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Predictive monitoring and therapeutic immune biomarkers in the management of clinical complications of COVID-19

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ABSTRACT

The coronavirus disease-2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), appears with a wide spectrum of mild-to-critical clinical complications. Many clinical and experimental findings suggest the role of inflammatory mechanisms in the immunopathology of COVID-19. Hence, cellular and molecular mediators of the immune system can be potential targets for predicting, monitoring, and treating the progressive complications of COVID-19. In this review, we assess the latest cellular and molecular data on the immunopathology of COVID-19 according to the pathological evidence (e.g., mucus and surfactants), dysregulations of pro- and anti-inflammatory mediators (e.g., cytokines and chemokines), and impairments of innate and acquired immune system functions (e.g., mononuclear cells, neutrophils and antibodies). Furthermore, we determine the significance of immune biomarkers for predicting, monitoring, and treating the progressive complications of COVID-19. We also discuss the clinical importance of recent immune biomarkers in COVID-19, and at the end of each section, recent clinical trials in immune biomarkers for COVID-19 are mentioned.

Abbreviations: AAK-1, activated protein (AP) 2 associated kinase 1; Ab, antibody; ACE, angiotensin-converting enzyme; ACEI, ACE inhibitor; AEC, alveolar epithelial cells; AICD, activation-induced cell death; Ang, angiotensin; APC, antigen-presenting cell; APTT, activated partial thromboplastin time; ARB, Ang II receptor blocker; ARDS, acute respiratory distress syndrome; AT1R, Ang II receptor type 1; BALF, bronchoalveolar lavage fluid; BEC, bronchial epithelial cell; BTK, Bruton tyrosine kinase; C3 and C5, complement proteins; ChiCTR, chinese clinical trial registry; CCL, chemokine (C-C motif) ligand; CCR, chemokine (C-C motif) ligand receptor; C-GAS-STING, cGAMP binds to stimulator of interferon genes; COVID-19, coronavirus disease-2019; CP, convalescent plasma; CQ, chloroquine; CRP, c-reactive protein; CRS, cytokine release syndrome; CT, computerized tomography; CTL, cytotoxic T lymphocyte; CXCL, chemokine (C-X-C motif) ligand; CXCR, chemokine (C-X-C motif) ligand receptor; DIC, disseminated intravascular coagulation; dsRNA, double-stranded RNA; ESR, erythrocyte sedimentation rate; FcγR, Fc gamma receptor; Fio2, fraction of inspired oxygen; GAK, G-associated kinase; GM-CSF, granulocyte-macrophage colony-stimulating factor; GzmB, granzyme B; HCQ, hydroxychloroquine; HLA, human leukocyte antigen; HLH, hemophagocytic lymphohistiocytosis; HR-2, heptad repeat region-2; ICU, admissions to intensive care units; IFITM, interferon-induced transmembrane protein; IFN, interferon; IL, interleukin; IP-10, interferon (IFN)-γ inducible protein-10; IRF-1, IFN regulatory factor 1; ISG, induction of IFN-stimulated gene; IVIg, intravenous immunoglobulin; JAK, janus kinase; JUN, c-Jun N-terminal kinases; KL-6, Krebs von den Lungen-6; LAG-3, lymphocyte-activation gene 3; LDH, lactate dehydrogenase; LWR, lymphocyte-to-WBCs ratio; LY6E, lymphocyte antigen 6 family member E; mAb, monoclonal antibody; MCP, monocyte chemoattractant protein; MDA-5, melanoma differentiation-associated protein-5; MERS, middle east respiratory syndrome; MIP, macrophage inflammatory proteins; MOF, multiple organ failure; MUC, mucin; nAb, neutralizing antibody; N, nucleocapsid; NCT, clinicaltrials.gov identifier; NFkB, nuclear factor kappa-light-chain-enhancer of activated B cells; NK, natural killer; NKRF, NFkB repressing factor; NLR, neutrophil-to-lymphocyte ratio; NLRP3, nod-like receptor protein 3; NSP, non-structural proteins; NTD, N terminal domain; ORF-1ab, open reading frame 1ab; Pao2, partial pressure of oxygen; PCT, procalcitonin; PD1, programmed cell death protein 1; PKR, protein kinase R; PLR, platelet-to-lymphocyte ratios; PRR, pattern recognition receptors; PT, prothrombin time; RA, rheumatoid arthritis; RAS, regulator of the renin-angiotensin system; RBD, receptor-binding domain; rBP-C33Leu, recombinant surfactant protein C analogue; rhACE2-Fc fusion proteins, recombinant human ACE2-Fc fusion proteins; rhIL-1ra, recombinant human IL-1 receptor; RIG, retinoic acid-inducible gene-I; rIL7, recombinant IL-7; RLR, RIG-I-like receptors; RT-qPCR, real time-quantitative PCR; S1PR, sphingosine-1-phosphate receptors; SAA, serum amyloid A; SARS, severe acute respiratory; SARS-CoV, severe acute respiratory syndrome coronavirus; scFv, single-chain variable fragment; siRNA, small interfering RNA; SP, surfactant; SPo2, arterial oxygen saturation; S-protein, spike-protein; srhACE2, soluble recombinant human (srh)ACE2; ssRNA, single-stranded RNA; TGF, transforming growth factor; Th, helper T cell; TIM-3, T-cell immunoglobulin mucin 3; TLR, toll like receptor; TMPRSS2, transmembrane serine protease 2; TNF-α, tumor necrosis factor; Treg, regulatory T cells; VEGF, vascular endothelial growth factor; WBC, white blood cell.

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1. Introduction

The coronavirus disease-2019 (COVID-19) is an infectious disease caused by a new β-coronavirus called severe acute respiratory syndrome coronavirus (SARS-CoV)-2 [1]. The first case of SARS-CoV-2 infection was reported in December 2019 from Wuhan, China, and rapidly became a pandemic disease around the world. By September 30, 2020, 33,502,430 cases of COVID-19 had been confirmed by laboratory tests, of which 1,004,421 had passed away [2]. Based on the results of previous studies, SARS-CoV-2 expands at the original $R_0 = 2.2–2.6$ expansion rate, meaning that on average each infected individual has the potential to transmit the infection to 2.2–2.6 persons. Compared to other respiratory viruses from the same family, the mortality rate is lower in patients with COVID-19 (2.8 %) than in patients with severe acute respiratory syndrome (SARS) (9.19 %) or Middle East respiratory syndrome (MERS) (34.4 %); however, COVID-19 is more lethal than the seasonal flu (less than 0.1 %) [3,4].

SARS-CoV-2 infection appears with a broad spectrum of clinical manifestations. Up to 81 % of patients are asymptomatic or have mild pneumonia symptoms such as fever, cough, fatigue, and myalgia. In 14 % of cases, viral pneumonia is seen with severe symptoms such as dyspnea, respiratory rate ≥30 beats/min, partial pressure of oxygen (PaO2)/fraction of inspired oxygen (FiO2) <300, arterial oxygen saturation (SpO2) ≤93 %, and lung infiltrates >50 %. Finally, 5 % of patients demonstrate critical symptoms such as acute respiratory distress syndrome (ARDS), shock, and multiple organ failure (MOF) which, in 2.3 % of cases, result in death [5]. In addition, COVID-19 has a high phenotypic similarity with other clinical conditions such as respiratory viral infections, lung contusion and pulmonary complications after sepsis [6]. Hence, the early diagnosis and treatment of COVID-19 is impossible or very difficult when relying only on the clinical symptoms of the disease.

Whereas chest computerized tomography (CT) scan is a confirmatory method with high sensitivity for the diagnosis and monitoring of patients with COVID-19, its specificity is low [7]. A chest CT scan demonstrates ground-glass opacity around the shadow and pleural effusion in the peripheral and lower portion of the lungs, which diffuses to the center and eventually throughout the lungs along with the progression of the disease [6]. According to the computable score defined for chest CT scans, higher scores are associated with more advanced forms of COVID-19 [6]. Fortunately, the low specificity of the CT scan can be compensated by the real time-quantitative PCR (RT-qPCR) technique. Thus, SARS-CoV-2 open reading frame (ORF)-1ab and nucleocapsid (N) genes are detected in specimens of bronchoalveolar lavage, endotracheal aspirate, nasopharyngeal swab, and sputum using specific primers and probes [7]. Although clinical symptoms along with CT scan and RT-qPCR results largely confirm the diagnosis of COVID-19, major problems exist in the prediction, monitoring, and treatment of COVID-19 complications before their incidence.

Many clinical and experimental findings have suggested the role of cellular and molecular changes in the immunopathology of COVID-19 complications, as summarized in Fig. 1. Accordingly, it has been proposed that the investigation of cellular and molecular changes in the immune system can be very helpful for identifying biomarkers related

