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NARRATIVE REVIEW

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# COVID-19 illness: Different comorbidities may require different immunological therapeutic targets

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## Abstract

**Background:** The SARS-CoV-2 pandemic has led to more than 6,870.000 deaths worldwide. Despite recent therapeutic advances, deaths in Intensive Care Units still range between 34 and 72%, comprising substantial unmet need as we move to an endemic phase. The general agreement is that in the first few days of infection, antiviral drugs and neutralizing monoclonal antibodies should be adopted. When the patient is hospitalized and develops severe pneumonia, progressing to a systemic disease, immune modifying therapy with corticosteroids is indicated. Such interventions, however, are less effective in the context of comorbidities (e.g., diabetes, hypertension, heart failure, atrial fibrillation, obesity and central nervous system-CNS diseases) which are by themselves associated with poor outcomes. Such comorbidities comprise common and some distinct underlying inflammatory pathobiology regulated by differential cytokine taxonomy.

**Methods:** Searching in the PubMed database, literature pertaining to the biology underlying the different comorbidities, and the data from the studies related to various immunological treatments for the Covid-19 disease were carefully analyzed.

**Results:** Several experimental and clinical data have demonstrated that hypertension and atrial fibrillation present an IL-6 dependent signature, whereas diabetes, obesity, heart failure and CNS diseases may exhibit an IL-1a/b predominant signature. Distinct selective cytokine targeting may offer advantage in treating severe COVID-19 illness based on single or multiple associated comorbidities. When the patient does not immediately respond, a broader target range through JAKs pathway inhibitors may be indicated.

**Conclusions:** Herein, we discuss the biological background associated with distinct comorbidities which might impact the SARS-CoV-2 infection course and how these should to be addressed to improve the current therapeutic outcome.

KEYWORDS

atrial fibrillation, comorbidities, COVID-19, diabetes, heart failure, hypertension, obesity

## 1 | INTRODUCTION

SARS-CoV-2 (coronavirus type 2) has led to substantial overload of the healthcare systems in many countries and has caused more than 6,870,000 deaths worldwide as of January 2023. The most urgent need is for an antiviral agent capable of stopping the infectivity of all variants, thereby sparing lung and other organ damage. Molnupiravir and paxlovid may help at the onset of the disease. However, currently the effectiveness of vaccines remains our primary defence against recurrent infectious waves. SARS-CoV-2 can damage several organs such as kidney, heart, central nervous system and gastrointestinal tract besides the lung, behaving as a systemic illness.[1-5] Mortality is mainly due to lung damage C-ARDS (COVID-acute respiratory distress syndrome) and lung or multi-organ failure.[6-8] When the illness progresses, a proposed cytokine release syndrome occurs, leading to adoption of the therapeutic approach to CRS (cytokine release syndrome) post-CAR-T (chimeric antigen receptor-modified T) cell therapy for acute leukaemia or lymphomas.

## 2 | CRS BIOLOGY OF SEVERE SARS-COV-2 AND SIMILARITIES TO CRS OF CAR-T CELL THERAPY

In SARS-CoV-2 pneumonia, the first highly activated cells are alveolar type 2 (AT2) pneumocytes that, following the infection, release cytokines recruiting immune cells. Alveolar macrophages, endothelial cells, natural killer (NK) cells and polymorphonuclear cells (PMNs) are subsequently recruited and activated, starting a hyperinflammatory cascade (Figure 1). Conversely, in CAR-T cell therapy, genetically engineered T cells expressing CAR molecules that recognize tumour antigens are the first activated cells; several studies have demonstrated that in due course, macrophage lineages are the effector cells.[9-10]

Yet, in SARS-CoV-2 infection, organ injury typically exceeds what would normally be expected for the pathogen alone in a viral infection and in fact, grade 4 CRS is a more frequent event than in CAR-T cell-treated patients.[11] In particular, the severe organ damage has been considered inflammation-dependent, similar to what happens in the CRS occurring after CAR-T cell therapy in which CAR-T activation leads to proliferation of T cells and release of high amounts of cytokines and chemokines by immune cells, particularly monocytes/macrophages and dendritic cells.[9-11] For this reason, it is still a matter of debate whether the cytokine burden is the major player,[12] or whether a more complex biology landscape occurs, with different phases presenting specific biology that may impact treatment choices and outcomes.[13]

