as influenza, RSV, MERS CoV and SARS CoV induce CCL2 production by target cells. (Created with Biorender.com.)

(HCMV), and respiratory viruses such as influenza, respiratory syncytial virus (RSV), severe acute respiratory syndrome (SARS CoV), middle east respiratory syndrome (MERS CoV), and SARS CoV-2 are known to induce CCL2 [42] (Figure 2). In case of HIV infection, CCL2 not only recruits the permissive monocytes and CD4+ T cells to the site of infection, but also elevates the viral load by promoting viral replication via a feedback-loop mechanisms [10, 11, 43, 44]. Furthermore, HIV viraemic patients at advance stage of the disease tend to harbour higher frequency of circulating CCL2-positive inflammatory monocyte subsets compared to aviraemic and healthy controls [45]. On the other hand, HCV infection-triggered CCL2 production by the hepatocytes and Kupffer cells found to correlate with disease severity [46]. With regards to respiratory infections, RSV not only upregulates CCR2 but also correlates with severity of disease pathogenesis as well [47]. CCL2 is also overexpressed during influenza infection [48, 49] and administration of a CCL2 antagonist was found to suppress pulmonary hyperinflammation in influenza infected mice [50]. Induction of CCL2 is well established for MERS and SARS-CoV infections as monocytes, macrophages, and T cells are recruited via CCL2 to infection sites causing hyperinflammation and lung injuries [51]. Indeed, CCL2 levels observed in BALF of SARS CoV infected patients correlate with increased frequency of alveolar macrophages [52–54]. In addition, in vitro studies have also revealed CCL2 expression by some of the primary human cells and cell-lines. For example, primary alveolar and bronchial epithelial cells [55], human monocyte-derived macrophages (MDMs) [56], and dendritic cells [51] produce CCL2 following SARS CoV-2 infection. This was also true for human monocytic (THP-1) [57] and lung epithelial cell line A549 [58]. Together, these studies underscore a key role of CCL2 in virus-induced immunopathology. An elaborated view on CCL2 in SARS CoV-2 infection is described in the following sections of this review.

3 | COVID-19 Pathogenesis: An Overview

SARS CoV-2 is an enveloped virus consisting of spike (S) glycoprotein, membrane (M), envelope (E) and nucleocapsid (N) proteins with positive-sense single-stranded RNA as genome. Spike glycoproteins consist of two subunits, the S1 subunit binds to ACE2 receptor while S2 subunit facilitates the virus fusion with the membrane of target cells (Figure 3). Binding of spike protein to ACE2 causes cleavage by transmembrane serine protease 2 (TMPRSS2) that subsequently activates the S2 subunit to initiate fusion and release of viral genomic RNA into the target cells [59, 60]. Infection of SARS CoV-2 triggers the release of a plethora of inflammatory mediators leading to a systemic hyperinflammation referred to as CRS, a hallmark of COVID-19. A detailed overview on COVID-19 associated hyperinflammation is published elsewhere [61, 62]. Inflammatory mediators are either produced by the cells infected by the virus or by otherwise activated cell types. However, CRS has been described as the culprit behind the high mortality observed in severe COVID-19 patients suffering from acute respiratory distress syndrome (ARDS) and multi-organ failure. COVID-19 associated key immunopathological features are discussed below.

3.1 | Dysregulated Cytokine/Chemokine Network and Cytokine Release Syndrome

Multiple studies have demonstrated the persistence of IL-6, IL-1β, TNF-α, IFN-γ, CCL2, IL-10, CCL3 and CXCL10 during SASRS-CoV-2 infection [63, 64]. Among these cytokines, IL-6 plays a central role in COVID-19 pathogenesis and remains the major driver of systemic CRS. An analysis of 123 patients with severe (76.19%) and mild (30.39%) COVID-19 reported elevated levels of IL-6 in all patients [65, 66]. IL-6 causes excessive inflammation and activates C-reactive protein (CRP) to promote COVID-19-associated pneumonia, thrombo-inflammation and multiple organ damage [67]. In addition, IL-6 is also involved in cadherin decomposition and mast cell secretion of histamine resulting in an increased vascular permeability (peripheral oedema), hypotension, and hypoxia. In contrast to IL-6, persistence of high levels of CCL2, CXCL10, CCL3 and TNF-α are predominantly detected in patients admitted to intensive care unit (ICU) rather than in non-ICU patients [68]. However, next to vascular leakage, IL-6 also plays a crucial role in the initiation of coagulation and complement activation ultimately leading to blockage of small-calibre blood vessels including capillaries and probably

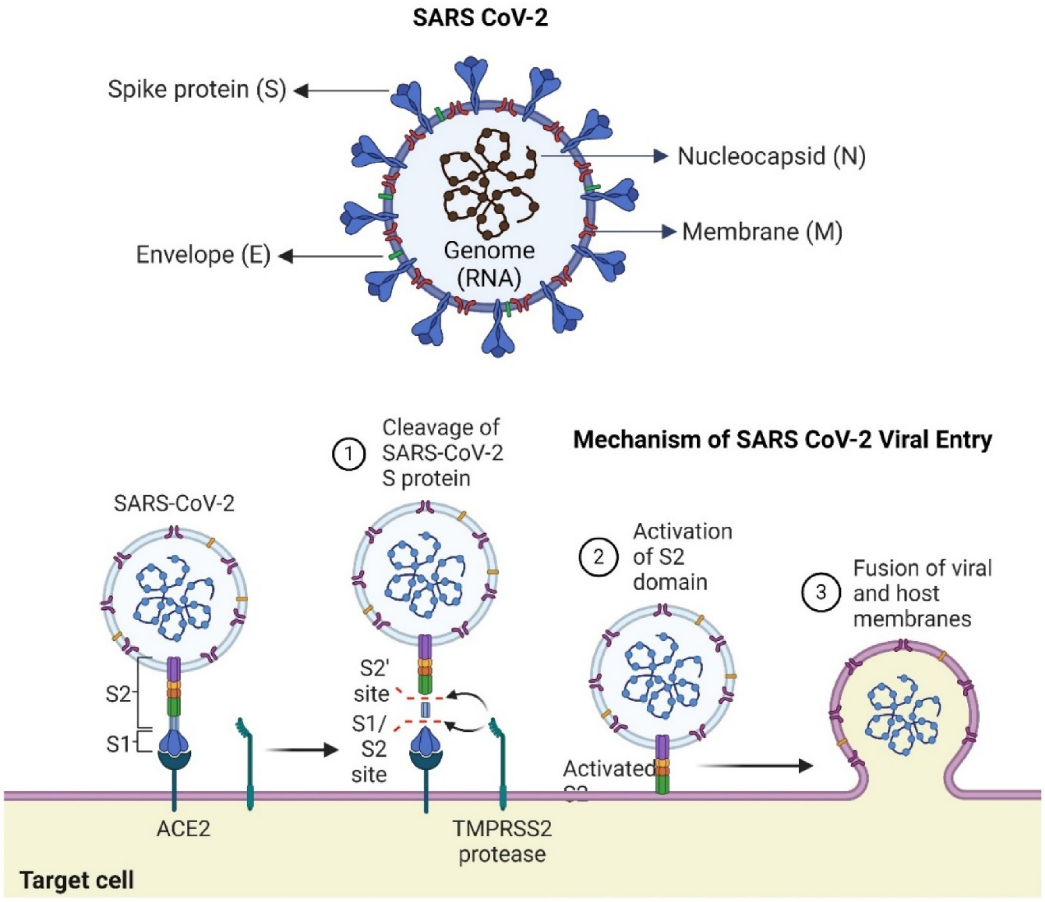

FIGURE 3 | SARS CoV-2 structure and cellular entry. SARS CoV-2 is comprised of four major structural proteins, spike (S), membrane (M), envelope (E) and nucleocapsid (N), and a positive-sense single-stranded RNA as genome. Below illustration depicts the mechanism of SARS CoV-2 entry and sequential events that occur during the cellular infection. (Created with Biorender.com.)

arterioles [67, 69] and, thus, the development of disseminated intravascular coagulation (DIC), a hallmark phenomenon of CRS [70]. Considering the predominant contribution of IL-6 to COVID-19 severity, IL-6-receptor monoclonal antibody tocilizumab had been recommended during the pandemic to limit systemic inflammation and disease progression [71, 72]. From a prognostic point of view, the ratio of IL-6 and D-Dimer, a by-product of blood clot degradation used as predictive biomarker of coagulation disorder in COVID-19 [73] has been suggested as a reliable early predictor of COVID-19-associated pneumonia and overall systemic disease development. In addition to above cytokines, chemokines markedly contribute to CRS as abundant CCL2, CXCL10, CCL3 and CCL4 were detected in the PBMCs and BALF of COVID-19 patients [19, 74, 75].

3.2 | Perturbed Immune System

A perturbed immune system is the hallmark of COVID-19. Early release of inflammatory mediators following SARS CoV-2 infection triggers widespread infiltration of innate (monocytes, macrophages, neutrophils, basophils, eosinophils, and NK cells) and adaptive (T- and B-cells) immune cells at the site of infection or inflammation. For example, marked infiltration of monocytes and macrophages were observed in COVID-19 cases with typical diffuse alveolar injury [76]. A significant rise of neutrophils was detected more in severely rather than mildly affected COVID-19 patients [77]. In contrast, strong reduction in hyperactivated peripheral $CD4^+$ and $CD8^+$ T lymphocytes has been reported in ARDS cases [78]. NK cell frequency, however, was significantly reduced in severe COVID-19 patients [66]. Given the altered immune cell frequencies, formation of a high neutrophil: lymphocyte ratio together with low levels of basophils, eosinophils, monocytes, NK cells, T- and B-cells is now considered a predictive factor of multi-organ failure and death in COVID-19 patients [79]. The apparent reduction in hyperactivated CD4+ and CD8+ T lymphocytes could result from enhanced apoptosis in these cell populations [6, 80]. Interestingly, increased levels of pathogenic IL-17 producing Th17 cells were observed in severe cases of COVID-19 [81]. In addition, skewing of CD4+ T cells towards a hyperactivated IFN-γ secreting helper CD4+ T (Th1) phenotype appears to profoundly contribute to COVID-19 pathogenesis [82].