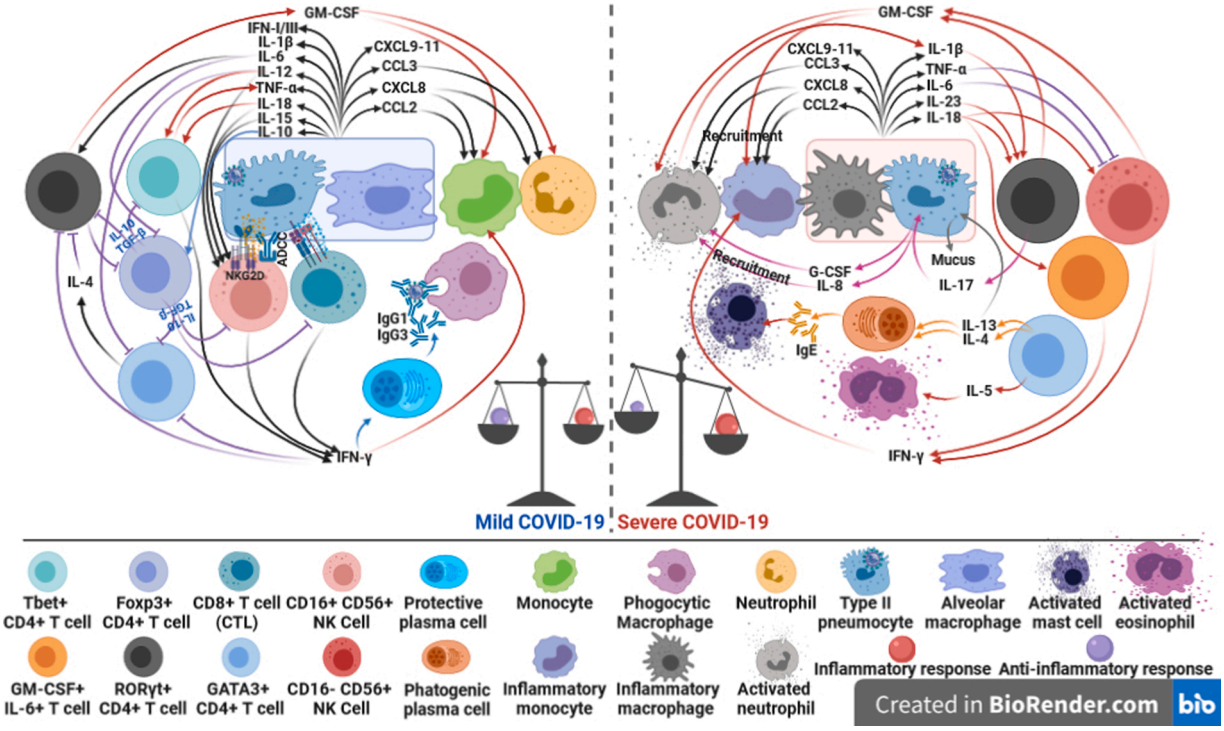

Fig. 1. The interplay between cells and immune mediators may impact deviation to the healing (mild COVID-19) or toxic (Severe COVID-19) responses. Lung imunopathology in COVID-19 is a result of imbalance in the inflammatory and anti-inflammatory responses. As it is suggested in the left diagram, there is a balance between pro-inflammatory (red arrows) and anti-inflammatory (purple arrows) responses in the lung of mild COVID-19 cases. Type I and III IFNs and IL-1β, IL-6, IL-12, IL-15, IL-18 and IL-10 as well as CCL2/3 and CXCL8-11 produced by alveolar macrophages and pneumocyte type II cells recruit and activate monocyte/macrophages, Tbet+ CD4+ T cells, CD16+ CD56+ NK cells, CTLs and IgG1/3 producing plasma cells. In this balanced immune response, replication of virus is inhibited, virus is neutralized and the scene is cleared from viral particles and apoptotic cells. The presence of Foxp3+ CD4+ Treg cells and GATA3+ CD4+ Th2 cells which produce IL-10 and TGF-β and counteract Tbet+ CD4+ Th1 responses results in a protective and healing response. On the other hand, compromised Foxp3+ CD4+ Treg cells and GATA3+ CD4+ Th2 responses, or hyperactivation of alveolar macrophages favors activation of IL-6+ GM-CSF+ CD4+ T cell/macrophage, CD16- CD56+ NK cell, and RORγt+ CD4+ Th17/neutrophil/monocyte axes as well as Th2 and mast cell pro-inflammatory cytokines secretion, and IgE production by plasma cells (Right diagram). These responses are associated with capillary permeability and damage into the interstitial space and the alveolar tissue.
ADCC, antibody-dependent cellular cytotoxicity; CCL, chemokine (C-C motif) ligand; CXCL, chemokine (C-X-C motif) ligand; GM-CSF, granulocyte-macrophage colony-stimulating factor; G-CSF, granulocyte-colony stimulating factor; IFN, interferon; IL, interleukin; TGF, transforming growth factor; TNF, tumor necrosis factor.

to the prediction, monitoring, and treatment of COVID-19 complications [8,9].

The aim of the current review is to describe the latest information on currently proposed immune biomarkers and their roles in the pathobiology of COVID-19 to identify potential targets for predicting, monitoring, and treating adverse clinical outcomes in patients, which are summarized in Tables 1 & 2 . In addition, we summarize the clinical significance of recent immune biomarkers in COVID-19 along with the ongoing clinical trials on immune biomarkers for treating the progressive complications of COVID-19 (Table 3).

2. Immune system biomarkers

2.1. Tissue biomarkers

2.1.1. Angiotensin-converting enzyme (ACE) 2 and angiotensin (Ang) II

The depletion of ACE2 from infected respiratory cells membranes and subsequent elevation of ACE2 extracellular domain in blood circulation are due to ACE2 shedding or decreased expression that can be a potential predictive marker of response to treatment and pulmonary complications in COVID-19 patients [10]. Although the depletion or blockade of ACE2 reduces virus entry to alveolar epithelial cells (AECs), the increasing Ang II will have more destructive effects on lung tissue [11]. On the contrary, ACE inhibitors (ACEI) and/or Ang II receptor blockers (ARBs) reduce destructive effects of Ang II on lung tissue, while they promote the expression of ACE2 receptors which potentially increase SARS-CoV-2 entry to cells [11,12]. Nevertheless, Vaduganathan et al. suggest that ACEIs/ARBs may be beneficial rather than harmful in COVID-19 patients with lung injury [13]. Hence, SARS-CoV invasion blockers such as anti-ACE2 antibodies (Abs), recombinant human (rh) ACE2-Fc fusion proteins, soluble recombinant human (srh)ACE2, and specific ACE2 inhibitors along with Ang II-dependent lung damage inhibitors such as ARBs, ACEI, srACE2, and srAng 1-7 could be promising therapeutic approaches in COVID-19 [14,15]. However, to relieve COVID-19 symptoms, whether blockade of the virus entry by ACE2 inhibitors is more effective or harnessing the destructive effects of Ang II by inhibiting ACE1 and Ang II receptor type 1 (AT1R) requires further investigation. Currently, two clinical trials, namely NCT04311177 and NCT04312009, are underway to address this question.

2.1.2. Mucins (MUCs)

The lung pathology of COVID-19 patients results in an increase in mucinous secretions. Accordingly, the large amounts of mucus observed in the airways of COVID-19 patients, which lead to mucosal thickening and can be considered as a prognostic factor for severe complications [16]. MUC-1 and MUC-5AC are main glycoproteins in the airways that are markedly increased in the aspirated sputum from the tracheas of COVID-19 patients. These mucins play important roles in microvascular infarction and interstitial fibrosis by inducing the infiltration of mononuclear cells into inflamed lungs [17,18]. Krebs von den Lungen (KL)-6, as a sub molecule of MUC-1, is expressed on the surface of bronchial epithelial cells (BECs) and AEC-II, and is released into serum in respiratory epithelial cell injuries [19]. Hence, the assessment of KL-6 serum level is useful for detecting the presence of ARDS, evaluating disease activity, and predicting clinical outcomes [19]. A previous study has suggested that KL-6 levels in bronchoalveolar lavage fluid (BALF) are associated with the severity of lung injury and neutrophilic inflammation [20]. Although many reference centers across Europe use KL-6 for predicting, monitoring, and treating the pulmonary symptoms of COVID-19 patients, recent independent studies showed no significant difference in KL-6 levels between COVID-19 patients with and without clinical symptoms [21,22]. A phase II trial is underway to evaluate the safety and efficacy of fostamatinib in COVID-19 patients. Fostamatinib is a spleen tyrosine kinase (SYK) inhibitor which reduces MUC-1 protein abundance [23]. Conversely, Plante et al. suggested a protective role of MUC-4 in female mice (not observed in male mice) with SARS disease

Table 1
Prognostic and monitoring immune biomarkers in COVID-19.

Biomarkers	Mechanistics pathways
ACE2	Increases virus entry, Ang 1−7 and Ang 1−9, and decreases Ang II [11,12,13]
MUC-1 and 5AC	Promote infiltration of immune cells, microvascular infarction, and interstitial fibrosis [17,18,19,21]
Surfactants	Stabilize the alveolar surface [25], support innate-immunity [25], and prevent viral attachment [26]
IL-6	Recruits and activates inflammatory cells [30], induces apoptosis of T cells through the Fas/FasL pathway [33], and impairs cytotoxicity of NK cells [118]
IL-1β	Induces inflammatory cell activation [30] and elevates vascular permeability [76]
IL-18	Promotes the activation of T and NK cells, and the production of IFN-γ [83] and antibodies [85]
TNF-α	Recruits and activates inflammatory cells [30], downregulates NKp46 from the surface of NK cells [119], contributes to NK cell differentiation [119], inhibits T cell recirculation by promoting retention in lymphoid organs and attachment to endothelium [98]
GM-CSF	Recruits and activates neutrophils, monocytes and macrophages [30]
IFN-I	Stimulates NK cell activation, macrophages proliferation, HLA-I expression and IFN production [53], and inhibits T cell recirculation by promoting retention in lymphoid organs and attachment to endothelium [98]
WBC counts and NLR/PLR	Elevated WBC, NLR and PLR are due to the increased neutrophils accompanied by the decrease in lymphocytes, monocytes, dendritic cells, and eosinophils counts in peripheral blood, which are caused by the absorption of these cells into inflamed tissue [65]
T cells	Decline in total CD4+ and CD8+ T cells [114,122], γδ T cells [102,132], Treg cells [75] and memory CD4+ T cells [75], as well as increase in frequency of polyclonal GM-CSF+ IL-6+ CD4+ T cells [31] and CCR4+/CCR6+ Th17 cells [18], naïve CD4+ T cell and activated CD4+/CD8+ T cells [75] associated with high levels of inflammation
Monocytes and macrophages	High frequency of CD14+ HLA-DR+ IL-1β and Ficolin-1+ monocyte-derived macrophages and decrease in tissue reparative alveolar macrophages in the BALF associated with the severity of lung injury [29,104]
Neutrophile	Infiltration of neutrophils to lungs and differentiation to inflammatory neutrophils under the effects of inflammatory mediators [29] and Ang II [15], which induce further tissue injuries by activating various inflammatory mechanisms [108]
Eosinophils, basophils and mast cell	Decrease in frequencies of eosinophils and basophils in pripheral blood [75,109] and increase in infiltration of Th2/eosinophil [110] and mast cells in lungs tissue associated with higher release of chymase, protease, triptase and inflamatory mediators in the inflamed site [15,29,111]
NK cell	Decrease in frequencies [18,75] and cytotoxicity [116], as well as increase in cytokine production [116] and exhaustion markers [95,117] in NK cells promote detrimental inflammation without effective immune responses against virus.
Anti-SARS-CoV-2 N/S-IgM/IgG Abs	N/S-IgM Abs appear in the first week and decrease in the third week after symptoms onset in mild disease, while N/S-IgG Abs increase in the second week and are detectable for 60 days [141]. All antibodies are produced earlier in patients with severe disease than in patients with mild disease except S-IgG Ab [142]. N/S-IgM and N-IgG Abs correlate with increased lung complications while high levels of S-IgG Ab are associated with decreased inflammation [142].