### Research in context

#### Evidence before this study

Uncontrolled studies showed some clinical benefit in different cohorts of severe-critical COVID-19 pneumonia, through targeting IL6, IL1 or GM-CSF. The SARS-CoV-2-induced cytokine release syndrome (CRS) is different from chimeric antigen receptor-modified T (CAR-T) cell therapy-associated one, in which IL6 and IL1 are the main players, while high plasma levels of IL6, IL8, GM-CSF, IL-10 and others have been demonstrated in SARS-CoV-2-induced CRS. No clear stratifiers can currently explain whether different cytokines are involved in different phases of the disease. Data suggest that only some patients respond rapidly and recover from the acute severe illness and this likely has an explainable immune phenotype.

#### Added value of this study

Several comorbidities (e.g. diabetes, hypertension, heart failure, atrial fibrillation, obesity and CNS diseases) have been linked to a poor outcome in patients progressing to severe acute respiratory distress syndrome in COVID-19 disease, suggesting that different comorbidities present distinct immune-inflammatory landscapes, with different cytokines involved in their pathogenesis.

The present review dissected the distinct biological background characterizing various comorbidities, in terms of cytokine taxonomy, which might be related to differential disease course after SARS-CoV-2 infection suggesting a possible decisional algorithm aimed to improve the clinical outcome.

#### Implications of all the available evidence

The assessment of key players, in terms of cytokine milieu, in SARS-CoV-2-infected individuals should be considered within the context of concomitant comorbidities, which will improve at its best the success of tailored therapeutic interventions.

Data suggest that the most aggressive pneumonia during SARS-CoV-2 infection (COVID-19 ARDS) differs from CRS of CAR-T treatment because mainly dependent on a dysregulated immune host response characterized by increased PTEN (phosphatase and tensin homologue