4 | Role of CCL2 in SARS-CoV-2-Induced CRS

In addition to systemic CCL2 elevation, lung autopsies of COVID-19 patients have revealed infiltration of CCR2-expressing macrophages, neutrophils and T cells indicating a crucial role for CCL2 in COVID-19-associated pulmonary inflammation [83]. Among immune cells, CCR2+ monocytes constitute the major infiltrate in BALF as well as in lung tissue of COVID-19 patients presenting with CRS [83]. This was further supported by single-cell RNA sequencing (scRNA-Seq) analysis where severe and moderate COVID-19 patients demonstrated higher numbers of CCR2+ monocytes than mildly affected patients and healthy individuals [19]. Other studies have reported early induction of CCL2 and CCR2+ monocyte as well as macrophage infiltration into lungs of severe COVID-19 patients [20]. These studies provide strong evidence of CCL2 involvement in COVID-19-associated CRS. A hypothetical model on how SARS CoV-2-induced CCL2 can regulate COVID-19 immunopathogenesis and CRS-associated multi-organ dysfunction (Figure 4). SARS-CoV-2 infects alveolar epithelial cells where it replicates to produce more virions. However, this process subsequently induces CCL2 production and secretion by the infected cells which then initiates recruitment of CCR2+ monocytes, macrophages, neutrophils, and T cells to the site of infection. In addition to infecting epithelial cells, SARS CoV-2 exposure of innate immune cells such as macrophages and dendritic cells can also trigger the release of CCL2 which in turn may further enhance the infiltration of CCR2+ cells from the circulatory blood system. The newly recruited immune cells could subsequently be activated by CCL2 and other inflammatory factors, an activation loop that could support the generation of a cytokine storm manifesting as CRS in COVID-19 patients.

Besides, proinflammatory cytokines and chemokines, a recent study reported elevated levels of galactin-9 (Gal-9) in COVID-19 patients that positively correlates with CCL2 [84]. Interestingly, this correlation was found to be significant with respect to Wuhan isolates and delta but not omicron variant [85], suggesting differential impact of these variants on host CCL2 responses. Moreover, another study demonstrated Gal-9 to enhance SARS CoV-2 replication and inflammation in airway epithelial cell [86]. These studies shed light on role of Gal-9 in SARS CoV-2-induced hyperinflammation and therefore, could potentially be considered as potential surrogate marker of COVID-19 disease severity [87].

Several reports of Kawasaki-like multi-system inflammatory syndrome (MIS-C) have been described in children and adolescents during COVID-19 pandemic [88–92]. Kawasaki disease is a systemic acute inflammatory condition with unknown aetiology [93, 94]. The disease is mainly characterised by profound vasculitis affecting mainly the coronary arteries [89]. Occurrence of inflammatory monocytes and macrophages in the vascular lesions strongly points towards the marked secretion of cytokines and chemokines as elevated levels of inflammatory chemokines including CCL2 has been reported in Kawasaki disease [95]. Involvement of CCL2 in Kawasaki diseases was supported by a study where gamma globulin treatment found to lower the monocyte frequency in the circulation [96]. However, analysis of cardiac tissues obtained from patients of Kawasaki disease describes an association of matrix bound CCL2 with monocyte infiltration, and acute vasculitis [97]. Involvement of CCL2 with vasculitis in Kawasaki disease as well as their marked elevation in COVID-19 patients indicate towards overlapping mode of pathogenesis, however, this need to be thoroughly investigated.

5 | Role of CCL2 in CRS Associated Multi-Organ Dysfunction

CRS remains the leading cause of multi-organ dysfunction and mortality among severe COVID-19 patients. Affected patients

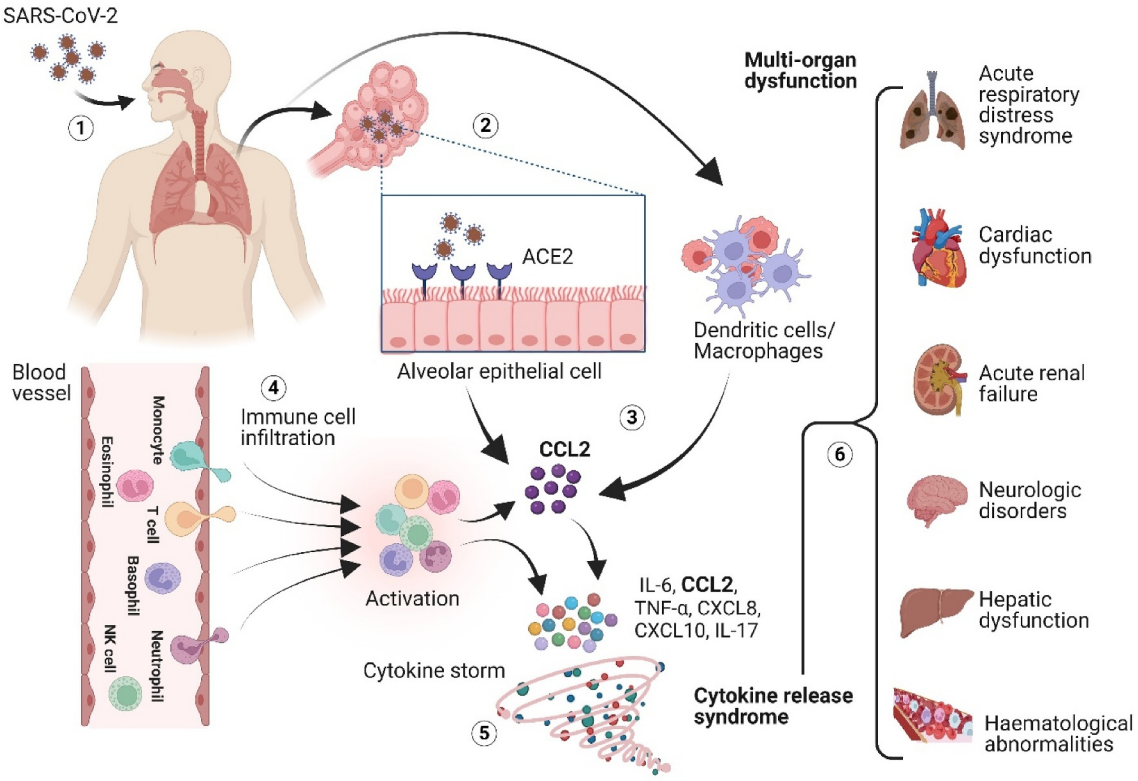

FIGURE 4 | CCL2 in COVID-19 pathogenesis, CRS and multi-organ dysfunction. Illustration showing potential mechanisms of CCL2-driven immunopathogenesis, CRS, and multi-organ dysfunction. SARS CoV-2 enters via nasal root into lung (1) and infects alveolar epithelial cells to secrete CCL2 (2). The virus can also activate myeloid cells such as monocytes/macrophages and dendritic cells in the lung to produce CCL2 (3). Enriched CCL2 instigates the infiltration of CCR2+ monocytes, macrophages, neutrophils, T cells from blood to the site of infection (4). Infiltrated immune cells can be activated by various inflammatory mediators including CCL2 leading to cytokine storm/CRS (5) which eventually causes multi-organ dysfunction (6). (Created with Biorender.com.)

mainly suffer from acute lung failure, acute kidney injury, acute liver failure, cardiovascular diseases, haematological abnormalities, and neurological disorders (Figure 4). SARS-COV-2 mediated endothelial cell damage, infiltration of inflammatory cells, and blood coagulation abnormalities are considered pathological events contributing to multi-organ dysfunction [4, 6, 98].

5.1 | CCL2 in ARDS

ARDS remains the leading cause of death due to acute respiratory failure among severe COVID-19 patients while the majority of patients, even asymptomatic individuals, may develop lung consolidation [99, 100] or diffuse bilateral pneumonia [101]. In consequence to SARS CoV-2 exposure, abnormal secretion of pro-inflammatory cytokines and chemokines are major triggers of hyperactivation and apoptosis of alveolar epithelial and endothelial cells. Both events may result in hypoxia, oedema, and vascular leakage particularly in cases of COVID-19-associated ARDS. As described above, several inflammatory mediators including CCL2 are overexpressed in the alveolar macrophages [74, 75]. Elevated CCL2 levels during ARDS may be the driving force behind the massive infiltration of CCR2+ inflammatory cells. In addition, early secreted IL-6 and TNF-a upon SARS CoV-2 exposure may act on infiltrated immune cells to further release CCL2 which may further exacerbate the inflammatory responses in a feed-back loop mode. These findings indicate that the CCL2 milieu together with infiltrating CCR2+ inflammatory cells are critical in contributing to the progression and fatality of ARDS [21]. Furthermore, CCL2-mediated enhancement of procollagen synthesis by the fibroblasts could further add to ARDS associated fibroproliferative complications [35, 36].