ACE, angiotensin-converting enzyme; Ang, angiotensin; BALF, bronchoalveolar lavage fluid; GM-CSF, granulocyte-macrophage colony-stimulating factor; HLA, human leukocyte antigen; IFN, interferon; IL, interleukin; MUC, mucin; NLR, neutrophil-to-lymphocyte ratio; N, nucleocapsid; PLR, platelet-to-lymphocyte ratios; S, spike-protein; Th, helper T cell; TNF, tumor necrosis factor; WBC, white blood cell.

which can be explained by its anti-apoptotic and anti-inflammatory properties [24].

2.1.3. Surfactants (SPs)

SPs that originate from airway cells and AEC-II are also potential prognostic and therapeutic targets for respiratory outcomes in COVID-19 patients [25]. SPs are key factors in stabilizing the alveolar surface at air-liquid interaction sites and in supporting lung innate immunity [25]. SP-A and SP-D can bind to the carbohydrate moieties on the SARS-CoV-1 spike (*S*)-protein and prevent their attachment to the host cells. In this regard, SP-D has a higher binding affinity than SP-A [26]. A trial on adult New Zealand rabbits model with ARDS showed improved lung function when treated with low amounts of synthetic lung surfactant based recombinant surfactant protein C analogue (rSP-C33Leu) in a similar manner to natural surfactants [27]. Although BALF levels of SPs (particularly SP-D) are positively associated with good prognoses in lung diseases, the increased serum levels of SP-D in SARS-CoV-1 infections are considered to be caused by pulmonary leakage and can be a poor prognosis marker for respiratory system disorders and death [28].

2.2. Cytokine/Chemokine biomarkers

Cytokine upregulation, known as cytokine storm, is documented in SARS-CoV-2 infection. Tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-8, IL-10, IL-17, IL-18, granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon (IFN)-γ inducible protein-10 (IP-10), monocyte chemoattractant protein (MCP)-1, macrophage inflammatory proteins (MIP)-1A, and MIP-1B are parts of a wide array of inflammatory mediators that increase as a cytokine storm in the sera of COVID-19 patients [6,29]. Cytokine storm is the major cause of injuries in the lung and other tissues of COVID-19 patients through recruitment and activation of immune-inflammatory cells [30]. A study has shown the correlation between high levels of pro-inflammatory cytokines and chemokines and the progression of disease complications [29]. These inflammatory mediators, which are produced from certain subtypes of CD4+ T cells (GM-CSF+ IL-6+ CD4+ T) [31], pathogenic NK cells (CD16- CD56+ NK) [32], monocytes and macrophages (CD169+ macrophages) [33], can be potential targets for predicting, monitoring, and treating disease complications in COVID-19.

Although glucocorticoids that are often used in inflammatory diseases such as multiple sclerosis and rheumatoid arthritis (RA) may be considered a more effective therapeutic method for suppression of systemic inflammation in COVID-19 patients, conflicting results have been reported on their benefits in SARS-CoV-2 infection. One study has shown no significant correlation between corticosteroid use and the duration of virus clearance, length of hospital stay, symptom duration, severity of complications, and mortality rate [34]. Another study, however, has indicated that high doses of corticosteroids in the long term can increase the duration of virus clearance, admissions to intensive care units (ICUs), and mortality risk [35]. In addition, it has been reported that the early low-dose administration of corticosteroids significantly improves SpO2 and chest CT results and reduces mortality rates [36,37]. In the interim clinical management guidance released by the WHO for patients with COVID-19 pneumonia, low-to-moderate daily doses of corticosteroids are recommended [38], whereas most of the current data do not support the long-term benefits of corticosteroids.

One of the possible approaches to subsiding cytokine storms is to prevent their signaling pathways. In this regard, Janus kinase (JAK) inhibitors including baricitinib, ruxolitinib, and tofacitinib might be candidate targets in the inhibition of cytokine storms [39]. In addition, baricitinib blocks activated protein (AP) 2 associated kinase (AAK)-1 and G-associated kinase (GAK) and might also regulate the viral endocytosis of SARS-CoV-2 [40]. Assuming that both properties of baricitinib can be utilized in COVID-19, clinical trials NCT04321993, NCT04340232, and NCT04421027 for barcitinib monotherapy, NCT04401579 for baricitinib/remdesivir dual therapy, and NCT04320277 and NCT04358614

Table 2
Therapeutic immune biomarkers in COVID-19.

Biomarkers	Intervention	Mechanistic pathway
ACE2	Anti-ACE2 Abs, rhACE2-Fc fusion, srhACE2, and ACE2 inhibitors [14,15]	Blocking virus entry
ACE/Ang II	ACE inhibitors and srACE2 [13, 14,15]	Decreasing Ang II synthesis, and increasing Ang 1−7 and Ang 1−9 synthesis
Ang 1−7/ 1−9	srAng 1−7 and srAng 1−9 [14, 15]	Increasing Ang 1−7 and Ang 1−9 synthesis
AT1R	Ang II receptor blockers [13]	blocking AT1R signaling
MUC	SYK inhibitor (Fostamatinib) [23]	Reducing MUC-1 synthesis
	MUC-4 [24]	Anti-apoptotic and anti-inflammatory properties
Surfactants	SP-A and SP-D [26]	Preventing viral attachment to the host cells
Type I IFNs	In early phase: IFN-α2 [56], IFN-β [57] and IFN-α2b [58]	Increasing NK cell cytotoxicity, increasing proliferation of macrophages and NK cells, and enhancing the expression of HLA-I and IFN-I
	In late phase: IFN-α/β receptor blockers and antagonists [61]	Preventing excessive inflammatory responses
C3a/C5a	C3 inhibitors (AMY-101), anti-C5 mAb (eculizumab and ravulizumab), and anti-C5a mAb (IFX-1) [89,90]	Inhibiting complement activation and monocyte/ neutrophil migration to the sites of inflammation
IL-6	Tocilizumab (anti-IL-6R mAb), sarilumab (anti-IL-6R mAb) and siltuximab (anti-IL-6 mAb) [39,66,67]	Inhibiting the recruitment and activation of inflammatory cell, suppressing the apoptosis of T cells and increasing perforin and granzyme B production
	Colchicine [41]	Suppressing the activation of inflammasome and the formation of microtubule
TNF-α	TNF-α blockers [73] and anti-TNF-α [72,74]	Decreasing the expression of inflammatory mediators and adhesion molecules
	Colchicine [41]	Suppressing the activation of inflammasome and the synthesis of TNF-α
Il-1β	Anakinra (IL-1ra) [79,80,81]	Preventing the recruitment and activation of immune inflammatory cell and decreasing vascular permeability and leakage
IL-18	Tadekinig-α (nIL-18P) [87] and rIL-18BP [88]	Suppressing the activation of T and NK cells and the production of IFN-γ
GM-CSF	Namilumab, mavrilimumab and otilimab [31]	Inhibiting the recruitment and activation of neutrophils
IL-7	rIL-7 [83,137]	Promoting the expansion of lymphocytes, inhibiting apoptosis, reversal of T cell exhaustion, and expression of cell adhesion molecules
CCR2	siRNA-mediated silencing of CCR2 [107]	Decreasing macrophage recruitment to the sites of inflammation
NK cell	CYNK-001 [120]	Direct killing of infected cells and the induction of immune responses
anti-SARS-CoV-2 mAbs	CP [144,145,146], IVIg [147, 148,150], anti-RBD nAb [140, 151,152], ACE2-Fc and RBD-Fc fusions [155], anti-SARS-CoV-2 scFv [156]	Blocking the fusion, entry, and replication of the coronavirus

ACE, angiotensin-converting enzyme; Ang, angiotensin; AT1R, Ang II receptor type 1; C3a/C5a, complement proteins, CCR, chemokine (C-C motif) ligand receptor; CP, convalescent plasma; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; IVIg, intravenous immunoglobulin, mAb, monoclonal antibody; MUC, mucin; RBD, receptor-binding domain; rIL-7, recombinant IL-7; rIL-18BP, recombinant IL-18 binding protein; rhACE2-Fc fusion proteins, recombinant human ACE2-Fc fusion proteins; rhIL-1ra, recombinant human IL-1α; scFv, single-chain variable fragment; srhACE2,

soluble recombinant human; SP, surfactants; SYK, spleen tyrosine kinase; Th, helper T cell; TNF, tumor necrosis factor.

for baricitinib/lopinavir/ritonavir triple therapy are ongoing. In this regard, Contini et al. reported that fever, PaO2/FiO2, CRP, ICU transfer, length of hospital stay were reduced in the baricitinib-treated group compared with placebo-treated group (NCT04358614). Furthermore, NCT04362137, NCT04404361, and NCT04332042 are ongoing trials to address the possible use of ruxolitinib, pacritinib, and tofacitinib, respectively, in the treatment of COVID-19.

Tyrosine kinase inhibitors such as acalabrutinib and abivertinib that bind to Bruton tyrosine kinase (BTK) receptor and inhibit the phosphorylation of the receptor can be additional therapeutic agents for the treatment of moderate-to-severe COVID-19 with progressive cytokine storm. Accordingly, NCT04380688 and NCT04440007 are two clinical trials to evaluate the effectiveness of acalabrutinib and abivertinib in inhibition of cytokine storm, respectively.

Colchicine is another anti-inflammatory drug that has been registered for COVID-19 treatment (trials NCT04322682, NCT04328480, and NCT04326790). The mechanism of action of colchicine is to suppress the generation of microtubules, which would result in the inhibition of mobility, adhesion, and degranulation of immune cells. Furthermore, colchicine suppresses inflammasome activation and the synthesis of TNF-α and IL-6 [41].