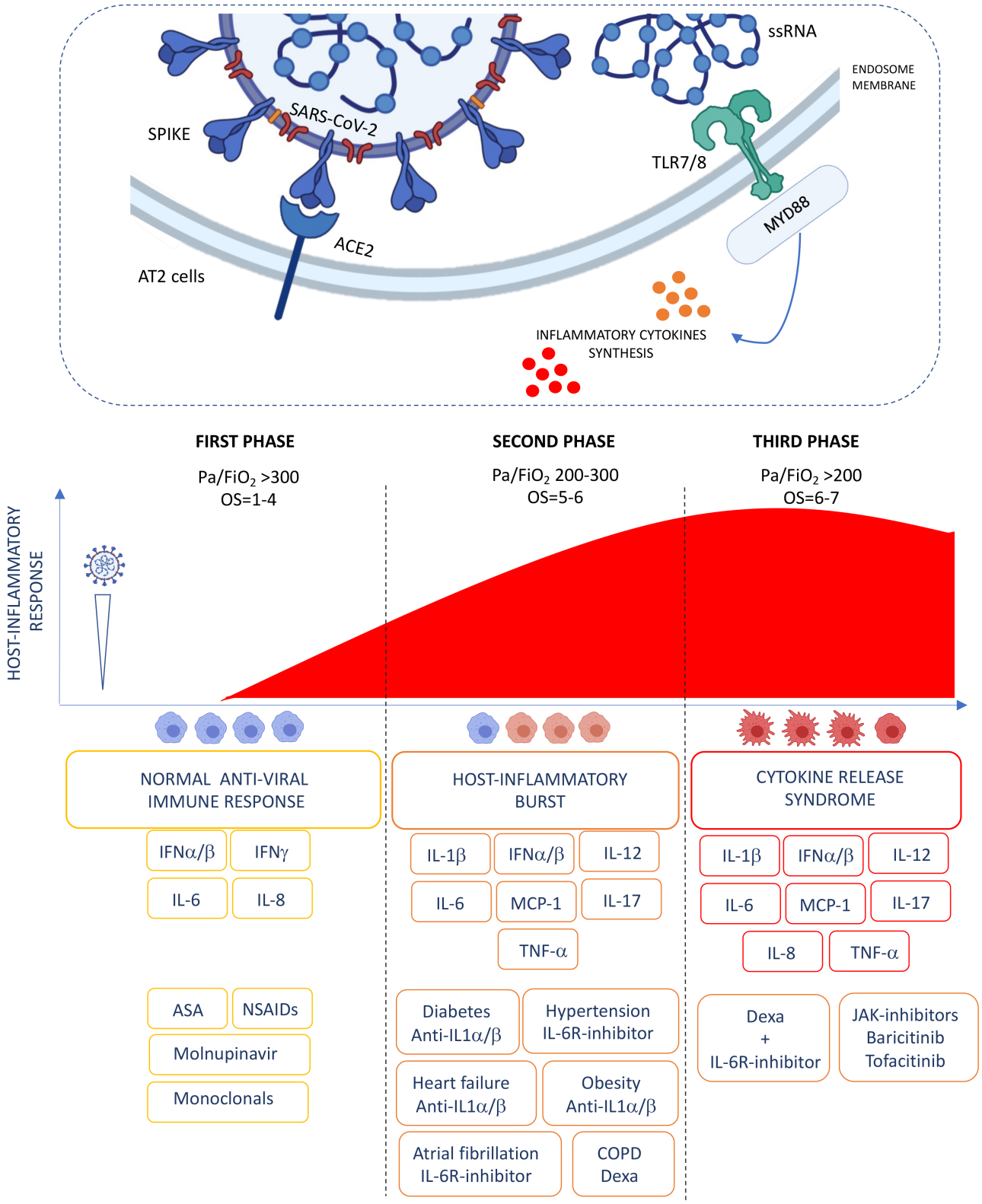


**FIGURE 1** Schematic of the host-immune response after SARS-CoV-2 infection (first phase) across host-inflammatory burst (second phase) and cytokine release syndrome in severe-critical COVID-19 (third phase). Progressive course of SARS-CoV-2-related pneumonia with different degrees of severity and various comorbidities, with different background inflammatory molecules as putative therapeutic targets.

deleted on chromosome 10) signalling, not involved in CAR-T CRS, and elevated expression of genes with noncanonical roles in inflammation and immunity, but with a decoupled interferon stimulated gene (ISG) expression, when compared to mild COVID.[14-15] In this context, distinct immune phenotypes in different phases

of the disease associated with COVID-19 severity have been confirmed in several studies, characterized by perturbation of memory B cells and plasmablasts ($CD20^+IgD^-CD38^{-/+}CD27^{-/+}$), naïve T cells ($CD38^+HLADR^-$, $CD38^-HLADR^-$), CD95pos NK cells and MAIT (mucosal-associated invariant T) cells.[16-17]

The most rational attempt at interpretation lies in understanding the differences related to the various phases of SARS-CoV-2 disease, critical for interpreting the biology of severe pneumonia, and to the comorbidities affecting individual patients.[18]

To better understand this phenomenon, we need to describe first the CRS related to CAR-T and then discuss the organ injuries in COVID-19 infection. The CAR-T-related CRS is triggered by the activation of T cells when their CARs engage the designated antigens on the malignant cells. The first treated 7-year-old boy with acute lymphoblastic leukaemia (ALL) who developed CRS after injection of CAR-T cells, manifested febrile neutropenia, hypotension, acute vascular leakage syndrome and acute respiratory distress syndrome.[19] Cytokine blockade with etanercept, a TNF inhibitor and tocilizumab, a monoclonal anti-IL6 receptor, promptly reversed the syndrome without interfering with the expansion of CAR-T cells. The second case, also a 7-year-old boy with ALL, developed fulminant hemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS) with multisystem organ failure that was rapidly controlled by one tocilizumab injection.[19] The pre-tocilizumab cytokine pattern showed elevated serum levels IFNγ, IL6, IL10, soluble IL2 receptor, MCP1 and IL8, while other cytokines comprising IL1β, IL2, IL4, IL5, IL7, IL12, IL13, IL17, TNFα and GM-CSF were not elevated. On the basis of these findings, IL6 became a primary therapeutic target in this syndrome. Tocilizumab did not improve neurotoxicity in trials. In cases failing tocilizumab, dexamethazone or in refractory cases, etanercept or IL1α/β receptor antagonist (Anakinra) were employed. The pattern of cytokines appears to be similar to that found in hemophagocytic lymphohistiocytosis (HLH).[19-20]