5.2 | CCL2 in Pulmonary Fibrosis

Pulmonary fibrosis is characterised by aberrant scarring of lung tissue that progressively results in lung dysfunction. Multiple inflammatory cytokines and chemokines are involved in this process, where CCL2 takes a central position in driving lung fibrosis. CCL2 contributes to fibrosis in multiple ways, by promoting infiltration of inflammatory cells, angiogenesis, fibroblast collagen synthesis, myofibroblast differentiation, fibroblast recruitment and survival [102, 103]. This pathway appears to be clinically relevant as patients with idiopathic pulmonary fibrosis exhibit elevated levels of CCL2 in BALF and serum [104, 105]. Moreover, occurrence of high frequency of $CD163^{+}$ monocyte-derived-macrophages potentially migrated in response to CCL2 found to exhibit strong profibrotic features during ARDS [106]. In addition, experimental animal models of pulmonary fibrosis also show elevated levels of CCL2 in the lung of fibrosis developing mice [107]. Moreover, CCR2-deficient mice were

protected from developing fibrosis [104]. These studies underscore the crucial role of CCL2 in lung fibrosis. Pulmonary fibrosis is one of the clinical manifestations of severe COVID-19 and is potentially driven by CCL2, a chemokine known to recruit fibrocytes and profibrotic macrophages to the lung [108]. Elevated pulmonary levels of CCL2 and the massive infiltration of CCR2+ monocytes into lung tissue of CIVID-19 patients, indicate that CCL2 is a major contributor to the pathogenesis of lung fibrosis during COVID-19.

5.3 | CCL2 in Adverse Cardiovascular System

A growing body of evidence supports the role of CCL2 in cardiovascular diseases including atherosclerosis [109], myocardial infraction [110], cardiomyopathy [111], and hypertension [112]. CCL2 is strongly associated with adverse cardiovascular outcomes including thrombus formation during COVID-19 [113]. The level of hyperactivated platelet generation, thrombus formation, and atherosclerosis appear to correlate with the expression levels of CCL2 [113–115]. One important feature of COVID-19 pathogenesis is increased neutrophil death (NETosis) that leads to formation of neutrophil extracellular traps (NETs), a prognostic marker of COVID-19-associated coagulopathy. CCL2 induced during this process functions to recruit myeloid cells to NET to promote a pro-inflammatory and a procoagulant state [116–118]. In a retrospective study, elevated CCL2 was found to correlate with activation of the coagulation cascade and severity of respiratory impairment [119]. Moreover, a recent study in animal model has demonstrated virus-induced ARDS to promote cardiac inflammation via CCR2+ macrophage expansion [120]. Involvement of CCL2 in cardiovascular abnormalities was well supported in an in vitro study where CCL2 treatment resulted in platelet aggregation and granule secretion, an effect that was efficiently abrogated using a CCR2 inhibitor or CCL2 neutralising antibody [114]. Therefore, blockade of the CCL2:CCR2 pathway could potentially reduce adverse cardiovascular-related anomalies in COVID-19 patients, by limiting the accumulation of inflammatory monocytes and other myeloid populations at infection site.

6 | Impact of SARV CoV-2 Variants and Vaccination on CCL2 Response

Given the significant predictive association of CCL2 with mortality among COVID-19 patients supports the notion of excessive infiltration of monocytes in the lung of infected individuals. Most of the studies describe the elevated levels of CCL2 in individuals infected with Wuhan strain, however, reports on other SARS CoV-2 variants are lacking until recently, a study demonstrated differential impact of Wuhan isolate, Delta variant and Omicron variant on host immune responses as individual infected with Wuhan strain and delta variants produce more or less similar levels of proinflammatory cytokine and chemokines than Omicron variants [85]. In contrast, plasma chemokines profiling of Wuhan and omicron infected COVID-19 individuals showed significantly elevated levels of CCL2 irrespective of the genetic variants [121]. However further investigations are required to have deeper insight on CCL2 responses to COVID-19 variants.

Impact of COVID-19 vaccination on host CCL2 is elusive. Recently, a study has shed light on this important issue. In a longitudinal study authors demonstrated lower levels of inflammatory markers such as TNF-α, IL-7, CCL2, CXCL8, CXCL10 and IL-29 in vaccinated compared to unvaccinated SARS CoV-2 -infected individuals [122]. Lowering of these inflammatory mediators perhaps could potentially explain the reduced inflammation associated with reduced COVID-19 severity. Therefore, extensive research is warranted to investigate inflammatory responses against various COVID-19 vaccines particularly, the CCL2 response.

7 | CCL2 as Prognostic Marker

Multiple studies have implicated an association of chemokines including CCL2 and CXCL10 with poor prognosis and mortality among COVID-19 patients [123, 124]. In addition, these chemokines also display different degrees of correlation with viral load and symptoms like asthenia, dyspnoea, anosmia [6]. For example, an elevated plasma CCL2 level positively correlates with COVID-19 viraemia [125]. Nasopharyngeal swab samples from ICU and non-ICU admitted COVID-19 patients revealed that CCL2 levels are correlated with poor prognosis, suggesting that CCL2 could serve as a predictive marker for COVID-19 progression [126, 127]. Moreover, the fatality rate was positively correlated with CCL2 in critically ill patients [128]. An association of CCL2 with COVID-19 prognosis has also emerged from autopsy findings of patients exhibiting massive CCR2+ monocytes and macrophages infiltration into the lung [75]. Similarly, in a retrospective study, elevated CCL2 correlates with the activation of the coagulation cascade and severity of respiratory impairment. CCL2 correlates with D-dimer indicating an unfavourable outcome in COVID-19 patients [119]. Hence based on the above studies, CCL2 may be considered as a prognostic marker in patients with COVID-19.

8 | CCL2:CCR2 Axis as Therapeutic Target

Given the critical role of CCL2 in SARS-CoV-2 pathogenesis, targeting the CCL2:CCR2 axis may offer potential therapeutic intervention to minimise COVID-19-associated hyperinflammation and multi-organ dysfunction. Some earlier studies on CCL2 blockade do show effectiveness against breast and prostate cancer [129, 130]. Moreover, a number of CCL2 and CCR2 inhibitors and monoclonal antibodies have been developed and tested in various human inflammatory diseases as well as in animal models of inflammation and viral infection. For example, Bindarit, an inhibitor of CCL2 found to inhibit macrophage infiltration in animal model of osteoarthritis [131] while anti-CCL2 monoclonal antibodies such as Carlumab and ABN912 found to be ineffective in human idiopathic fibrosis and rheumatoid arthritis respectively [132, 133]. A summary of agents targeting the CCL2:CCR2 axis is provided in Table 1. However, a detailed overview on drugs and compounds in viral and non-viral infections is described elsewhere [42]. The small

TABLE 1 | Therapeutic targeting of CCL2/CCR2 axis.

Agent	Type	Model/disease	Effects	Ref.
Bindarit	CCL2 inhibitor	Animal/osteoarthritis	Reduced macrophage infiltration	[131]
Anti-CCL2 antibody	CCL2 blocker	Animal/18-hACE2 mouse B.1.351 SARS-CoV-2 variant	Delayed virus-induced death	[134]
Carlumab	Anti-CCL2 monoclonal antibody	Human/idiopathic pulmonary fibrosis	No improvement	[132]
ABN912	Anti-CCL2 monoclonal antibody	Human/rheumatoid arthritis	No improvement instead disease worsening	[133]
Ingramon	Peptide inhibitor of CCL2	Human/in vitro/glioma	Inhibits monocyte migration	[135]
BMS-813160	CCR2/CCR5 dual antagonist	Animal/peritonitis	Inhibit monocytes and macrophages migration	[136]
Cenicriviroc	CCR2/CCR5 dual antagonist	Human/COVID-19	Reduces inflammation, inhibits SARS CoV-2 replication in vitro	[137] [138]
PF-04178903	CCR2 inhibitor	Animal/mouse influenza-infection	Suppresses lung immune pathology	[50]
CCX140-B	CCR2 inhibitor	Human/type-2 diabetes and nephropathy	Reduces inflammation and reno-protective effects	[139]

molecule antagonists BMS-813160 and BMS-687681, a dual inhibitor of CCR2 and CCR5, were found to suppress monocyte and macrophage infiltration in an animal model of peritonitis [136]. Leronlimab (CytoDyn, Inc, USA), a humanised anti-CCR5 monoclonal antibody developed to block HIV infection, has been reported to bring down plasma IL-6 levels as well as SARS CoV-2 viral load [140] is currently being tested in a phase II clinical trial (ClincialTrials.gov identifier NCT04347239) against COVID-19. Cenicriviroc (CVC, Tobira Therapeutics Inc, San Francisco, CA), a potent small-molecule CCR2/CCR5 inhibitor, has been shown to block HIV gp120 binding [141], and CCL2/CCL5 receptor binding [142] inhibits HIV RNA replication as well as inflammatory response in infected individuals [143–145]. Therefore, optimal administration of CVC during different phases of SARS CoV-2 infection may attenuate or prevent the inflammatory consequences of COVID-19 and could provide a beneficial effect by avoiding excessive monocyte recruitment. To test CVC efficacy in COVID-19 patients, at least 3 clinical trials, I-SPY/COVID Clinical Trial (ClincialTrials.gov identifier NCT04488081), ACTIV-1/NIAD/NIH Consortium Study (ClincialTrials.gov identifier NCT04593940), and Charité trial in Germany (NCT04500418), are currently ongoing. However, the I-SPY clinical trial has been discontinued due to poor recovery time of COVID-19 patients. Furthermore, a recent study revealed no difference in time to recovery in patients with COVID-19-associated pneumonia following abatacept, cenicriviroc, or infliximab administration (NCT04593940) [146]. Further studies are required to determine the utility, efficacy, and safety of CVC in treating patients with moderate to severe COVID-19.

9 | Conclusion and Future Prospect

In summary, the proinflammatory chemokine CCL2 appears to be a key mediator contributing to the pathogenesis of COVID-19. In addition to regulating immune cell trafficking, CCL2 is an important contributor to COVID-19-associated co-morbidities such as CRS, ARDS, fibrosis, and multi-organ dysfunction. Association of elevated CCL2 levels with COVID-19 severity, further underscores its prognostic value. Furthermore, the CCL2/CCR2 axis constitutes an attractive therapeutic target, which is currently under investigation through multiple clinical trials world-wide. Therefore, a comprehensive molecular understanding of the host response to infection may contribute to developing anti-inflammatory treatment strategies that might complement antiviral agents in severe cases. Future endeavours will be important to elucidate whether adjunct CCL2 blocking strategies can improve therapeutic outcomes in tandem with other therapeutic approaches recommended as COVID-19 treatment regimens. Currently, an ongoing clinical trial is being investigated, the CCR2/CCR5 blocker cenicriviroc (ClincialTrials.gov identifier NCT04500418). However, it will be important to conduct in-depth mechanistic studies involving preclinical animal models of SARS CoV-2 infections to identify potential new drug targets for the treatment of COVID-19, but foremost to initiate large-scale clinical trials for the various CCL2/CCL5 blockers established in the clinics to test their efficacy and safety among moderate and severe COVID-19 patients.