Nevertheless, the most effective treatment for COVID-19 can be based on synchronic inhibition of viral proliferation and systemic inflammation. Accordingly, in vitro studies have demonstrated that chloroquine (CQ) and hydroxychloroquine (HCQ) are effective in controlling SARS-CoV-2 infection by their antiviral and anti-inflammatory properties. The antiviral effects of CQ and HCQ are mediated by inhibition of endosomal maturation, which sequestrates virion particles in endolysosomes [42,43]. In addition, both medications suppress the presentation of antigen by antigen-presenting cells (APCs), the activation of T helper 1 (Th1) cells and macrophages, the synthesis of RNAs and proteins in thymocytes, and the signaling of toll-like receptors (TLRs), RIG-I-like receptors (RLRs) and cGAS-STING in immune cells [44,45]. Despite extensive studies on the effects of CQ and HCQ in COVID-19 patients, conflicting results have been obtained. A clinical trial without control group (untreated patients) in France has shown that HCQ in combination with azithromycin results in the reduction of disease duration, severity of pneumonia, and radiological abnormalities in COVID-19 patients [46]. Later, another study investigated the effects of HCQ on COVID-19 patients with hypoxic pneumonia in comparison with untreated patients (no-HCQ group) and did not observe any decrease in the rate of ICU admission or mortality in patients [47]. In two other randomized clinical trials (RCTs), Chen et al. reported controversial results. In an RCT (ChiCTR2000029559) on 62 patients with mild COVID-19, clinical symptoms were resolved one day earlier in patients who received 400 mg HCQ for 5 days (HCQ group) than in the no-HCQ group [48]. In a smaller RCT (NCT04261517) in which treatment continued for 7 days, no significant increase in negative PCR results or improvement of symptoms was observed [49]. In addition, one independent study in patients with severe COVID-19 who had received high-dose HCQ (600 mg/days) for 10 days showed poor results [50]. Furthermore, a meta-analysis on the therapeutic effects of HCQ in patients with COVID-19 showed no clinical benefits [51].

Sphingosine-1-phosphate receptors (S1PRs) are the natural anti-inflammatory molecules that significantly reduce cytokine storm caused by influenza virus infection [52]. Therefore, S1PRs stimulation may be a potential therapeutic approach for reducing inflammatory responses in COVID-19 patients. Hence, siponimod (a S1PR5 modulator) and fingolimod (a S1PR1, 3 and 5 modulator) can be candidate drugs for the treatment of COVID-19 complications. NCT04280588 is an ongoing clinical trial that is investigating the therapeutic effects of fingolimod in COVID-19 patients.

Another possible approach to predicting, monitoring, and treating COVID-19 complications would be the controlled application or administration of inflammatory cytokines or their inhibitors. The most common cytokines that are considered in this approach are discussed below.

2.2.1. Interferons (IFNs)

Type I and III IFNs are at the forefront of defense against viral infections and play critical roles in the induction of innate and adaptive immune responses. IFN-α/β antiviral function is mediated by several mechanisms, including promoting natural killer (NK) cell cytotoxicity, increasing macrophages proliferation, enhancing MHC-I expression, and elevating IFN production [53]. Type I IFNs (IFN-α/β) not only promote immune response to viral infection, but may also worsen the condition by increasing inflammation. Accordingly, it has been shown that high serum levels of IFN-α/β are associated with poor outcomes in SARS patients [54]. Type III IFN (IFN-λ), on the other hand, can induce antiviral effects without exacerbating inflammation [55]. In addition to the type of IFN, the timing of their production and their kinetic would be of importance. Accordingly, Trouillet-Assant et al. reported that COVID-19 patients who were able to control their disease demonstrated the highest levels of IFN-α2 on days 8 to 10 of symptom onset, which decreased after day 10 along with IL-6. Conversely, patients with advanced COVID-19 had very low serum levels of IFN-α2 on days 8 to 10 of symptom onset, but IL-6 remained high after day 10, which was associated with lung lesions and fatal outcomes [56]. However, IFN-β and IFN-λ were undetectable in the same patients [56]. Another study on mice models of MERS-CoV infection showed that early administration of IFN-β facilitated virus clearance, while delayed application of IFN-β can cause a cytokine storm and adverse complications [57]. It has also been shown that IFN-α2b administration with ribavirin can be effective in the treatment of MERS-CoV infection in the early phase [58]. In contrast, Arabi et al. observed no significant improvement in the outcomes of MERS patients who received type I IFNs along with ribavirin [59]. The data suggested that IFNs can play a therapeutic/preventive or a pathogenic role depending on their kinetics of production during the disease course [60]. Based on these reports, the late stages of COVID-19 may be the best time for the administration of IFN-α/β receptor blockers or antagonists to prevent excessive inflammatory responses [61]. However, in the early stages, rhIFN-β1 and IFN-α along with corticosteroids provided excellent results in the improvement of SARS-induced complications [62]. Hence, the efficacy and safety of IFN-α2b/rintatolimod and IFN-β-1α/remdesivir in COVID-19 patients are currently under investigation in two clinical trials registered as NCT04379518 and NCT04492475, respectively.

2.2.2. IL-6

IL-6 is a master pro-inflammatory cytokine and is considered to be a very valuable biomarker of systemic inflammation. The half-life of IL-6 is longer than that of other cytokines such as IL-1β, IL-8, GM-CSF, and TNF-α in protein levels [63]. Increased levels of IL-6 have been shown to be associated with higher levels of IFN-γ, GM-CSF, IL-2, IL-7, and IL-23; immune cell recruitment; Th17 differentiation; inflammasome activation; and cytokine release syndrome (CRS) [55]. Therefore, IL-6 may play a key role in the progression of clinical symptoms of COVID-19 and can be used as a potential immune biomarker for predicting and monitoring disease complications. Accordingly, previous studies have demonstrated that elevated serum levels of IL-6 are related to the increase in the rates of hospital admission, severity of symptoms, and death in COVID-19 patients [37,64]. Furthermore, the relationship between increased serum levels of IL-6, D-dimer (fibrin degradation products), and ferritin and the outcomes of COVID-19 have already been confirmed [65]. The combined use of IL-6 levels, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), ferritin, serum amyloid A (SAA), procalcitonin (PCT), cystatin C, cholinesteras, lactate dehydrogenase (LDH), D-dimer, prothrombin time (PT), and activated partial thromboplastin time (APTT) provide a more accurate measure of

Table 3
Recent clinical trials in immune biomarkers for preventing and treating the progressive complications of COVID-19.

Biomarkers	Intervention	Clinical Trials	Phase	Status
AT1R	AT1R inhibitors (Losartan)	NCT04311177	II	Recruiting
		NCT04312009		
	Jak1/2 inhibitor (Baricitinib)/Lopinavir/Ritonavir	NCT04320277	II/III	Not yet Recruiting
		NCT04358614	II/III	Completed
	Jak1/2 inhibitor (Baricitinib)/Remedsivir	NCT04401579	III	Active-Not Recruiting
Jak1/Jak2		NCT04321993	II	Recruiting
	Jak1/2 inhibitor (Baricitinib)	NCT04340232	II/III	Not yet Recruiting
		NCT04421027	III	Recruiting
	Jak1/2 inhibitor (Tofacitinib)	NCT04332042	II	Not yet Recruiting
	Jak1/2 inhibitor (Ruxolitinib)	NCT04362137	III	Recruiting
	Jak1/2 inhibitor (Pacritinib)	NCT04404361		
BTK	BTK inhibitor (Acalabrutinib)	NCT04380688	II	Active-Not Recruiting
	BTK inhibitor (Abivertinib)	NCT04440007		Not yet Recruiting
	Tubulin beta chain inhibitor (Colchicine)	NCT04322682	III	Recruiting
		NCT04328480		
		NCT04326790	II	Recruiting
Cytokine storm	Hydroxychloroquine	ChiCTR2000029740	IV	Recruiting
		ChiCTR2000029559		
		NCT04261517	III	Completed
	S1PR1, 3 and 5 modulator (Fingolimod)	NCT04280588	II	Recruiting
IFNs	IFN-α2b/Rintatolimod	NCT04379518	I & II	Recruiting
	IFN-β-1α/Remdesivir	NCT04492475	III	Recruiting
	anti-IL-6R mAb (Tocilizumab)	NCT04335071	II	Recruiting
		NCT04315480	II	Active-Not Recruiting
		NCT04331795	II	Completed
		NCT04317092	II	Recruiting
		NCT04320615	III	Completed
IL-6		NCT04372186	III	Active-Not Recruiting
	anti-IL-6R mAb (Tocilizumab)/Remdesivir	NCT04409262	III	Recruiting
	anti-IL-6R mAb (Tocilizumab)/Azithromycin/ Hydroxychloroquine	NCT04332094	II	Recruiting
	anti-IL-6R mAb (Sarilumab)	NCT04315298	II & III	Active-Not recruiting
	anti-IL-6R mAb (Sarilumab)/Azithromycin/ Hydroxychloroquine	NCT04341870	II & III	Suspended
	anti-IL-6R mAb (Tocilizumab)/anti-IL-6 mAb (Siltuximab)/IL-1R antagonist (Anakinra)	NCT04330638	III	Recruiting
IL-1β	IL-1R antagonist (Anakinra) /anti-IL-6R mAb (Tocilizumab)	NCT04339712	II	Recruiting
	anti-GM-CSF receptor-α mAb (Mavrilimumab)	NCT04397497	II	Not yet Recruiting
		NCT04463004	II	Recruiting
		NCT04399980		
GM-CSF		NCT04447469	II & III	Recruiting
	anti-GM-CSF mAb (Gimsilumab)	NCT04351243	II	Recruiting
	anti-GM-CSF mAb (Lenzilumab)	NCT04351152	III	Recruiting
	anti-GM-CSF mAb (Otilimab)	NCT04376684	II	Recruiting
	AMY-1 (C3 inhibitor agents 01)	NCT03694444	I and II	Recruiting
C3 and C5	anti-C5 mAbs (Eculizumab)	NCT04288713	Not mention	Available
	anti-C5 mAbs (Ravulizumab)	NCT04369469	III	Recruiting
		NCT04390464	IV	Recruiting
	anti-C5a mAbs (IFX-1)	NCT04333420	II/III	Recruiting
CCR5	anti-CCR5 mAb (Leronlimab)	NCT04343651	II	Active-Not recruiting
		NCT04347239	II/III	Recruiting
IL-7	Recombinant IL-7 (rIL-7)	NCT04407689	II	Recruiting
		NCT04379076		
		NCT04498325	I	Not yet Recruiting
		NCT04426210	II	Not yet Recruiting
		NCT04442178		
anti-SARS-CoV-2 mAbs	VIR-7831	NCT04545060	II/III	Recruiting
	REGN-COV2	NCT04425629	I/II	Recruiting
	LY-CoV555/ LY-CoV016	NCT04427501	II	Recruiting
	JS-016	NCT04441918	I	Recruiting
	STI-1499	NCT04454398	I	Not yet Recruiting
	AZD7442	NCT04507256	I	Recruiting
NK cell	Allogeneic NK cells (CYNK-001)	NCT04365101	I/II	Recruiting
Allogenic viral-specific T cell	Partially HLA-matched SARS-CoVSTs	NCT04401410	I	Not yet Recruiting