Experimental models show that IL1 and IL6 represent the main biological drivers synthesized by lymphocyte–monocyte cells activated after CAR-T cell therapy.[21-23] In animal models of CRS, blockade of CNS neurotoxicity occurred only after targeting IL1 but not IL6. This biology is often complicated by coagulation disorders, thromboembolism and disseminated coagulopathy[24-25] suggesting that endothelial-thrombotic vasculopathy could be a cause of organ damage. The biology of HLH[26] as well as that of MAS[20-21] seems similar. In childhood, HLH, IFNγ and IL10 are increased as well as IL6,[26] IL1 and IL18 in MAS.[27-28] Frontline therapy of HLH is dexamethazone and etoposide, yet resistant cases can respond to JAK2 inhibition via ruxolitinib.[29] In MAS, multiple organ failure (MOF) occurs acutely within 3 days, or progressively in 7 days. Three main phenotypes may occur: (i) Thrombocytopenia-associated MOF, with low ADAMTS13 activity (von Willebrand factor [vWF] cleaving protease), acute kidney injury with extensive endothelial activation and systemic vWF multimer thrombotic microangiopathy in brain, kidneys and lungs due to complement activation and thrombosis. Here, eculizumab and plasma exchange are key interventions. (ii) Acute liver failure, plus profound deficiency of NK and CTL (cytotoxic T lymphocyte) function. Here, dexamethazone, intravenous immunoglobulins (IVIG) and anti-IL1 or IL6R represent the main interventions. (iii) Immune paralysis, impaired ability to kill infection, in part due to concomitant treatments that were proved as inefficacious (dexamathazone and immunesuppressants). In these cases, tapering immunesuppressants drugs and use of GM-CSF may be lifesaving.[30]

These data suggest that not all CRS have the same drivers, and a more tailored approach very likely needs to be adopted, as usual, in critical care medicine. Does the same principle apply to COVID-19 and are the drivers of such distinctions identifiable?

## 3 | SARS-COV-2 PNEUMONIA

In SARS-CoV-2 pneumonia, the molecular and cellular mechanisms leading to lung infection have been well described in several reviews.[31-32] Moreover, different phases leading to critical lung failure and admission to intensive care units (ICUs), have been discussed.[33] The illness presents as an endothelial leuko-thrombosis (ELT) affecting the vessel tree, with increased coagulopathy, affecting the gastrointestinal tract through the infection of enterocytes, showing features of CNS vasculopathy or of peripheral neuropathy and presenting with several other clinical manifestations.[34-35] Critical cases are more often older subjects with several comorbidities, all involving the vascular trees including diabetes, hypertension, heart failure and atrial fibrillation or obesity.[36] Thus, systemic illness with ELT[37] affects already damaged organs. The virus infects endothelial cells,[38] activates platelets[39] and contributes to the cytokine burst, coagulopathy and the endothelial–alveolar function failure. A tailored therapy should therefore be adopted at different times.

Lung biopsy in two patients with cancer who had SARS-CoV-2 infection pathology revealed diffuse alveolar damage (DAD), hyaline membranes, fibrin exudates, mild lymphomonocytic infiltration and multinucleated giant cells (MGC).[40] In a further case of female patient, the right lower