Author Contributions

Abdul Wahid Ansari: writing–original draft, writing–review and editing. **Fareed Ahmad:** writing–review and editing. **Majid Ali Alam:** writing–review and editing. **Thesni Raheed:** writing–review and editing. **Ahmed Zaqout:** writing–review and editing. **Muna Al-Maslamani:** writing–review and editing. **Aamir Ahmad:** writing–review and editing. **Joerg Buddenkotte:** writing–review and editing. **Abdullatif Al-Khal:** writing–review and editing. **Martin Steinhoff:** writing–review and editing.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable because all data analysed in this review are from publicly available published articles.

References

1. F. Wu, S. Zhao, B. Yu, et al., "A New Coronavirus Associated With Human Respiratory Disease in China," *Nature* 579, no. 7798 (2020): 265–269, https://doi.org/10.1038/s41586-020-2008-3.

2. P. Zhou, X.-L. Yang, X.-G. Wang, et al., "A Pneumonia Outbreak Associated With a New Coronavirus of Probable Bat Origin," *Nature* 579, no. 7798 (2020): 270–273, https://doi.org/10.1038/s41586-020-2012-7.

3. R. Yan, Y. Zhang, Y. Li, L. Xia, Y. Guo, and Q. Zhou, "Structural Basis for the Recognition of SARS-CoV-2 by Full-Length Human ACE2," *Science* 367, no. 6485 (2020): 1444–1448, https://doi.org/10.1126/science.abb2762.

4. G. Chen, D. Wu, W. Guo, et al., "Clinical and Immunological Features of Severe and Moderate Coronavirus Disease 2019," *Journal of Clinical Investigation* 130, no. 5 (2020): 2620–2629, https://doi.org/10.1172/jci137244.

5. P. Mehta, D. F. McAuley, M. Brown, E. Sanchez, R. S. Tattersall, and J. J. Manson, "COVID-19: Consider Cytokine Storm Syndromes and Immunosuppression," *Lancet (London, England)* 395, no. 10229 (2020): 1033–1034, https://doi.org/10.1016/s0140-6736(20)30628-0.

6. C. Huang, Y. Wang, X. Li, et al., "Clinical Features of Patients Infected With 2019 Novel Coronavirus in Wuhan, China," *Lancet (London, England)* 395, no. 10223 (2020): 497–506, https://doi.org/10.1016/s0140-6736(20)30183-5.

7. A. Mantovani and S. Sozzani, "Chemokines," *Lancet (London, England)* 343, no. 8902 (1994): 923, https://doi.org/10.1016/s0140-6736(94)90048-5.

8. A. D. Luster, "Chemokines—Chemotactic Cytokines That Mediate Inflammation," *New England Journal of Medicine* 338, no. 7 (1998): 436–445, https://doi.org/10.1056/nejm199802123380706.

9. D. Rossi and A. Zlotnik, "The Biology of Chemokines and Their Receptors," *Annual Review of Immunology* 18, no. 1 (2000): 217–242, https://doi.org/10.1146/annurev.immunol.18.1.217.

10. A. W. Ansari, N. Bhatnagar, O. Dittrich-Breiholz, M. Kracht, R. E. Schmidt, and H. Heiken, "Host Chemokine (C-C Motif) Ligand-2 (CCL2) Is Differentially Regulated in HIV Type 1 (HIV-1)-Infected Individuals," *International Immunology* 18 (2006): 1443–1451.

11. M. Mengozzi, C. De Filippi, P. Transidico, et al., "Human Immunodeficiency Virus Replication Induces Monocyte Chemotactic Protein-1 in Human Macrophages and U937 Promonocytic Cells," *Blood* 93, no. 6 (1999): 1851–1857, https://doi.org/10.1182/blood.v93.6.1851.406k12_1851_1857.

12. A. W. Ansari, H. Heiken, M. Moenkemeyer, and R. E. Schmidt, "Dichotomous Effects of C-C Chemokines in HIV-1 Pathogenesis," *Immunology Letters* 110 (2007): 1–5, https://doi.org/10.1016/j.imlet.2007.02.012.

13. W. G. Glass, H. F. Rosenberg, and P. M. Murphy, "Chemokine Regulation of Inflammation During Acute Viral Infection," *Current Opinion in Allergy and Clinical Immunology* 3, no. 6 (2003): 467–473, https://doi.org/10.1097/00130832-200312000-00008.

14. K. Matsushima, C. G. Larsen, G. C. DuBois, and J. J. Oppenheim, "Purification and Characterization of a Novel Monocyte Chemotactic and Activating Factor Produced by a Human Myelomonocytic Cell Line," *Journal of Experimental Medicine* 169, no. 4 (1989): 1485–1490, https://doi.org/10.1084/jem.169.4.1485.

15. T. Yoshimura, E. A. Robinson, S. Tanaka, E. Appella, and E. J. Leonard, "Purification and Amino Acid Analysis of Two Human Monocyte Chemoattractants Produced by Phytohemagglutinin-Stimulated Human Blood Mononuclear Leukocytes," *Journal of Immunology* 142, no. 6 (1989): 1956–1962, https://doi.org/10.4049/jimmunol.142.6.1956.

16. I. F. Charo, S. J. Myers, A. Herman, C. Franci, A. J. Connolly, and S. R. Coughlin, "Molecular Cloning and Functional Expression of Two Monocyte Chemoattractant Protein 1 Receptors Reveals Alternative Splicing of the Carboxyl-Terminal Tails," *Proceedings of the National Academy of Sciences of the U S A* 91, no. 7 (1994): 2752–2756, https://doi.org/10.1073/pnas.91.7.2752.

17. M. W. Carr, S. J. Roth, E. Luther, S. S. Rose, and T. A. Springer, "Monocyte Chemoattractant Protein 1 Acts as a T-Lymphocyte Chemoattractant," *Proceedings of the National Academy of Sciences* 91, no. 9 (1994): 3652–3656, https://doi.org/10.1073/pnas.91.9.3652.

18. M. Gschwandtner, R. Derler, and K. S. Midwood, "More Than Just Attractive: How CCL2 Influences Myeloid Cell Behavior Beyond Chemotaxis," *Frontiers in Immunology* 10 (2019), https://doi.org/10.3389/fimmu.2019.02759.

19. M. Liao, Y. Liu, J. Yuan, et al., "Single-Cell Landscape of Bronchoalveolar Immune Cells in Patients With COVID-19," *Nature Medicine* 26, no. 6 (2020): 842–844, https://doi.org/10.1038/s41591-020-0901-9.

20. P. A. Szabo, P. Dogra, J. I. Gray, et al., "Longitudinal Profiling of Respiratory and Systemic Immune Responses Reveals Myeloid Cell-Driven Lung Inflammation in Severe COVID-19," *Immunity* 54, no. 4 (2021): 797–814.e6, https://doi.org/10.1016/j.immuni.2021.03.005.

21. D. Wang, B. Hu, C. Hu, et al., "Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China," *JAMA* 323, no. 11 (2020): 1061–1069, https://doi.org/10.1001/jama.2020.1585.

22. M. Del Cornò, A. Michienzi, A. Masotti, et al., "CC Chemokine Ligand 2 Down-Modulation by Selected Toll-Like Receptor Agonist Combinations Contributes to T Helper 1 Polarization in Human Dendritic Cells," *Blood* 114, no. 4 (2009): 796–806, https://doi.org/10.1182/blood-2009-01-199406.

23. P. Allavena, G. Bianchi, D. Zhou, et al., "Induction of Natural Killer Cell Migration by Monocyte Chemotactic Protein−1, −2 and −3," *European Journal of Immunology* 24, no. 12 (1994): 3233–3236, https://doi.org/10.1002/eji.1830241249.

24. M. J. Butcher and E. V. Galkina, "wRAPping Up Early Monocyte and Neutrophil Recruitment in Atherogenesis via Annexin A1/FPR2 Signaling," *Circulation Research* 116, no. 5 (2015): 774–777, https://doi.org/10.1161/circresaha.115.305920.

25. J. H. Wain, J. A. Kirby, and S. Ali, "Leucocyte Chemotaxis: Examination of Mitogen-Activated Protein Kinase and Phosphoinositide 3-Kinase Activation by Monocyte Chemoattractant Proteins-1, -2, -3 and -4," *Clinical and Experimental Immunology* 127, no. 3 (2002): 436–444, https://doi.org/10.1046/j.1365-2249.2002.01764.x.

26. S. J. Turner, J. Domin, M. D. Waterfield, S. G. Ward, and J. Westwick, "The CC Chemokine Monocyte Chemotactic Peptide-1 Activates Both the Class I p85/p110 Phosphatidylinositol 3-Kinase and the Class II PI3K-C2alpha," *Journal of Biological Chemistry* 273, no. 40 (1998): 25987–25995, https://doi.org/10.1074/jbc.273.40.25987.

27. M. Mellado, J. M. Rodríguez-Frade, A. Aragay, et al., "The Chemokine Monocyte Chemotactic Protein 1 Triggers Janus Kinase 2 Activation and Tyrosine Phosphorylation of the CCR2B Receptor," *Journal of Immunology* 161 (1998): 805–813.