AT1R, Ang II receptor type 1; BTK, Bruton tyrosine kinase; C3 and C5, complement proteins; CCR, chemokine (C-C motif) ligand receptor; ChiCTR, chinese clinical trial registry; GM-CSF, granulocyte-macrophage colony- stimulating factor; HLA, human leukocyte antigen; IFN, interferon; IL, interleukin; IL-6R. interleukin-6 receptor; mAb, monoclonal antibodies; Jak, janus kinase; NCT, clinicaltrials.gov identifier; NK, natural killer; rhuGM-CSF, human recombinant GM-CSF; S1PR, sphingosine-1-phosphate receptors.

poor prognosis in COVID-19 patients [6,37,65]. Whereas high levels of IL-6, D-dimer, and PT are associated with ARDS-dependent deaths in COVID-19 patients, high levels of IL-6 and D-dimer concomitant with low levels of PT are linked with disseminated intravascular coagulation (DIC)-dependent deaths [42,64]. IL-6 can also be a potential therapeutic target to reduce the detrimental responses of the immune system in COVID-19. Tocilizumab and sarilumab, two anti-IL-6 receptor monoclonal antibodies (mAbs), and siltuximab, an anti-IL-6 mAb, are IL-6 signaling pathway inhibitors with different properties that have been considered for use in severe-to-critical stages of COVID-19. The first data from China [66] and France [67] showed that tocilizumab is effective in treating severe complications in COVID-19 patients. Recently, several randomized, placebo-controlled phase III clinical trials such as NCT04372186 (EMPACTA), NCT04320615 (COVACTA), and NCT04409262 (REMDACTA) have showed conflicting results on the safety and efficacy of tocilizumab along with standard care in COVID-19 patients pneumonia. While, EMPACTA trial reported tocilizumab (plus standard care) was associated with improved respiratory function as well as reduce mortality, CONVACTA trial did not show improved clinical status in tocilizumab-treated patients compared with those who received placebo. Conflicted results are more evident in other studies. In a study on 239 severe COVID-19 patients who received tocilizumab plus standard care, cytokine storm was reduced compared with tocilizumab-untreated patients, but there was no significant difference in the mortality rate between the two groups [68]. Conversely, another study reported reduced inflammation and mortality after a single 400 mg dose of tocilizumab in severe COVID-19 patients [69]. In addition, several clinical trials including NCT04335071, NCT04315480, NCT04331795, NCT04317092, ChiCTR2000029765, and ChiCTR2000030196 for the use of tocilizumab, NCT04332094 for the use of tocilizumab/azithromycin/HCQ and NCT04330638 for the use of tocilizumab/siltuximab/anakinra in the treatment of COVID-19 complications are ongoing.

In association with clinical trials of sarilumab in COVID-19 patients, a multicenter, double-blind, phase II/III clinical trial was registered to determine the therapeutic effects of sarilumab (plus standard care) in patients with severe COVID-19 in the U.S. [70]. In phase III of this trial, sarilumab only modestly enhanced the treatment. Despite that, another trial such as NCT04341870, is studying the therapeutic effects of sarilumab plus azithromycin, HCQ and standard care in COVID-19 patients.

2.2.3. TNF-α

TNF-α is an inflammatory cytokine in the acute phase of inflammatory diseases that increases along with IL-6 and IL-10 in the serum and tissue of COVID-19 patients and is negatively correlated with T cell frequency [71]. In addition, serum levels of TNF-α are associated with severity of symptoms in COVID-19 patients [6]. Hence, there are some FDA (US) approved and off-label anti-TNF-α therapy that suggest TNF-α can be an appropriate target in COVID-19 [72]. Studies have shown that TNF-α blockers decrease IL-6 and IL-1β, adhesion molecules, and vascular endothelial growth factor (VEGF), which are the major factors in induction of capillary permeability [73]. Previous studies on the anti-TNF-α therapy of severe respiratory syncytial virus and influenza in mice suggest a rationale for the advantages of anti-TNF-α therapy in reducing some of the inflammatory processes that occur during viral pneumonia, such as COVID-19 pneumonia [74]. However, due to the high probability of opportunistic infections in anti-TNF therapy of inflammatory disease, it is necessary to perform pre-clinical trials on COVID-19.

2.2.4. IL-1β

IL-1β is another pro-inflammatory cytokine that increases in SARS-CoV-2 infection [6,75]. While IL-1β plays an important role in hematopoiesis, inflammation, and repair in steady state conditions, it increases vascular permeability and leakage in inflammatory diseases such as RA [76]. In relation to SARS-CoV-2 infection, Gong et al. found no correlation between IL-1β serum levels and disease severity in a cross-sectional study [77]. However, a previous study has shown that ion channel-forming M protein and ORF8b from SARS-CoV are stimulators for Nod-like receptor protein (NLRP)-3 that promote the production and release of IL-1β and IL-18 by activating caspase-1 [78]. Accordingly, one of the promising treatments for reducing inflammatory responses in COVID-19 can be neutralization of IL-1β by the IL-1R natural antagonist (IL-1ra), as is observed in inflammatory diseases such as RA [79]. Two clinical trials in Italy [80] and France [81] have shown that in patients who received high doses of anakinra along with standard treatments (hydroxychloroquine, lopinavir/ritonavir) and standard care, respiratory function significantly improved as well as CRP leves and mortality rates reduced within 21 days. In addition, NCT04339712 and NCT04330638 trials have been registered to evaluate further the effectiveness of anakinra/tocilizumab dual therapy and tocilizumab/siltuximab/anakinra triple therapy, respectively.

2.2.5. IL-18

Studies have shown that IL-18 is a component of cytokine storm and increases during SARS-CoV-2 infection, thereby playing a role in the immunopathology of COVID-19 [82,83]. The majority of IL-18 is produced as a premature precursor by mononuclear cells. Similar to IL-1β, this precursor is then cleaved by caspase-1 and is converted to mature and active IL-18 [84]. IL-18 in combination with other cytokines of the cytokine storm, such as IL-12 and IL-15, play important roles in the activation of T and NK cells as well as the production of IFN-γ [83]. Based on the model presented by Wen et al., IL-18 might play a major role in the production of antibodies by mediating the interaction between B and dendritic cells in COVID-19 patients with late recovery [85]. The high levels of IL-18 in sera and/or inflammatory tissues of patients with Still's disease are good indicators of disease activity with therapeutic potential [86]. Accordingly, the successful use of Tadekinig-α (nIL-18 binding protein) for the treatment of Still's disease [87] as well as the effectiveness of rIL-18BP for the treatment of a girl with life-threatening hemophagocytic lymphohistiocytosis (HLH) [88] have nominated IL-18BP as a potential candidate for COVID-19 treatment. However, there is no clinical evidence for this suggestion, and clinical trials are needed to evaluate the efficacy and safety of IL-18BPs in COVID-19.

2.2.6. GM-CSF

GM-CSF is one of the inflammatory mediators involved in the cytokine storm of COVID-19 which is released by GM-CSF+ IFN-γ+ Th1 cells, CD14+ CD16+ GM-CSF+ macrophages, and human pulmonary microvascular endothelial cells. It has been suggested that blocking GM-CSF signaling may inhibit complications of the virus. Therefore, GM-CSF can be a potential target for the monitoring and treatment of COVID-19 [31]. Hence, gimsilumab, lenzilumab, and otilimab (multiple anti-GM-CSF mAbs) are currently in the clinical trial phase (NCT04351243, NCT04351152 and NCT04376684, respectively) for the treatment of COVID-19. In addition, NCT04397497, NCT04463004, NCT04399980, and NCT04447469 are four new clinical trials purposed to investigate the efficacy of mavrilimumab (a human anti-GM-CSF receptor-α mAb) in COVID-19. These clinical trials reported that mavrilimumab along with oxygen therapy, assisted ventilation, and adjuvant therapy (HCQ, AZT, lopinavir–ritonavir) was beneficial for COVID-19 patients with systemic hyper-inflammation.

2.2.7. Other cytokines

Studies have shown IL-2 [6], IL-2R [77], IL-4 [85], IL-10 [6,77], IL-8 [77], chemokine (C-X-C motif) ligand 9–11 (CXCL9-11), MCP-1, MIP-1A, and chemokine (C-C motif) ligand 5 (CCL5) [71] are other immune system mediators that their increased levels can be associated with the severity of clinical symptoms in COVID-19 patients. Evidently, these studies are limited and further studies are needed to determine the predictive and therapeutic power of these inflammatory mediators.

2.3. Complement system biomarkers

Recent observations have suggested that activation of the complement system (C3 and C5 depletion), as a first line defense system against pathogens, can contribute to ARDS symptoms of coronavirus diseases [89]. In addition, the analyses of lung biopsy specimens in patients with severe COVID-19 have shown that tissue deposition of C3a and C5a fragments of complement proteins increase during disease progression. Hence complement proteins can be considered as prognostic and therapeutic indicators in COVID-19 [90]. The results of clinical trials on C3 inhibitor agents such as AMY-101 (NCT03694444), anti-C5 mAbs such as eculizumab (NCT04288713) and ravulizumab (NCT04369469 and NCT04390464), and anti-C5a mAb such as IFX-1 (NCT04333420) have augmented hopes for COVID-19 therapies. These therapeutic methods reduce inflammatory responses by inhibiting the activity of the distal complement components and preventing the formation of the membrane attack complex, as well as decreasing inflammatory cytokine levels and suppressing monocyte/neutrophil migration into the lungs [89,90]. The very short half-life of complement mediators is the main hurdle in using them as biomarkers. However, serum and tissue changes of complement mediators along with clinical inflammatory indicators such as CRP, IL-6, and ferritin can be helpful in predicting complications of COVID-19 [91,92].