lobectomy done for a benign nodule, presenting with an early phase pneumonia, showed accumulation of AMs, perivascular lymphocytes along with AT2 hyperplasia, in combination with several MGCs was seen.[41] IL6 and GM-CSF are the main drivers of MGC recruitment and formation.[42] During the initial phase of SARS-CoV-2 infection, endothelial cells, infected by SARS-CoV-2 entering through ACE2 receptor, become activated. In this stage, endothelial cell pathology is not fully appreciated, even though computerized tomography perfusion scan has demonstrated vascular hypoperfusion, with surrounding areas of hyperperfusion,[43] even in the very early phases of the disease,[38] persisting in the rescue-healing-fibrotic phase. The pathophysiology of the vasculopathy has been attributed to a process of ELT inflammation with abnormal neutrophil extracellular traps (NETs)–platelet interaction.[43-46] The majority of pneumonia patients improved, and the median length of hospitalization among survivors is 10–13 days.[47] A minority entered into respiratory failure, and even fewer developed C-ARDS or CRS and needed mechanical ventilation in ICUs.[47] The mortality rate among patients admitted to the ICU ranges from 34% to 72%, depending on the study and characteristics of the patient population.[47-49] The major risk factors for poor outcome have been well identified (such as age, obesity, smoking, diabetes, arterial hypertension, heart failure and atrial fibrillation). The main steps leading to an amplification of the inflammatory-immune response have also been described,[45-46] yet two points need to be highlighted: (i) the AT2 cells are fundamental because they produce the surfactant proteins, which allow to maintain the integrity and function of the alveoli, without collapsing, and constitutively express IL8 and MCP-1, and (ii) when virally infected, AT2 produce type 1 IFN (IFNα/β), type 2 IFN (IFN γ), IL6, IL8, and MCP-1, IL1β, GM-CSF, TGFβ.

The analysis of cytokine plasma levels in SARS-CoV-2-infected asymptomatic patients showed high IL6 and IFNγ, while symptomatic patients showed high IFNα2, and critically ill patients showed high IL6 and low IFNα2, suggesting that various phases might underpin different biology systemically[50]; the analysis of bronchoalveolar lavage fluid (BALF) cells demonstrated that AMs and PMNs prevailed in critically ill patients with high expression of IL8, IL6 and IL1β.[51] The increased expression of IFNα2 is critical, being crucial for virus clearance but also inducer of ACE2 gene expression.[52]

Importantly, GM-CSF is key to maintain surfactant function and, if lacking, such as in autoimmune alveolar proteinosis,[53] abnormal accumulation of surfactant, with impaired oxygenation, may occur. Yet, it is a strong amplifier of the innate immune inflammatory response. The AT2-secreted chemokines and cytokines recruit AMs and PMNs that further enrich the cytokine milieu with GM-CSF, IL17, TNFα, TGFβ, VEGF and others. AT2 co-cultivated with AMs produce high levels of TNFα and IL6 (Table 1). An increased vessel permeability is induced mainly by IFNγ, VEGF, TNFα, IL6 and TGFβ, while other cytokines as GM-CSF and IFNα have protective effects.[54-56] Despite persuasive preclinical rationale, the MASH-COVID trial showed that mavrilimumab, a monoclonal antibody to the GM-CSF receptor, did not improve survival in severe patients (PaO2/FiO2 137).[57] Therefore, the best therapeutic approach to resolve the COVID-19-related pneumonia should aim to tailor the target to the biological phase of the disease. Perhaps different comorbidities lead to a hierarchical choice?

## 4 | TWO MAIN PHENOTYPES OF ICU—C-ARDS IN THE FINAL PHASE OF THE COVID-19 ILLNESS

Transcriptomic, histologic and cellular profiling of post-mortem and normal lung tissues has revealed two main phenotypes of COVID-19 pneumonia when compared to other types of pneumonia.[58] Type 1 was characterized by high expression of type 1 IFN genes (the AT2 cells were rich in SARS-CoV-2 nucleocapsids) and by high expression of IL1β, IL6/TNF, IFNβ/IFNα, CCL2/CXCL9/CXCL19/CXCL11. By contrast, type 2 was characterized by low expression of type 1 IFN genes, and by enrichment of $CD3^{pos}$,

**TABLE 1** Cytokines and chemokines demonstrated to be constitutively expressed by pneumocytes (Alveolar type 2 cells: AT2), expressed when infected and expressed when co-cultivated with alveolar macrophages (AMs).

| Cyto-/chemokines expressed by AT2 | Constitutive expression | Infected-cells expression | Co-stimulated cells expression |
|---|---|---|---|
| IL8 | + | + | + |
| MCP-1 | + | + | + |
| IFNα/β | | + | + |
| IFNγ | | + | + |
| IL1α/β | | + | + |
| IL6 | | + | + |
| GM-CSF | | + | + |
| TGFβ | | + | + |
| VEGF | | | + |
| TNFα | | + | + |
| IL17 | | | + |
| IP-10/CXCL10 | | + | + |
| CXCL16 | | + | + |

*Note*: The biological complexity of the co-stimulated cells raises the key point of the main drivers in the various clinical settings.