28. S. L. Deshmane, S. Kremlev, S. Amini, and B. E. Sawaya, "Monocyte Chemoattractant Protein-1 (MCP-1): An Overview," *Journal of Interferon & Cytokine Research* 29, no. 6 (2009): 313–326, https://doi.org/10.1089/jir.2008.0027.

29. T. J. Standiford, S. L. Kunkel, S. H. Phan, B. J. Rollins, and R. M. Strieter, "Alveolar Macrophage-Derived Cytokines Induce Monocyte

Chemoattractant Protein-1 Expression From Human Pulmonary Type II-Like Epithelial Cells," *Journal of Biological Chemistry* 266, no. 15 (1991): 9912–9918, https://doi.org/10.1016/s0021-9258(18)92905-4.

30. R. M. Strieter, R. Wiggins, S. H. Phan, et al., "Monocyte Chemotactic Protein Gene Expression by Cytokine-Treated Human Fibroblasts and Endothelial Cells," *Biochemical and Biophysical Research Communications* 162, no. 2 (1989): 694–700, https://doi.org/10.1016/0006-291x(89)92366-8.

31. B. P. Barna, J. Pettay, G. H. Barnett, P. Zhou, K. Iwasaki, and M. L. Estes, "Regulation of Monocyte Chemoattractant Protein-1 Expression in Adult Human Non-Neoplastic Astrocytes Is Sensitive to Tumor Necrosis Factor (TNF) or Antibody to the 55-kDa TNF Receptor," *Journal of Neuroimmunology* 50, no. 1 (1994): 101–107, https://doi.org/10.1016/0165-5728(94)90220-8.

32. H. Sahin and H. E. Wasmuth, "Chemokines in Tissue Fibrosis," *Biochimica et Biophysica Acta, Molecular Basis of Disease* 1832, no. 7 (2013): 1041–1048, https://doi.org/10.1016/j.bbadis.2012.11.004.

33. C. Baeck, X. Wei, M. Bartneck, et al., "Pharmacological Inhibition of the Chemokine C-C Motif Chemokine Ligand 2 (Monocyte Chemoattractant Protein 1) Accelerates Liver Fibrosis Regression by Suppressing Ly-6C(+) Macrophage Infiltration in Mice," *Hepatology* 59, no. 3 (2014): 1060–1072, https://doi.org/10.1002/hep.26783.

34. X. Liu, A. M. Das, J. Seideman, et al., "The CC Chemokine Ligand 2 (CCL2) Mediates Fibroblast Survival Through IL-6," *American Journal of Respiratory Cell and Molecular Biology* 37, no. 1 (2007): 121–128, https://doi.org/10.1165/rcmb.2005-0253oc.

35. C. M. Hogaboam, C. L. Bone-Larson, S. Lipinski, et al., "Differential Monocyte Chemoattractant Protein-1 and Chemokine Receptor 2 Expression by Murine Lung Fibroblasts Derived From Th1- and Th2-Type Pulmonary Granuloma Models," *Journal of Immunology* 163, no. 4 (1999): 2193–2201, https://doi.org/10.4049/jimmunol.163.4.2193.

36. C. E. Rose, Jr., S. J. Sung, and S. M. Fu, "Significant Involvement of CCL2 (MCP-1) in Inflammatory Disorders of the Lung," *Microcirculation* 10, no. 3-4 (2003): 273–288, https://doi.org/10.1080/mic.10.3-4.273.288.

37. N. Banba, T. Nakamura, M. Matsumura, H. Kuroda, Y. Hattori, and K. Kasai, "Possible Relationship of Monocyte Chemoattractant Protein-1 With Diabetic Nephropathy," *Kidney International* 58, no. 2 (2000): 684–690, https://doi.org/10.1046/j.1523-1755.2000.00214.x.

38. B. M. Beker, M. G. Corleto, C. Fieiras, and C. G. Musso, "Novel Acute Kidney Injury Biomarkers: Their Characteristics, Utility and Concerns," *International Urology and Nephrology* 50, no. 4 (2018): 705–713, https://doi.org/10.1007/s11255-017-1781-x.

39. N. G. Frangogiannis, S. Shimoni, S. M. Chang, et al., "Evidence for an Active Inflammatory Process in the Hibernating Human Myocardium," *American Journal of Pathology* 160, no. 4 (2002): 1425–1433, https://doi.org/10.1016/s0002-9440(10)62568-0.

40. N. G. Frangogiannis, O. Dewald, Y. Xia, et al., "Critical Role of Monocyte Chemoattractant Protein-1/CC Chemokine Ligand 2 in the Pathogenesis of Ischemic Cardiomyopathy," *Circulation* 115, no. 5 (2007): 584–592, https://doi.org/10.1161/circulationaha.106.646091.

41. B. Patel, S. S. Bansal, M. A. Ismahil, et al., "CCR2(+) Monocyte-Derived Infiltrating Macrophages Are Required for Adverse Cardiac Remodeling During Pressure Overload," *JACC: Basic to Translational Science* 3, no. 2 (2018): 230–244, https://doi.org/10.1016/j.jacbts.2017.12.006.

42. M. Ranjbar, A. Rahimi, Z. Baghernejadan, A. Ghorbani, and H. Khorramdelazad, "Role of CCL2/CCR2 Axis in the Pathogenesis of COVID-19 and Possible Treatments: All Options on the Table," *International Immunopharmacology* 113 (2022): 109325, https://doi.org/10.1016/j.intimp.2022.109325.

43. A. W. Ansari, H. Heiken, D. Meyer-Olson, and R. E. Schmidt, "CCL2: A Potential Prognostic Marker and Target of Anti-Inflammatory Strategy in HIV/AIDS Pathogenesis," *European Journal of Immunology* 41, no. 12 (2011): 3412–3418, https://doi.org/10.1002/eji.201141676.

44. P. Cinque, L. Vago, M. Mengozzi, et al., "Elevated Cerebrospinal Fluid Levels of Monocyte Chemotactic Protein-1 Correlate With HIV-1 Encephalitis and Local Viral Replication," *AIDS* 12, no. 11 (1998): 1327–1332, https://doi.org/10.1097/00002030-199811000-00014.

45. A. W. Ansari, D. Meyer-Olson, and R. E. Schmidt, "Selective Expansion of Pro-Inflammatory Chemokine CCL2-Loaded CD14+CD16+ Monocytes Subset in HIV-Infected Therapy Naïve Individuals," *Journal of Clinical Immunology* 33, no. 1 (2013): 302–306, https://doi.org/10.1007/s10875-012-9790-0.

46. S. Fahey, E. Dempsey, and A. Long, "The Role of Chemokines in Acute and Chronic Hepatitis C Infection," *Cellular and Molecular Immunology* 11, no. 1 (2014): 25–40, https://doi.org/10.1038/cmi.2013.37.

47. P. T. Morrison, M. Sharland, L. H. Thomas, et al., "Chemokine-Receptor Upregulation and Disease Severity in Respiratory Syncytial Virus Infection," *Clinical Immunology* 128, no. 1 (2008): 85–93, https://doi.org/10.1016/j.clim.2008.03.460.

48. J. Zhou, D. Wang, R. Gao, et al., "Biological Features of Novel Avian Influenza A (H7N9) Virus," *Nature* 499, no. 7459 (2013): 500–503, https://doi.org/10.1038/nature12379.

49. J. Guo, F. Huang, J. Liu, et al., "The Serum Profile of Hypercytokinemia Factors Identified in H7N9-Infected Patients Can Predict Fatal Outcomes," *Scientific Reports* 5, no. 1 (2015): 10942, https://doi.org/10.1038/srep10942.

50. K. L. Lin, S. Sweeney, B. D. Kang, E. Ramsburg, and M. D. Gunn, "CCR2-Antagonist Prophylaxis Reduces Pulmonary Immune Pathology and Markedly Improves Survival During Influenza Infection," *Journal of Immunology* 186, no. 1 (2011): 508–515, https://doi.org/10.4049/jimmunol.1001002.

51. H. K. W. Law, C. Y. Cheung, H. Y. Ng, et al., "Chemokine Up-Regulation in SARS-Coronavirus-Infected, Monocyte-Derived Human Dendritic Cells," *Blood* 106, no. 7 (2005): 2366–2374, https://doi.org/10.1182/blood-2004-10-4166.

52. J. M. Nicholls, L. L. M. Poon, K. C. Lee, et al., "Lung Pathology of Fatal Severe Acute Respiratory Syndrome," *Lancet (London, England)* 361, no. 9371 (2003): 1773–1778, https://doi.org/10.1016/s0140-6736(03)13413-7.

53. S. Rosseau, P. Hammerl, U. Maus, et al., "Phenotypic Characterization of Alveolar Monocyte Recruitment in Acute Respiratory Distress Syndrome," *American Journal of Physiology – Lung Cellular and Molecular Physiology* 279, no. 1 (2000): L25–L35, https://doi.org/10.1152/ajplung.2000.279.1.l25.

54. K. W. Tsang, P. L. Ho, G. C. Ooi, et al., "A Cluster of Cases of Severe Acute Respiratory Syndrome in Hong Kong," *New England Journal of Medicine* 348, no. 20 (2003): 1977–1985, https://doi.org/10.1056/nejmoa030666.

55. L. He, Y. Ding, Q. Zhang, et al., "Expression of Elevated Levels of Pro-Inflammatory Cytokines in SARS-CoV-Infected ACE2+ Cells in SARS Patients: Relation to the Acute Lung Injury and Pathogenesis of SARS," *Journal of Pathology* 210, no. 3 (2006): 288–297, https://doi.org/10.1002/path.2067.

56. C. Y. Cheung, L. L. M. Poon, I. H. Y. Ng, et al., "Cytokine Responses in Severe Acute Respiratory Syndrome Coronavirus-Infected Macrophages In Vitro: Possible Relevance to Pathogenesis," *Journal of Virology* 79, no. 12 (2005): 7819–7826, https://doi.org/10.1128/jvi.79.12.7819-7826.2005.