2.4. Cell biomarkers

Clinical studies have shown that leukocytosis, lymphocytopenia, and thrombocytopenia are important laboratory findings in the majority of COVID-19 patients at the time of hospitalization, which can be helpful criteria for assessing the progression of complications. These findings were more evident in patients with severe COVID-19 compared to non-severe cases [6,42]. Several studies have shown the relationship between changes of leukocyte frequency and progression of COVID-19 symptoms toward ARDS syndrome, MOF, and death [37,65]. Accordingly, Henry et al. indicated that white blood cell (WBC) counts in COVID-19 patients with severe manifestations increase moderately, while this parameter significantly increases in COVID-19 victims. Elevated WBC counts are due to increased neutrophils accompanied by a decrease in lymphocytes, monocytes, dendritic cells, and eosinophils counts in peripheral blood [65]. Such alterations lead to increased neutrophil-to-lymphocyte ratio (NLR) values (a well-known marker of systemic inflammation and infection) and decreased values of lymphocyte-to-WBCs ratio (LWR). Hence, the NLR and LWR can be considered as predictive and monitoring indicators for severe forms and fatal outcomes of COVID-19 [75]. Interestingly, Qu et al. showed that high platelet-to-lymphocyte ratios (PLRs) at the time of platelet peak could be considered as an independent poor prognostic factor for COVID-19 outcomes [93]. Lymphopenia associated with neutrophilia in COVID-19 patients may be due to several mechanisms. The most common mechanisms are: 1) recruitment of lymphocytes and monocytes from blood into the sites of infection [94]; 2) activation-induced cell death (AICD) of lymphocytes due to increased expression of Fas under the influence of IL-6 [33]; 3) lymphoid organ atrophies and lymphocyte turnover impairment that may be related to the over-activation and exhaustion of lymphocytes [95,96]; 4) inhibition of lymphocyte proliferation by acidosis [97]; and 5) suppression of T cell recirculation in the blood by promoting the attachment of T cells to the endothelium of lymphoid organs under the influence of IFN-I and TNF-α [98].

During non-specific symptoms that occur in the early stage of COVID-19 (1–14 days), lymphocyte counts in the peripheral blood are either normal or slightly reduced. The significant changes become evident approximately 7–14 days after the onset of the primary symptoms [99]. Subjects with mild symptoms of COVID-19 demonstrate a decrease in the number of lymphocytes on day 7, which subsequently returns to its normal range after several more days [64]. Therefore, sequential evaluation of lymphocyte count fluctuations may be a prognostic and monitoring indicator for disease outcome. One study found that if lymphocyte counts at days 10–12 after the onset of symptoms are less than 20 % and drop to less than 5 % at days 17–19, it will be associated with a poor prognosis of the disease [100].

2.4.1. Myeloid cells

Myeloid cells, such as dendritic cells and macrophages, are important immune system regulators in mucosal infections [101]. The accumulation of mononuclear cells such as T cells, dendritic cells, and monocytes/macrophages in the lung tissue is the first pathological data in patients with COVID-19 which is accompanied by a decrease in mononuclear cells in peripheral blood as well as an increase in CRS and lung complications [18]. Previous reports have confirmed that the increased expression of inflammatory genes (such as IL1β, FOS, JUN, CXCR4, MIP-1B, and IFN regulatory factor (IRF)-1) is associated with the proliferation of CD14+ human leukocyte antigen (HLA)-DR^{lo} inflammatory monocyte [85,102], IFN-γ-driven immune responses, and IL-1β-associated inflammasome signatures [103] in the peripheral blood of COVID-19 patients. Interestingly, several studies reported that the high frequency of CD14+ HLA-DR^{lo} inflammatory monocyte-derived macrophages and Ficolin-1+ monocyte-derived macrophages in the BALF of patients with severe COVID-19 symptoms was accompanied by a decrease in the frequency of tissue reparative alveolar macrophages. Inflammatory macrophages account for as much as 80 % of total BALF cells in patients with severe COVID-19, while in patients with mild disease and in healthy individuals, this number is only approximately 60 % and 40 %, respectively [31,104]. In addition, CD14+ CD16+ GM-CSF+ and CD14+ CD16+ IL-6+ monocytes were shown to be higher in patients compared to healthy control group. It seems that CXCR3 and/or CCR2+ inflammatory monocytes are recruited into the inflamed sites in response to the high production of MCP-1, MIP-1A, CCL8, CXCL6, and CXCL11 and are differentiated to inflammatory macrophages under the effect of cytokines such as IFN-γ [29,31,104]. Inflammatory macrophages can promote dysfunctional immune responses by several mechanisms, including the engagement of TLR and RLRs, increasing antibody dependent enhancement, inducing pyroptosis, stimulating the complement activation, and delaying the cellular response [8]. A study in animal models has shown that delayed IFN-I production and the accumulation of inflammatory monocyte/macrophages in the alveolar lumen cause increased levels of inflammatory mediators, dysfunction of T cell responses, and vascular leakage [105]. On the other hand, the persistence of inflammatory macrophages followed by a high density of anti-inflammatory responses in the later stages of immune response (repairing phase) may participate in fibrotic complications and dependence on mechanical ventilation based on the extent of tissue damage [106]. Hence, the various subtypes of macrophages may be biomarkers for monitoring COVID-19 recovery. In animal studies, small interfering RNA (siRNA)-mediated silencing of CCR2 is an effective treatment approach which reduces macrophage recruitment to the sites of inflammation [107].

2.4.2. Neutrophils

Several studies have demonstrated that patients with severe COVID-19 symptoms have higher neutrophil counts in their peripheral blood [42,75]. Another study, carried out by Zhou et al., showed a high frequency of inflammatory neutrophils at the site of infection, which was associated with adverse outcomes of COVID-19 complications. Based on this study, neutrophils infiltrate to the site of inflammation in response to the high production of chemokines such as CXCL1, CXCL2, CXCL8, CXC10, MCP-1, and CCL7 and differentiate to inflammatory neutrophils under the effects of high levels of IL-17F, IL-1β, TNF-α, and IL-6 [29]. Neutrophilia has been defined as a risk factor for the progression of ARDS toward death in COVID-19 patients [42]. Hence, pathological studies on Ace2 knockout mice showed that mice with severe ARDS have a higher accumulation of neutrophils in the lungs compared to the control group. This phenomenon maybe due to increased serum and

pulmonary levels of Ang II which can activate neutrophils and other immune cells through AT1R [15]. While such neutrophils may exert important antiviral effector functions, they also secrete IFN-γ, IL-6, and MCP-1 that attract and activate further immune cells such as T lymphocytes and monocytes, which may contribute to accentuated immune responses in COVID-19 [108].

2.4.3. Eosinophils, basophils and mast cells

Several studies in COVID-19 patients revealed that subjects with severe symptoms of the disease exhibit a decrease in frequencies of eosinophils and basophils in their blood, which can worsen with COVID-19 exacerbation [75,109]. In addirion, animal models of SARS-CoV immunopathology have demonstrated infiltration of Th2/eosinophil in lesion sites [110]. Therefore, eosinopenia associated with increased CRP can be a potential indicator for the rapid and effective prognosis of patients with COVID-19 [111]. Delayed improvement in eosinophil counts may also be a sign of poor response to therapies in patients [112]. Furthermore, lung pathological data of COVID-19 patients indicates an increased activity of attracted mast cells and a higher release of chymase in the inflamed site that lead to the conversion of Ang I to Ang II [15,29].

2.4.4. NK cells

NK cells along with cytotoxic T lymphocytes (CTLs) play key roles in virus eradication during respiratory infections through direct cytotoxicity and cytokine secretion [113]. Two consecutive analyses of NK cell subsets have shown that the frequencies of NK cells were decreased in the peripheral blood of COVID-19 patients with severe symptoms, and such a decrement was more obvious in critical patients [18,75]. This phenomenon is due to either the infiltration of NK cells into peripheral tissues or the disregulation of NK cell maturation [114]. Based on the relative expression of the CD16 and CD56 markers, NK cells are divided into two subgroups: CD16+ CD56+ NK cells (NK1) with strong cytotoxic activity and CD16- CD56+ NK cells (NK2) with the capability of high level cytokine production and slight cytotoxic activity [32]. Mature NK1 subsets form the majority of NK cells in healthy lung, but CXCR3+ NK cells are increased in lungs infected with viruses in response to CXCL9–11 [115]. In patients with severe COVID-19, the NK1 cells show impaired cytotoxicity, increased cytokine production [116], and elevated expression of exhaustion markers such as NKG2A (a major NK cell-inhibitor receptor) [95], programmed cell death protein (PD)-1, T-cell immunoglobulin mucin (TIM)-3, and lymphocyte-activation gene (LAG)-3 [117]. Other studies have indicated that high levels of IL-6 and TNF-α along with lower numbers of NK1 cells significantly correlate with the severity of clinical symptoms in COVID-19 patients [6,114]. It is likely that IL-6 impairs perforin and granzyme B (GzmB) production [118], while TNF-α downregulates NKp46 (a major NK cell-activating receptor) [119]. It has been shown that tocilizumab and anti-TNF-α can restore NK1 cell functions in COVID-19 patients [118]. A recently identified placental human stem cell-derived allogeneic NK cell (CYNK-001), that has the potential of directly killing SARS-CoV-2 infected cells as well as the indirect induction of immune responses has been studied in COVID-19 patients (NCT04365101) [120]. However, there are controversies over the efficacy and safety of NK cell therapy for SARS-CoV-2 infections, so more testing is necessary.

2.4.5. T cells

Although changes in the WBC counts are considered to be clinical indicators of the progression of COVID-19 disease, investigating the changes in each lymphocyte subtype might be very interesting for the prediction of disease complications. Of note, CD4+ T cell subsets are central coordinators of immune responses which provide a wide array of functions to help antibody production, activation of immune cells, survival and maintenance of cellular effector functions as well as immune memory formation. Therefore, studying their subsets would be of utmost importance. On the other hand, studying CD8+ T cells subsets, as the main effector cells in the direct killing of viral infected cells, can be helpful in determining the relative significance of T cell subsets and cellular immunity in the defensce against COVID-19 and its immunopathology [121]. Accordingly, similar to the acute phase of SARS and MERS diseases, COVID-19 patients with severe symptoms exhibit an extreme decline in total CD4+ and CD8+ T cells in their circulation [122], while patients with mild symptoms have normal to slightly higher T cell counts [123]. This decrease in T cells is likely to be caused by high levels of pro-inflammatory cytokines such as IL-6, IFN-I, and TNF-α in peripheral blood [71,82]. A high concentration of IL-6 may induce apoptosis of T cells through the Fas/FasL pathway [33], while TNF-α and IFN-I may promote the attachment and retention of T cells in lymphoid organs [124]. T cells express a high level of HLA-DR, CD25, CD69, CD38, Ki-67, as well as the FOS, JUN, and KLF6 genes in patients with severe disease [85,104,125], which is due to the activation of cells under the influence of high serum levels of inflammatory cytokines such as IFN-γ, IL-12, IL-1β, and MCP [126]. Braun et al. demonstrated that the stimulation of CD4+ T cells using overlapping peptide pools of S protein increased CD38, HLA-DR, and Ki-67 expression in CD137+ CD154+ CD4+ T cells [127]. Generally, the activation of CD8+ T cells was greater than that of CD4+ T cells [75,125]. Of note, there were low frequencies of CD4+ T cells specific for C-terminal S protein epitopes in about one-third of SARS-CoV-2 seronegative donors that lacked activation markers. These responses may be attributed to the cross-reactivity between CoVs specific CD4+ memory T cells which recruit an amplified primary response against SARS-CoV-2 [127]. In this regard, NCT04343651 in phase II and NCT04347239 in phase II/III are two clinical trials to evaluate the safety and efficacy of leronlimab, an anti-CCR5 mAb, in mild-to-moderate and severe-to-critical COVID-19, respectively. Laboratory results of these studies showed increased CD8+ T cell percentages, normalization of CD4+/CD8+ T cell ratios, and resolving cytokine storm, including reduced IL-6, IFN-I and TNF-α levels which correlated with COVID-19 patient improvement.