$CD8^{pos}$, $CD8PD1^{pos}$, $CD68^{pos}163^{pos}$ and $CD3^{pos}C5b\text{-}9^{pos}$ immune deposits. Type 1 is clearly a molecular immune-inflammatory phenotype,[58] whereas type 2 is a cellular immune-inflammatory phenotype. As discussed above, data from several studies have supported the evidence of distinct immune phenotypes associated with COVID-19 disease severity.[14-17] The different phenotypes can both present with lung tissue oedema (ground glass opacity-GGO) and vessel damage. Other post-mortem tissue analysis from SARS-CoV-2-infected patients revealed that 79 genes were differentially expressed when compared to influenza pneumonitis, along with microvessel thrombosis (NETs–platelets thrombosis), and endothelialitis (with endothelial cells showing SARS-CoV-2 intracellularly) represented by endothelial damage and intussusception angiogenesis.[59] Perhaps the greater degree of endothelial inflammation and thrombosis in the lungs from SARS-CoV-2-infected patients contributed to the relative frequency of sprouting angiogenesis observed in these patients. The largest available European pathology study confirmed several findings,[60] whereas out of 80 post-mortem autopsies in Germany, 40% had signs of major or minor vessel thrombosis.[61] Summarizing, the viral infection leads to lung damage and may evolve to an endothelial leuko-thrombo-inflammation that determines lung failure, MOF and death.

## 5 | COMORBIDITIES AND BIOLOGIC PROGRESSION OF VIRAL-INFLAMMATION

Comorbidities and age will likely confer substantial systemic impact on resultant pathology. In particular, distinct comorbidities (i.e. diabetes, hypertension, heart failure, atrial fibrillation and obesity) and their association might impact on the cytokine taxonomy of individual patients providing novel insights for the identification of driving factors of COVID-19 disease (Figure 2).

### 5.1 | Diabetes

Among different inflammatory soluble mediators, IL1β, IL6 and TNFα were shown to induce insulin resistance.[62-63] In particular, IL6 not only directly promotes angiogenesis but also supports it through VEGF and may be a major mediator of retinal inflammation and neovascularization of increased glomerular basement membrane thickening, which is a crucial lesion of diabetic kidney disease. Moreover, IL6 induces NET formation in healthy subjects, while high glucose blunts IL6 effects, predisposing diabetic patients to infections because of loose and lower trap-NET formation.[64] IL1β directly increases vascular endothelial cell permeability, while TNFα is a key factor in the pathogenesis of diabetic neuropathy and neuropathic pain.[65] While waiting for the long-term results of the EXTEND trial (anti-IL6 in diabetes),[66] IL1α/β has been the only target that led to improve glycemia and beta-cell secretory function and reduced markers of systemic inflammation in a controlled double-blind trial.[65] In the Save-More trial, in which IL1Ra (Anakinra) did show that anti-IL1α/β can decrease mortality, the major comorbidity was diabetes.[67] Accordingly, IL1α/β more than IL6 appears to be the key target for patients with diabetes, as a main comorbidity.

### 5.2 | Arterial hypertension

Multiple proinflammatory cytokines, including TNF-α, IL17, IL1 and interferon-γ (IFNγ), cause blood pressure (BP) increase and renal injury.[68-71] Preclinical studies showed that TNF promotes sodium retention during hypertension, possibly via the stimulation of TNF receptor 2 rather than TNF receptor 1.[72] In rats, TNF inhibition attenuates glomerular and tubular injury determined by hypertension of several causes. However, when analysing the data obtained from a meta-analysis of 11 randomized controlled trials, comprising 6321 patients, anti-TNFα therapy associates with a significantly increased risk of developing hypertension in patients with RA,[73] suggesting that anti-TNFα should be avoided in COVID-19 patients with hypertension. Conversely, infusion of exogenous IL1 promotes natriuresis, while endogenous IL1 may potentiate hypertension through several actions that impact renal function, along with TGFβ and IL17 also determines negative impacts, with hypertensive patients having three folds higher peripheral blood levels of IL17A.[74] Key experimental data show that IL-6 contributes to hypertension and enhances sodium and volume resorption in vivo. Moreover, IL-6 plasma levels directly correlate with BP in hypertensive subjects, being reduced by treatment with angiotensin II-receptor blockade,[68-69] suggesting an important role of IL6 in hypertension. In support, in a nonrandomized trial in which hypertension was the main comorbidity in COVID-19 patients, anti-IL6 proved to reduce mortality compared with the standard of care.[75] Accordingly, IL6 may be seen as the primary target in patients with hypertension as main comorbidity.