57. L. Gu, S. Tseng, R. M. Horner, C. Tam, M. Loda, and B. J. Rollins, "Control of TH2 Polarization by the Chemokine Monocyte Chemoattractant Protein-1," *Nature* 404, no. 6776 (2000): 407–411, https://doi.org/10.1038/35006097.

58. Y.-T. Yen, F. Liao, C.-H. Hsiao, C.-L. Kao, Y.-C. Chen, and B. A. Wu-Hsieh, "Modeling the Early Events of Severe Acute Respiratory Syndrome Coronavirus Infection In Vitro," *Journal of Virology* 80, no. 6 (2006): 2684–2693, https://doi.org/10.1128/jvi.80.6.2684-2693.2006.

59. M. Hoffmann, H. Kleine-Weber, S. Schroeder, et al., "SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor," *Cell* 181, no. 2 (2020): 271–280.e8, https://doi.org/10.1016/j.cell.2020.02.052.

60. W. Li, M. J. Moore, N. Vasilieva, et al., "Angiotensin-Converting Enzyme 2 Is a Functional Receptor for the SARS Coronavirus," *Nature* 426, no. 6965 (2003): 450–454, https://doi.org/10.1038/nature02145.

61. M. Merad and J. C. Martin, "Pathological Inflammation in Patients With COVID-19: A Key Role for Monocytes and Macrophages," *Nature Reviews Immunology* 20, no. 6 (2020): 355–362, https://doi.org/10.1038/s41577-020-0331-4.

62. A. S. S. Girija, E. M. Shankar, and M. Larsson, "Could SARS-CoV-2-Induced Hyperinflammation Magnify the Severity of Coronavirus Disease (COVID-19) Leading to Acute Respiratory Distress Syndrome?" *Frontiers in Immunology* 11 (2020): 1206, https://doi.org/10.3389/fimmu.2020.01206.

63. Y. Chi, Y. Ge, B. Wu, et al., "Serum Cytokine and Chemokine Profile in Relation to the Severity of Coronavirus Disease 2019 in China," *Journal of Infectious Diseases* 222, no. 5 (2020): 746–754, https://doi.org/10.1093/infdis/jiaa363.

64. D. Blanco-Melo, B. E. Nilsson-Payant, W.-C. Liu, et al., "Imbalanced Host Response to SARS-CoV-2 Drives Development of COVID-19," *Cell* 181, no. 5 (2020): 1036–1045.e9, https://doi.org/10.1016/j.cell.2020.04.026.

65. N. Chen, M. Zhou, X. Dong, et al., "Epidemiological and Clinical Characteristics of 99 Cases of 2019 Novel Coronavirus Pneumonia in Wuhan, China: A Descriptive Study," *Lancet (London, England)* 395, no. 10223 (2020): 507–513, https://doi.org/10.1016/s0140-6736(20)30211-7.

66. S. Wan, Q. Yi, S. Fan, et al., "Relationships Among Lymphocyte Subsets, Cytokines, and the Pulmonary Inflammation Index in Coronavirus (COVID-19) Infected Patients," *British Journal of Haematology* 189, no. 3 (2020): 428–437, https://doi.org/10.1111/bjh.16659.

67. T. Tanaka, M. Narazaki, and T. Kishimoto, "Immunotherapeutic Implications of IL-6 Blockade for Cytokine Storm," *Immunotherapy* 8 (2016): 959–970, https://doi.org/10.2217/imt-2016-0020.

68. M. Bassetti, A. Vena, and D. R. Giacobbe, "The Novel Chinese Coronavirus (2019-nCoV) Infections: Challenges for Fighting the Storm," *European Journal of Clinical Investigation* 50, no. 3 (2020): e13209, https://doi.org/10.1111/eci.13209.

69. C. A. Hunter and S. A. Jones, "IL-6 as a Keystone Cytokine in Health and Disease," *Nature Immunology* 16, no. 5 (2015): 448–457, https://doi.org/10.1038/ni.3153.

70. N. Pathan, C. A. Hemingway, A. A. Alizadeh, et al., "Role of Interleukin 6 in Myocardial Dysfunction of Meningococcal Septic Shock," *Lancet (London, England)* 363, no. 9404 (2004): 203–209, https://doi.org/10.1016/s0140-6736(03)15326-3.

71. A. C. Gordon, P. R. Mouncey, F. Al-Beidh, et al., "Interleukin-6 Receptor Antagonists in Critically Ill Patients With COVID-19," *New England Journal of Medicine* 384, no. 16 (2021): 1491–1502, https://doi.org/10.1056/nejmoa2100433.

72. J. Zhao, W. Cui, and B.-P. Tian, "Efficacy of Tocilizumab Treatment in Severely Ill COVID-19 Patients," *Critical Care* 24, no. 1 (2020): 524, https://doi.org/10.1186/s13054-020-03224-7.

73. F. Khan, T. Tritschler, S. R. Kahn, and M. A. Rodger, "Venous Thromboembolism," *Lancet (London, England)* 398, no. 10294 (2021): 64–77, https://doi.org/10.1016/s0140-6736(20)32658-1.

74. Z. Zhou, L. Ren, L. Zhang, et al., "Heightened Innate Immune Responses in the Respiratory Tract of COVID-19 Patients," *Cell Host & Microbe* 27, no. 6 (2020): 883–890.e2, https://doi.org/10.1016/j.chom.2020.04.017.

75. R. L. Chua, S. Lukassen, S. Trump, et al., "COVID-19 Severity Correlates With Airway Epithelium-Immune Cell Interactions Identified by Single-Cell Analysis," *Nature Biotechnology* 38, no. 8 (2020): 970–979, https://doi.org/10.1038/s41587-020-0602-4.

76. Y.-M. Gao, G. Xu, B. Wang, and B.-C. Liu, "Cytokine Storm Syndrome in Coronavirus Disease 2019: A Narrative Review," *Journal of Internal Medicine* 289, no. 2 (2021): 147–161, https://doi.org/10.1111/joim.13144.

77. R. Chen, L. Sang, M. Jiang, et al., "Longitudinal Hematologic and Immunologic Variations Associated With the Progression of COVID-19 Patients in China," *Journal of Allergy and Clinical Immunology* 146, no. 1 (2020): 89–100, https://doi.org/10.1016/j.jaci.2020.05.003.

78. Z. Xu, L. Shi, Y. Wang, et al., "Pathological Findings of COVID-19 Associated With Acute Respiratory Distress Syndrome," *Lancet Respiratory Medicine* 8, no. 4 (2020): 420–422, https://doi.org/10.1016/s2213-2600(20)30076-x.

79. J.-Y. Chen, K. Qiao, F. Liu, et al., "Lung Transplantation as Therapeutic Option in Acute Respiratory Distress Syndrome for Coronavirus Disease 2019-Related Pulmonary Fibrosis," *Chinese Medical Journal* 133, no. 12 (2020): 1390–1396, https://doi.org/10.1097/cm9.0000000000000839.

80. J. R. Tisoncik, M. J. Korth, C. P. Simmons, J. Farrar, T. R. Martin, and M. G. Katze, "Into the Eye of the Cytokine Storm," *Microbiology and Molecular Biology Reviews* 76, no. 1 (2012): 16–32, https://doi.org/10.1128/mmbr.05015-11.

81. C. Qin, L. Zhou, Z. Hu, et al., "Dysregulation of Immune Response in Patients With Coronavirus 2019 (COVID-19) in Wuhan, China," *Clinical Infectious Diseases* 71, no. 15 (2020): 762–768, https://doi.org/10.1093/cid/ciaa248.

82. Y. Zhou, B. Fu, X. Zheng, et al., "Pathogenic T-Cells and Inflammatory Monocytes Incite Inflammatory Storms in Severe COVID-19 Patients," *National Science Review* 7, no. 6 (2020): 998–1002, https://doi.org/10.1093/nsr/nwaa041.

83. T. Yoshikawa, T. E. Hill, N. Yoshikawa, et al., "Dynamic Innate Immune Responses of Human Bronchial Epithelial Cells to Severe Acute Respiratory Syndrome-Associated Coronavirus Infection," *PLoS One* 5, no. 1 (2010): e8729, https://doi.org/10.1371/journal.pone.0008729.

84. N. Bozorgmehr, S. Mashhouri, E. Perez Rosero, et al., "Galectin-9, a Player in Cytokine Release Syndrome and a Surrogate Diagnostic Biomarker in SARS-CoV-2 Infection," *mBio* 12, no. 3 (2021), https://doi.org/10.1128/mBio.00384-21.

85. S. Shahbaz, N. Bozorgmehr, J. Lu, et al., "Analysis of SARS-CoV-2 Isolates, Namely the Wuhan Strain, Delta Variant, and Omicron Variant, Identifies Differential Immune Profiles," *Microbiology Spectrum* 11, no. 5 (2023): e0125623, https://doi.org/10.1128/spectrum.01256-23.

86. L. Du, M. S. Bouzidi, A. Gala, et al., "Human Galectin-9 Potently Enhances SARS-CoV-2 Replication and Inflammation in Airway Epithelial Cells," *Journal of Molecular Cell Biology* 15, no. 4 (2023), https://doi.org/10.1093/jmcb/mjad030.

87. H. Iwasaki-Hozumi, Y. Maeda, T. Niki, et al., "Plasma N-Cleaved Galectin-9 Is a Surrogate Marker for Determining the Severity of COVID-19 and Monitoring the Therapeutic Effects of Tocilizumab," *International Journal of Molecular Sciences* 24, no. 4 (2023): 3591, https://doi.org/10.3390/ijms24043591.

88. J. C. Burns, "The Etiologies of Kawasaki Disease," *Journal of Clinical Investigation* 134, no. 5 (2024), https://doi.org/10.1172/JCI176938.