2.4.5.1. Th1 cells and CTLs. Recent works have shown that Th1 cells and CTLs along with monocytes play a crucial role in viral control and in reducing the innate immune responses by inducing specific, effective, and robust responses against the virus. Nevertheless, similar to autoimmune diseases, the dysregulation of these responses may lead to COVID-19 immunopathology and may be associated with the severity and progression of the disease [31,128]. Hence, in critically severe COVID-19 patients observed a decreased frequency of IFN-γ+ CD4+ T and GzmB+ perforin+ CD8+ T cells as well as an increased frequency of polyclonal GM-CSF+ CD4+ T cells which could produce high levels of IL-6 and GM-CSF [31,95].

2.4.5.2. Regulatory T cells (Treg). Treg cells which play a critical role in the maintenance of immune tolerance, especially in mucosal tissues, decrease in the early phase in patients with severe COVID-19 [75]. The reduction of Treg cells might contribute to the development of lung complications in COVID-19 patients. In this regard, the lack of control on the inflammatory cells, especially CD8+ T cells, may cause an exacerbated pro-inflammatory profile and severe symptoms in the acute phase of infection, which should be considered in vaccine design [75,122].

2.4.5.3. Th17. It has been shown that the frequencies of CCR4+ and CCR6+ Th17 cells with higher levels of inflammatory functions increase in patients with COVID-19 [18]. This can be due to the effects of IL-6 and IL-23 that are produced from activated macrophages and virus-infected AECs [129].

Furthermore, Th17 plays an important role in severe lung damage and mortality due to respiratory tract infections. In this regard, Th17 cells play a part in the cytokine storm by producing IL-17 and GM-CSF which mobilize neutrophils and eosinophils from bone marrow to the inflammation site [130].

2.4.5.4. Th2. Similar to SARS, the poor outcomes of COVID-19 may be associated with Th2 cell-produced cytokines [131]. Th2 differentiation can be due to either the absence of strong signals for Th1 and Th17 differentiation in the early stages of infection or to high levels of IL-4, IL-5, and IL-10 production in the later stages of infection [6]. However, experiments on SARS-CoV-1 in animal models have shown that Th2 can contribute to SARS-CoV-2 immunopathology through the recruitment and activation of eosinophils [110]. Furthermore, γδ T cells that have a protective role in viral pneumonia decrease in severe COVID-19 patients [102,132].

2.4.5.5. Naïve, effector, and memory T cells. One of the most important aspects of T cells-mediated immunity is the differentiation of naïve T cells into activated and memory T cell subsets. Naïve, activated, and memory T cell populations are in a balanced relationship in order to maintain the efficiency of immune responses and homeostasis in the steady state [75,133]. In CD4+ T cell populations, an increase in naïve and activated cells as well as a decrease in memory cells are observed in patients with severe COVID-19 than non-severe patients [75]. In CD8+ T cell populations, naïve and memory cells do not show much difference, but activated cell population greatly increases in patients with severe disease compared to milder cases [75]. However, by using large complementary peptide pools comprising S protein SARS-CoV-2 epitopes, Weiskopf et al. showed that, based on CD45RA and CCR7 expression, the phenotype of CD4+ and CD8+ T cells in moderate-to-severe patients is very limited 10 days after the initial onset of symptoms [134]. These cells were characterized by the phenotype of central-memory CD4+ T cells and effector-memory CD8+ T cell [134]. Similarly, Wen et al. showed that patients in the late recovery stage had a higher frequency of naïve CD4+ T cells, CD8+ T cells, and effector-memory CD4+ T cells, while the frequencies of central-memory CD4+ T cells, Treg, effector-memory CD8+ T cells, and effector CD8+ T cells were decreased [85]. Thus, evaluation of the frequency, function, and phenotypic properties of SARS-CoV-2 specific CD4+ and CD8+ T cells might be helpful in predicting, monitoring, and treating COVID-19 complications.

2.4.5.6. Deviations in T cell responses. Studies have shown that high serum levels of pro-inflammatory cytokines such as IL-6, IL-10, IL-23, and TNF-α in the fatal group are associated with decreased counts, increased activation, and enhanced expression of exhaustion markers of T cells (PD-1, TIM-3 and LAG-3) [117]. These markers are expressed in higher quantities in CD8+ T cells than in CD4+ T cells and in severe versus mild cases [31,71]. In COVID-19 patients with mild symptoms, IFN-γ-producing T cells are specific for N, M, and S proteins of SARS-CoV-2, but only N-specific T cells are detectable in subjects post recovery [135]. Several studies have shown that CD4+ and CD8+ T cells isolated from patients with severe disease produce smaller amounts and less variety of cytokines in response to PMA [95,96,122]. The studies on the function of CD8+ T cells in severe COVID-19 have been controversial. Whereas a study showed the cytotoxicity and degranulation of CD8+ T cells were decreased in peripheral blood [95], another study demonstrated that GzmB and perforin were increased in CD8+ T cells extracted from the blood and BALF of severe patients [96,104]. These conflicting results may be due to differences in sampling time during the course of the disease in different studies. Because deviations in immune responses from Th1/macrophage, CTL and NK to Th17/neutophils and Th2/eosinophils occur under the influence of pro-inflammatory cytokines during disease progression and lead to a decrease in virus clearance, an increase in the cell pyroptosis, a decrease in apoptotic cells removal, and an increase in lung inflammation [131]. Therefore, the results can vary depending on the stage of immune responses, its kinetics of deviations under the influence of HLA, and the repertoire of naïve and activated T cells [136].

IL-7 is the main cytokine in the homeostasis of the immune system by promoting the expansion of lymphocytes, inhibition of apoptosis, reversal of T cell exhaustion, and expression of cell adhesion molecules [83]. Interestingly, the administration of recombinant (r)IL-7 causes treatment of T cell exhaustion and restores CD4+ T cells without a hyperinflammatory response or clinical deterioration in HIV infection [137]. Hence, IL-7 can be a superb therapeutic candidate for the treatment of COVID-19 complications. So far, five clinical trials have been registered to evaluate this strategy (NCT04407689, NCT04379076, NCT04498325, NCT04426201 and NCT04442178).

Allogeneic virus-specific T cell therapy is another treatment strategy that targets SARS-CoV-2. This approach is in phase I trial (dose finding) followed by a pilot study in hospitalized severe COVID-19 patients (NCT04401410).

2.4.6. Humoral immunity

Given the limitations of CT scan and RT-qPCR methods for the diagnosis, prognosis, and monitoring of COVID-19 complications, simple and rapid immune-based methods that target viral antigens or antiviral antibodies are needed as soon as possible. For this purpose, the first step must be determining the kinetics and dynamics of humoral immune responses in COVID-19 patients. Also currently, several studies are investigating the effectiveness of humoral immunity against SARS-CoV-2 [138,139]. In one of these studies B cell responses and follicular T cell responses are shown to occur around 7 days after the onset of COVID-19 clinical manifestations [125]. Furthermore, SARS-CoV-2-specific N/S-IgM/IgG Abs are commonly detected in the order of days after infection [140]. A study has shown that SARS-CoV-2-specific N/S-IgM Abs appear in the first week, reach a peak in the second week, and decrease in the third week after the onset of symptoms in non-severe patients, while N/S-IgG Abs increase in the second week, reach a peak in the third week, begin to decline by 8 weeks, and are detectable for 60 days post-symptom onset [141]. All antibodies are produced earlier in severe patients than in non-severe patients except S-IgG Ab which is delayed (Fig. 2). Of note, the combined assessment of N/S-IgM/IgG Abs improved the detection of COVID-19 patients, especially in the first week when it could detect up to 75 % of patients infected with SARS-CoV-2 [142].

It has been shown that the increase in N/S-IgM and N-IgG Abs in the first three weeks after symptom onset is correlated with increases in CRP and lung complications. However, the high levels of S-IgG Ab in the third week after the onset of symptoms are associated with decreased inflammation [142]. It seems that while N-IgM Ab and N-IgG Ab indicate the presence and progression of infection before the virus packing stage, respectively, the S-IgM Ab promotes the pro-inflammatory processes and symptoms of the disease by complement activation and antibody-dependent enhancement (ADE). Conversely, after neutralization of the virus, S-IgG Ab reduces inflammation through the Fc gamma receptor (FcγR)-mediated phagocytosis of immune complexes in the late stage of infection. Therefore, the identification and measurement of N/S-specific IgM/IgG antibodies can be effective in the diagnosis, prognosis, and monitoring of COVID-19.