### 5.3 | Heart failure

The effects of SARS-CoV-2 infection on the heart have been described as the COVID cardiovascular syndrome.[3] In case of hemodynamic instability or left ventricular ejection fraction (LVEF) <50, anti-cytokine therapy could be adopted. Hospitalized SARS-CoV-2-infected patients have

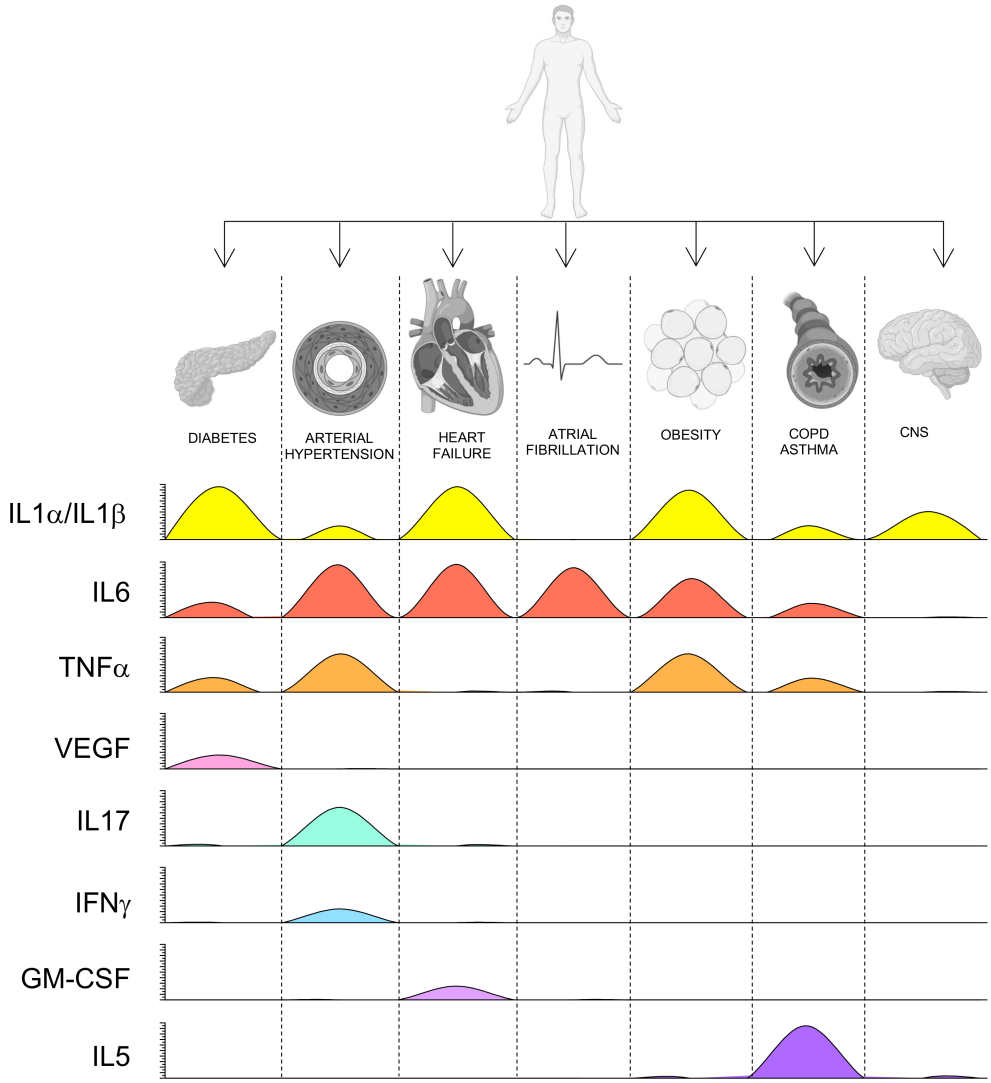


**FIGURE 2** Schematic of taxonomy of cytokines expression based on concomitant comorbidities.

two major clinical phenotypes of heart failure (HF): HF with preserved ejection fraction (pEF) and with reduced ejection fraction (rEF). In the first subtype, anti-IL1α/β therapy failed to improve peak Vo2 and VE/Vco2 slope in a group of obese patients with pEF heart failure,[2] while patients with rEF showed an improvement with a treatment lasting 12 weeks.[71]

The CANTOS trial has demonstrated that persistent inflammation due to increased IL6 plasma levels associated with a 43% increased risk of major cardiovascular events (MACE) was partially covered by anti-IL1β treatment as canakinumab.[74] In the ARISTOTLE trial, plasma levels of IL6 were found to be associated with an increased mortality despite anticoagulation[76] and colchicine could prevent atrial fibrillation by inhibiting IL1β-dependent IL6 release and atrial fibrosis.[77] Moreover, IL1β (and IL6) favours NETosis and thrombus formation acting on tissue factor synthesis. Data show that NETosis and atherosclerosis can be halted antagonizing IL6.[78-79]

Exogenous GM-CSF was found to exacerbate heart failure, and in mice deficient in GM-CSF or its receptor (GM-CSFR), GM-CSF impaired healing after MI recruiting inflammatory leukocytes. In some patients with MI, GM-CSF enhanced angiogenesis.[78-81]

In the RECOVERY trial, in which severe COVID-19 patients were randomized to standard of care or anti-IL6, few patients were treated with DEXA, and the major comorbidities were diabetes and heart disease, and tocilizumab treatment reduced mortality.[82] Based on these data, targeting IL1α/β first, and eventually IL6 in patients with rEF, might be the best approach to control heart disease.