89. T. Hara, K. Furuno, K. Yamamura, et al., "Assessment of Pediatric Admissions for Kawasaki Disease or Infectious Disease During the COVID-19 State of Emergency in Japan," *JAMA Network Open* 4 (2021): e214475, https://doi.org/10.1001/jamanetworkopen.2021.4475.

90. A. S. Harahsheh, S. Shah, F. Dallaire, et al., "Kawasaki Disease in the Time of COVID-19 and MIS-C: The International Kawasaki Disease Registry," *Canadian Journal of Cardiology* 40, no. 1 (2024): 58–72, https://doi.org/10.1016/j.cjca.2023.06.001.

91. L. Verdoni, A. Mazza, A. Gervasoni, et al., "An Outbreak of Severe Kawasaki-Like Disease at the Italian Epicentre of the SARS-CoV-2 Epidemic: An Observational Cohort Study," *Lancet (London, England)* 395, no. 10239 (2020): 1771–1778, https://doi.org/10.1016/s0140-6736(20)31103-x.

92. N. Ouldali, M. Pouletty, P. Mariani, et al., "Emergence of Kawasaki Disease Related to SARS-CoV-2 Infection in an Epicentre of the French COVID-19 Epidemic: A Time-Series Analysis," *Lancet Child & Adolescent Health* 4, no. 9 (2020): 662–668, https://doi.org/10.1016/s2352-4642(20)30175-9.

93. F. Esper, E. D. Shapiro, C. Weibel, D. Ferguson, M. L. Landry, and J. S. Kahn, "Association Between a Novel Human Coronavirus and Kawasaki Disease," *Journal of Infectious Diseases* 191, no. 4 (2005): 499–502, https://doi.org/10.1086/428291.

94. M. Pouletty, C. Borocco, N. Ouldali, et al., "Paediatric Multisystem Inflammatory Syndrome Temporally Associated With SARS-CoV-2 Mimicking Kawasaki Disease (Kawa-COVID-19): A Multicentre Cohort," *Annals of the Rheumatic Diseases* 79, no. 8 (2020): 999–1006, https://doi.org/10.1136/annrheumdis-2020-217960.

95. Y. Shikishima, T. Saeki, and N. Matsuura, "Chemokines in Kawasaki Disease: Measurement of CCL2, CCL22 and CXCL10," *Asian Pacific Journal of Allergy & Immunology* 21 (2003): 139–143.

96. M. Terai, T. Jibiki, A. Harada, et al., "Dramatic Decrease of Circulating Levels of Monocyte Chemoattractant Protein-1 in Kawasaki Disease After Gamma Globulin Treatment," *Journal of Leukocyte Biology* 65, no. 5 (1999): 566–572, https://doi.org/10.1002/jlb.65.5.566.

97. M. Wong, E. D. Silverman, and E. N. Fish, "Evidence for RANTES, Monocyte Chemotactic Protein-1, and Macrophage Inflammatory Protein-1 Beta Expression in Kawasaki Disease," *Journal of Rheumatology* 24 (1997): 1179–1185.

98. F. Ahmad, M. Kannan, and A. W. Ansari, "Role of SARS-CoV-2-Induced Cytokines and Growth Factors in Coagulopathy and Thromboembolism," *Cytokine & Growth Factor Reviews* 63 (2022): 58–68, https://doi.org/10.1016/j.cytogfr.2021.10.007.

99. G. Grasselli, T. Tonetti, A. Protti, et al., "Pathophysiology of COVID-19-Associated Acute Respiratory Distress Syndrome: A Multicentre Prospective Observational Study," *Lancet Respiratory Medicine* 8, no. 12 (2020): 1201–1208, https://doi.org/10.1016/s2213-2600(20)30370-2.

100. H. Shi, X. Han, N. Jiang, et al., "Radiological Findings From 81 Patients With COVID-19 Pneumonia in Wuhan, China: A Descriptive Study," *Lancet Infectious Diseases* 20, no. 4 (2020): 425–434, https://doi.org/10.1016/s1473-3099(20)30086-4.

101. W.-J. Guan, Z.-Y. Ni, Y. Hu, et al., "Clinical Characteristics of Coronavirus Disease 2019 in China," *New England Journal of Medicine* 382, no. 18 (2020): 1708–1720, https://doi.org/10.1056/nejmoa2002032.

102. R. Salcedo, M. L. Ponce, H. A. Young, et al., "Human Endothelial Cells Express CCR2 and Respond to MCP-1: Direct Role of MCP-1 in Angiogenesis and Tumor Progression," *Blood* 96, no. 1 (2000): 34–40, https://doi.org/10.1182/blood.v96.1.34.013a49_34_40.

103. Y. Ding, H. Wang, H. Shen, et al., "The Clinical Pathology of Severe Acute Respiratory Syndrome (SARS): A Report From China," *Journal of Pathology* 200, no. 3 (2003): 282–289, https://doi.org/10.1002/path.1440.

104. C. P. Baran, J. M. Opalek, S. McMaken, et al., "Important Roles for Macrophage Colony-Stimulating Factor, CC Chemokine Ligand 2, and Mononuclear Phagocytes in the Pathogenesis of Pulmonary Fibrosis," *American Journal of Respiratory and Critical Care Medicine* 176, no. 1 (2007): 78–89, https://doi.org/10.1164/rccm.200609-1279oc.

105. M. Suga, K. Iyonaga, H. Ichiyasu, N. Saita, H. Yamasaki, and M. Ando, "Clinical Significance of MCP-1 Levels in BALF and Serum in Patients With Interstitial Lung Diseases," *European Respiratory Journal* 14, no. 2 (1999): 376–382, https://doi.org/10.1183/09031936.99.14237699.

106. D. Wendisch, O. Dietrich, T. Mari, et al., "SARS-CoV-2 Infection Triggers Profibrotic Macrophage Responses and Lung Fibrosis," *Cell* 184, no. 26 (2021): 6243–6261.e27, https://doi.org/10.1016/j.cell.2021.11.033.

107. M. N. Sarafi, E. A. Garcia-Zepeda, J. A. MacLean, I. F. Charo, and A. D. Luster, "Murine Monocyte Chemoattractant Protein (MCP)-5: A Novel CC Chemokine That Is a Structural and Functional Homologue of Human MCP-1," *Journal of Experimental Medicine* 185, no. 1 (1997): 99–109, https://doi.org/10.1084/jem.185.1.99.

108. B. B. Moore, J. E. Kolodsick, V. J. Thannickal, et al., "CCR2-Mediated Recruitment of Fibrocytes to the Alveolar Space After Fibrotic Injury," *American Journal Of Pathology* 166, no. 3 (2005): 675–684, https://doi.org/10.1016/s0002-9440(10)62289-4.

109. M. K. Georgakis, J. Bernhagen, L. H. Heitman, C. Weber, and M. Dichgans, "Targeting the CCL2-CCR2 Axis for Atheroprotection," *European Heart Journal* 43, no. 19 (2022): 1799–1808, https://doi.org/10.1093/eurheartj/ehac094.

110. T. M. Behr, X. Wang, N. Aiyar, et al., "Monocyte Chemoattractant Protein-1 Is Upregulated in Rats With Volume-Overload Congestive Heart Failure," *Circulation* 102, no. 11 (2000): 1315–1322, https://doi.org/10.1161/01.cir.102.11.1315.

111. F. Leuschner, G. Courties, P. Dutta, et al., "Silencing of CCR2 in Myocarditis," *European Heart Journal* 36, no. 23 (2015): 1478–1488, https://doi.org/10.1093/eurheartj/ehu225.

112. E. Bush, N. Maeda, W. A. Kuziel, et al., "CC Chemokine Receptor 2 Is Required for Macrophage Infiltration and Vascular Hypertrophy in Angiotensin II-Induced Hypertension," *Hypertension (New York)* 36, no. 3 (2000): 360–363, https://doi.org/10.1161/01.hyp.36.3.360.

113. S. Laurance, F.-R. Bertin, T. Ebrahimian, et al., "Gas6 Promotes Inflammatory (CCR2(hi)CX3CR1(lo)) Monocyte Recruitment in Venous Thrombosis," *Arteriosclerosis, Thrombosis, and Vascular Biology* 37, no. 7 (2017): 1315–1322, https://doi.org/10.1161/atvbaha.116.308925.

114. D. Liu, Y. Cao, X. Zhang, et al., "Chemokine CC-Motif Ligand 2 Participates in Platelet Function and Arterial Thrombosis by Regulating PKCα-P38MAPK-HSP27 Pathway," *Biochimica et Biophysica Acta – Molecular Basis of Disease* 1864, no. 9 (2018): 2901–2912, https://doi.org/10.1016/j.bbadis.2018.05.025.

115. P. K. Henke, C. G. Pearce, D. M. Moaveni, et al., "Targeted Deletion of CCR2 Impairs Deep Vein Thombosis Resolution in a Mouse Model," *Journal of Immunology* 177, no. 5 (2006): 3388–3397, https://doi.org/10.4049/jimmunol.177.5.3388.

116. A. S. Ondracek and I. M. Lang, "Neutrophil Extracellular Traps as Prognostic Markers in COVID-19: A Welcome Piece to the Puzzle," *Arteriosclerosis, Thrombosis, and Vascular Biology* 41, no. 2 (2021): 995–998, https://doi.org/10.1161/atvbaha.120.315633.

117. T. M. Hofbauer, A. S. Ondracek, A. Mangold, et al., "Neutrophil Extracellular Traps Induce MCP-1 at the Culprit Site in ST-Segment Elevation Myocardial Infarction," *Frontiers in Cell and Developmental Biology* 8 (2020): 564169, https://doi.org/10.3389/fcell.2020.564169.

118. F. Tacke, D. Alvarez, T. J. Kaplan, et al., "Monocyte Subsets Differentially Employ CCR2, CCR5, and CX3CR1 to Accumulate Within Atherosclerotic Plaques," *Journal of Clinical Investigation* 117, no. 1 (2007): 185–194, https://doi.org/10.1172/jci28549.