2.4.6.1. Convalescent plasma (CP). There are different therapeutic methods based on adoptive transfer of neutralizing antibodies (nAbs) for the treatment of COVID-19 patients at the early stages of clinical deterioration. A rapid prophylactic and therapeutic strategy for COVID-19 can be administration of CP, which is derived from the plasma of recovered COVID-19 individuals [140]. A study has indicated that sera from COVID-19 patients could neutralize BALF-isolated SARS-CoV-2 of severe patients [143]. For this purpose, individuals who have recovered from COVID-19 and have a high plasma titer of anti-SARS-CoV-2 Abs are identified using serological tests [140]. Although CP therapy is an FDA-approved treatment for severe COVID-19 patients [144], further controlled and randomized trials are required to determine the optimum amount, frequency, and time of CP transfusions. In a recent effort,

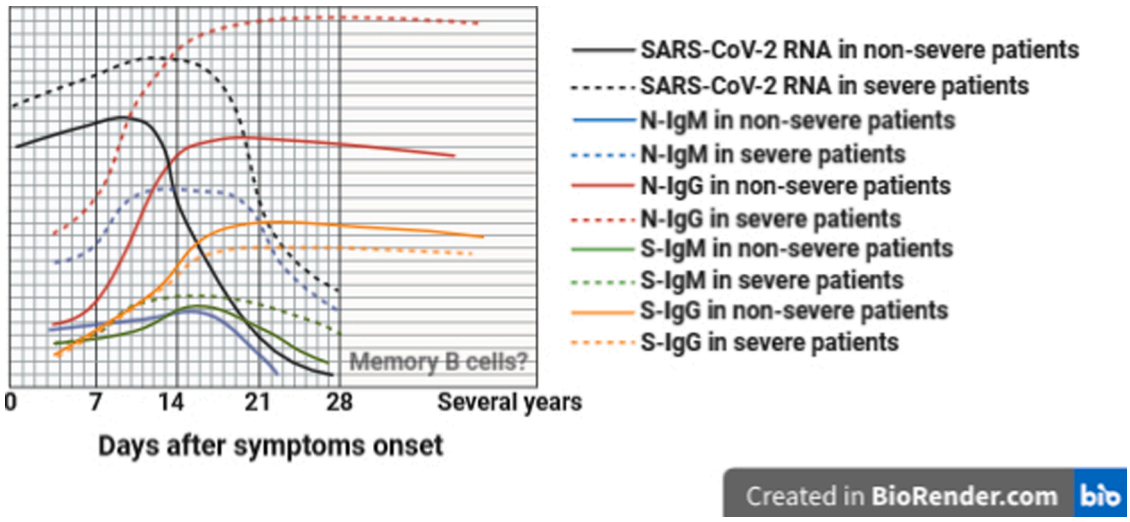

Fig. 2. Kinetics of SARS-CoV-2-specific N/S-IgM/IgG antibodies and viral RNA in patients with severe COVID-19 (dashed line) versus non-severe COVID-19 (solid line). SARS-CoV-2-specific N/S-IgM/IgG Abs are detectable between first and second weeks post-symptom onset in sera and inversely correlate with viral RNA titers. All antibodies are produced earlier and in higher levels in severe patients than in non-severe patients except S-IgG Ab which is delayed.
N, nucleocapsid; S, spike-protein.

injection of CP that was collected two weeks after recovery led to the highest titers of anti-SARS-CoV-2 neutralizing antibody in recipient patients [145]. In addition, patients who received one dose of 200 mL CP with a titer above 1:640 of anti-SARS-CoV-2 Abs were significantly improved within three days [146].

2.4.6.2. Intravenous immunoglobulin (IVIg). IVIg therapy is another Ab-based treatment strategy that uses polyclonal IgG pools isolated from healthy donors to treat numerous inflammatory diseases, including ARDS and vasculitis [147]. A previous study has shown that treatment with IVIg was effective on early stages of SARS and MERS diseases. Thus, IVIg can be another option for COVID-19 patients with severe symptoms [148]. Although a few COVID-19 patients did respond to a high dose of IVIg, the high cost and adverse side effects restrict its general use [149]. Currently, several clinical trials are underway to evaluate IVIg therapy in COVID-19 patients worldwide [150].

2.4.6.3. Monoclonal Abs (mAbs). Evidence show that mAbs are suitable candidates for the treatment of COVID-19. S protein fragments including N terminal domain (NTD), receptor-binding domain (RBD), and heptad repeat region (HR)-2 are the most immunogenic targets for anti-SARS-CoV-2 nAbs production which block virus entry to the cells [151]. Among these antibodies, anti-RBD nAb are commonly detected in COVID-19 patients [140]. Therefore, RBD can be a potential target for the induction of two arms of humoral immunity during the acute phase of disease. The two arms of humoral immunity that form anti-SARS-CoV-2 vaccination strategies include 1) long-lived plasma cells with the ability to resolve the primary infection by secreting nAb and to inhibit reinfection by inducing serological memory, and 2) memory B cells with the capability of responding to reinfection by producing new high-affinity plasma cells. Recent studies have shown that $CD38^{hi}$ $CD27^{hi}$ antibody-secreting cells (induced plasma cells) and RBD-specific CD19+ IgG+ memory cells appear between the second to fourth weeks after symptom onset in the peripheral blood of severe and recently recovered cases of COVID-19 [125,140]. Antiviral mAbs can be effective against the fusion, entry, and replication of the coronavirus. In independent efforts, RBD-specific memory B cells were separated from recently recovered patients and cloned in heavy and light variable regions of Ab genes for the production of recombinant mAbs. Accordingly, 31B5, 32D4, P2C-2F6, and P2C-1F11 clones derived from COVID-19 patients produced human anti-RBD mAbs with high neutralizing potential that can inhibit ACE2-RBD binding [140,152]. The S309 clone derived from SARS-CoV-1 infected patients, however, secreted human anti-RBD mAbs with poor neutralizing potential and without ACE2-RBD binding ability [116]. In addition, R325, R302, R007, and 47D11 clones, all specific for S1-SARS-CoV-1 or MERS-CoV-1, produce recombinant anti-S1 mAbs that have neutralizing potential without ACE2-RBD binding ability [153]. CR3022 is also a human monoclonal IgG1 antibody produced against SARS-CoV-1 RBD which neither neutralizes the virus nor inhibits ACE2-RBD binding [154]. Also, VIR-7831, REGN-COV2, LY-COV555/ LY-COV016, JS-016, STI-1499, and AZD7442 are other mAbs that are in different phases of clinical trials to be evaluated for safety and efficacy in COVID-19 patients (NCT04545060, NCT04425629, NCT04427501, NCT04441918, NCT04454398, and NCT04507256, respectively).

Other treatments based on mAbs include the use of ACE2-Fc and RBD-Fc fusions, resulting from the binding of the ACE2 or RBD extracellular domain and the Fc portion of the antibodies. These fusion proteins neutralize both SARS-CoV-1 and SARS-CoV-2 in laboratory conditions [155]. In addition, a single-chain variable fragment (scFv) against SARS-CoV-2 (also known as n3130) has been demonstrated to neutralize SARS-CoV-2 without inhibiting ACE2/RBD [156].

Notably, the association of higher titers of anti-SARS-CoV-2 antibodies with more severe clinical cases suggests that a strong humoral response alone is not sufficient to prevent severe disease [138]. It is likely that high antibody titers promote virus entry via ADE, activate macrophages and the complement system, which can amplify systemic inflammatory responses. This is especially possible when non-neutralizing virus-specific IgGs are produced against virus [157]. Of note, ADE has not yet been detected in COVID-19, and no evidence exists that SARS-CoV-2-specific antibodies play a role in the immunopathology of COVID-19 [158]. However, this is a possibility that should be considered in designing therapeutic strategies.

3. Challenges

There is a bulk of potential immune biomarkers that are related with COVID-19 complications in the late phase or cases with severe-to-critical symptoms. However, they cannot necessarily be used as prognostic biomarkers for COVID-19 complications in the early phase or in cases with asymptomatic-to-mild symptoms. Hence, universal profiling of asymptomatic-to-mild cases as well as longitudinal studies

are needed to identify the useful immune biomarkers for early identification of COVID-19 complications. Viral replication and its antigens are among the major factors that can affect hyper-inflammation, tolerance, and consequently, complications and mortality in COVID-19 patients. As a result, accurate prediction, monitoring, and treatments for COVID-19 complications cannot be made without methods to evaluate cellular or tissue viral replication rate or original infective dose estimation. In addition, other factors that can affect associations between immune biomarkers and disease complications are confounding variables including gender, age, and comorbidities that should be taken into account. Differences in sampling time during the course of the disease may add to the ambiguity of the results, which should be considered in the interpretation and comparison of different studies.

4. Concluding remarks and recommendations

In summary, COVID-19 is a polyphasic inflammatory disease in which cytokine storm and inflammatory cells play a critical role. One can coclude that the timing of cytokines production as well as their kinetics and relative concentrations are major determinants of the outcome of inflammation. To this end, in the early phase of COVID-19 the early rise in inflammatory mediators followed by their decline as a result of anti-inflammatory responses may correlate with milder disease, however, if the rise in inflammtory cytokines delayed (weak response) or is not followed by anti-inflammatory response (too much inflammation) the disease worsens by tissue damage caused by the recruitment of white blood cells. The coordinated action of cytokines and chemokines in inflammatory sites, orchestrates recruitment and differentiation of immune cells. The recruited monocytes and neutrophils have an inflammatory phenotype which is further intensified by the inflammatory milieu in the lung. In the late phase of COVID-19, the continous stimulation of the immune cells (supposedly by viral antigens or cytokines), exhaustion of lymphocytes and leukocytes, and skewed T cell (Th2) and NK cell (NK2) response result in uncontrolled and uncoordinated tissue fibrosis and organ dysfunction.

Current data suggests that in both early and late phases of COVID-19 disease, increased levels of ACE2, Ang II, MUC-1 and MUC-5A/C, SP-D, IL-6, TNF-α, IL-1β, CRP, SAA, Ferritin, PCT, ESR, D-dimer, PT, PTT, C3a and C5a are associated with poor prognosis. However, elevated serum IFN-I, Ang 1−7, and Ang 1−9 levels in early phase are indicators of good prognosis and elevated IFN-I in late phase is a measure of poor prognosis of the disease. Regarding cellular biomarkers, increase in the NLR and PLR as well as leukocytosis, lymphopenia, eosinopenia, monocytopenia, basophilopenia, and thrombocytopenia are measures of poor prognosis in both early and late disease. To add another layer of complexity, the subsets of lymphocytes show differential increase or decrease in each phase. Accordingly, the decrease in Th1, CTL, Treg, and NK1 subsets and the increase in CCR4+ CCR6+ Th17 cells in early phase correlate with poor prognosis, while in the late phase Th2, Tregs, and NK2 increase with severity of the disease.

Consequently, in the very early stages of SARS-CoV-2 infection, administration of IFN-I, srhACE2/ACEI/ARBs, JAK inhibitors, BTK inhibitors, S1PR1 agonists, respiratory SP-D, CP, IVIg, and mAbs may be of importance as candidates of immunotherapy. In late COVID-19, administration of IFN-I antagonists, IFN-I receptor blockers, and rIL-7 as well as CYNK-101 and allogeneic viral-specific T cells, needs to be further evaluated for the efficacy and safety.

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Declarations of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cytogfr.2020.10.002.

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