119. D. Nieri, T. Neri, G. Barbieri, et al., "C-C Motive Chemokine Ligand 2 and Thromboinflammation in COVID-19-Associated Pneumonia: A Retrospective Study," *Thrombosis Research* 204 (2021): 88–94, https://doi.org/10.1016/j.thromres.2021.06.003.

120. J. Grune, G. Bajpai, P. T. Ocak, et al., "Virus-Induced Acute Respiratory Distress Syndrome Causes Cardiomyopathy Through Eliciting Inflammatory Responses in the Heart," *Circulation* 150, no. 1 (2024): 49–61, https://doi.org/10.1161/circulationaha.123.066433.

121. Z. R. Korobova, N. A. Arsentieva, N. E. Liubimova, et al., "A Comparative Study of the Plasma Chemokine Profile in COVID-19 Patients Infected With Different SARS-CoV-2 Variants," *International Journal of Molecular Sciences* 23, no. 16 (2022): 9058, https://doi.org/10.3390/ijms23169058.

122. X. Zhu, K. A. Gebo, A. G. Abraham, et al., "Dynamics of Inflammatory Responses After SARS-CoV-2 Infection by Vaccination Status in the USA: A Prospective Cohort Study," *Lancet Microbe* 4, no. 9 (2023): e692–e703, https://doi.org/10.1016/s2666-5247(23)00171-4.

123. F. Coperchini, L. Chiovato, G. Ricci, L. Croce, F. Magri, and M. Rotondi, "The Cytokine Storm in COVID-19: Further Advances in Our Understanding the Role of Specific Chemokines Involved," *Cytokine & Growth Factor Reviews* 58 (2021): 82–91, https://doi.org/10.1016/j.cytogfr.2020.12.005.

124. A. Pum, M. Ennemoser, T. Adage, and A. J. Kungl, "Cytokines and Chemokines in SARS-CoV-2 Infections-Therapeutic Strategies Targeting Cytokine Storm," *Biomolecules* 11, no. 1 (2021): 91, https://doi.org/10.3390/biom11010091.

125. J.-S. Kwon, J. Y. Kim, M.-C. Kim, et al., "Factors of Severity in Patients With COVID-19: Cytokine/Chemokine Concentrations, Viral Load, and Antibody Responses," *American Journal of Tropical Medicine and Hygiene* 103, no. 6 (2020): 2412–2418, https://doi.org/10.4269/ajtmh.20-1110.

126. B. Sierra, A. B. Pérez, E. Aguirre, et al., "Association of Early Nasopharyngeal Immune Markers With COVID-19 Clinical Outcome: Predictive Value of CCL2/MCP-1," *Open Forum Infectious Diseases* 7, no. 10 (2020): ofaa407, https://doi.org/10.1093/ofid/ofaa407.

127. Y. Huang, S. Chen, Z. Yang, et al., "SARS-CoV-2 Viral Load in Clinical Samples From Critically Ill Patients," *American Journal of Respiratory and Critical Care Medicine* 201, no. 11 (2020): 1435–1438, https://doi.org/10.1164/rccm.202003-0572le.

128. Y. Chen, J. Wang, C. Liu, et al., "IP-10 and MCP-1 as Biomarkers Associated With Disease Severity of COVID-19," *Molecular Medicine* 26, no. 1 (2020): 97, https://doi.org/10.1186/s10020-020-00230-x.

129. Z. G. Fridlender, G. Buchlis, V. Kapoor, et al., "CCL2 Blockade Augments Cancer Immunotherapy," *Cancer Research* 70, no. 1 (2010): 109–118, https://doi.org/10.1158/0008-5472.can-09-2326.

130. B.-Z. Qian, J. Li, H. Zhang, et al., "CCL2 Recruits Inflammatory Monocytes to Facilitate Breast-Tumour Metastasis," *Nature* 475, no. 7355 (2011): 222–225, https://doi.org/10.1038/nature10138.

131. H. Raghu, C. M. Lepus, Q. Wang, et al., "CCL2/CCR2, But Not CCL5/CCR5, Mediates Monocyte Recruitment, Inflammation and Cartilage Destruction in Osteoarthritis," *Annals of the Rheumatic Diseases* 76, no. 5 (2017): 914–922, https://doi.org/10.1136/annrheumdis-2016-210426.

132. G. Raghu, F. J. Martinez, K. K. Brown, et al., "CC-Chemokine Ligand 2 Inhibition in Idiopathic Pulmonary Fibrosis: A Phase 2 Trial of Carlumab," *European Respiratory Journal* 46, no. 6 (2015): 1740LP–1750, https://doi.org/10.1183/13993003.01558-2014.

133. J. J. Haringman, D. M. Gerlag, T. J. M. Smeets, et al., "A Randomized Controlled Trial With an Anti-CCL2 (Anti-Monocyte Chemotactic Protein 1) Monoclonal Antibody in Patients With Rheumatoid Arthritis," *Arthritis & Rheumatism* 54, no. 8 (2006): 2387–2392, https://doi.org/10.1002/art.21975.

134. S. Lee, G. Y. Yoon, S. J. Lee, et al., "Immunological and Pathological Peculiarity of Severe Acute Respiratory Syndrome Coronavirus 2 Beta Variant," *Microbiology Spectrum* 10, no. 5 (2022): e0237122, https://doi.org/10.1128/spectrum.02371-22.

135. T. L. Krasnikova, T. I. Arefieva, E. A. Pylaeva, and M. V. Sidorova, "Ingramon, a Peptide Inhibitor of MCP-1 Chemokine, Reduces Migration of Blood Monocytes Stimulated by Glioma-Conditioned Medium," *Bulletin of Experimental Biology and Medicine* 160, no. 4 (2016): 480–482, https://doi.org/10.1007/s10517-016-3201-0.

136. R. J. Cherney, P. Anjanappa, K. Selvakumar, et al., "BMS-813160: A Potent CCR2 and CCR5 Dual Antagonist Selected as a Clinical Candidate," *ACS Medicinal Chemistry Letters* 12, no. 11 (2021): 1753–1758, https://doi.org/10.1021/acsmedchemlett.1c00373.

137. D. C. Files, F. Tacke, A. O'Sullivan, P. Dorr, W. G. Ferguson, and W. G. Powderly, "Rationale of Using the Dual Chemokine Receptor CCR2/CCR5 Inhibitor Cenicriviroc for the Treatment of COVID-19," *PLoS Pathogens* 18, no. 6 (2022): e1010547, https://doi.org/10.1371/journal.ppat.1010547.

138. M. Okamoto, M. Toyama, and M. Baba, "The Chemokine Receptor Antagonist Cenicriviroc Inhibits the Replication of SARS-CoV-2 In Vitro," *Antiviral Research* 182 (2020): 104902, https://doi.org/10.1016/j.antiviral.2020.104902.

139. D. de Zeeuw, P. Bekker, E. Henkel, et al., "The Effect of CCR2 Inhibitor CCX140-B on Residual Albuminuria in Patients With Type 2 Diabetes and Nephropathy: A Randomised Trial," *Lancet Diabetes & Endocrinology* 3, no. 9 (2015): 687–696, https://doi.org/10.1016/s2213-8587(15)00261-2.

140. B. K. Patterson, H. Seethamraju, K. Dhody, et al., "CCR5 Inhibition in Critical COVID-19 Patients Decreases Inflammatory Cytokines, Increases CD8 T-Cells, and Decreases SARS-CoV2 RNA in Plasma by Day 14," *International Journal of Infectious Diseases* 103 (2021): 25–32, https://doi.org/10.1016/j.ijid.2020.10.101.

141. M. Baba, K. Takashima, H. Miyake, et al., "TAK-652 Inhibits CCR5-Mediated Human Immunodeficiency Virus Type 1 Infection In Vitro and Has Favorable Pharmacokinetics in Humans," *Antimicrobial Agents and Chemotherapy* 49, no. 11 (2005): 4584–4591, https://doi.org/10.1128/aac.49.11.4584-4591.2005.

142. M. M. Byron, M. D'Antoni, T. Premeaux, E. Lefebvre, and L. Ndhlovu, "Dual CCR2/CCR5 Antagonism by Cenicriviroc Efficiently Inhibits Both MCP-1 and RANTES Induced Chemokine Receptor Internalization in Murine Pro-Inflammatory Monocytes (CCR6P.221)," *Journal of Immunology* 194, no. 1_Supplement (2015): 187.8, https://doi.org/10.4049/jimmunol.194.supp.187.8.

143. M. Thompson, M. Saag, E. DeJesus, et al., "A 48-Week Randomized Phase 2b Study Evaluating Cenicriviroc Versus Efavirenz in Treatment-Naive HIV-Infected Adults With C-C Chemokine Receptor Type 5-Tropic Virus," *AIDS* 30, no. 6 (2016): 869–878, https://doi.org/10.1097/qad.0000000000000988.

144. S. L. Friedman, V. Ratziu, S. A. Harrison, et al., "A Randomized, Placebo-Controlled Trial of Cenicriviroc for Treatment of Nonalcoholic Steatohepatitis With Fibrosis," *Hepatology* 67, no. 5 (2018): 1754–1767, https://doi.org/10.1002/hep.29477.

145. V. Ratziu, A. Sanyal, S. A. Harrison, et al., "Cenicriviroc Treatment for Adults With Nonalcoholic Steatohepatitis and Fibrosis: Final Analysis of the Phase 2b CENTAUR Study," *Hepatology* 72, no. 3 (2020): 892–905, https://doi.org/10.1002/hep.31108.

146. J. A. O'Halloran, E. R. Ko, K. J. Anstrom, et al., "Abatacept, Cenicriviroc, or Infliximab for Treatment of Adults Hospitalized With COVID-19 Pneumonia: A Randomized Clinical Trial," *JAMA* 330, no. 4 (2023): 328–339, https://doi.org/10.1001/jama.2023.11043.