## 5.4 | Atrial fibrillation

A frequent observed comorbidity in hospitalized SARS-CoV-2-infected patients is atrial fibrillation (AF).[83]

These patients are treated with antiarrhythmic drugs and anticoagulants. Several studies reported that inflammation plays a key role in inducing and maintaining the arrhythmogenic status. Using an animal model of postoperative spontaneous atrial fibrillation (sPOAF), the IL6 knockout mouse is protected against the occurrence of sPOAF and the same study showed that humans with POAF had a higher IL-6 concentration in pericardial drainage.[84] Moreover, among 3762 adults with chronic kidney disease enrolled in the Chronic Renal Insufficiency Cohort (CRIC) Study, at baseline, 642 had history of AF, but only 44 had AF in ECG recording. During a mean follow-up of 3.7 years, 108 subjects developed new onset of AF. Plasma IL-6 levels arose as significantly associated with the presence of AF at baseline and with the new-onset AF.[85] In HL-1 mouse atrial cardiomyocytes, IL6 significantly decreased Connexin 40 and Connexin 43, whose expression in the atrium critically contribute to atrial conduction velocity and refractoriness heterogeneity, representing major determinants of re-entry mechanisms maintaining AF. Therefore, in patients with active inflammatory diseases, such as SARS-CoV-2 infection, it was shown that P-wave dispersion indices were increased, but rapidly dampened within a few days as C-reactive protein dropped to normal levels and IL6 plasma levels declined. In these patients, both P-wave dispersion indices and IL6 changes inversely associated with circulating connexin levels.[86] These data suggest that for AF patients, IL6 represents a putative therapeutic target.

## 5.5 | Obesity

Adipose tissue responds to overfeeding by raising the immune response. The inflammatory molecules, produced by the free fatty acids (FFA) in the three types of adipose depots (white, brown and beige) through TLR 2 and TLR 4 and recruitment of M1-like macrophages, are mainly IL1β, TNFα, IL6 and IL18, promoting insulin resistance.[87] Among these molecules, multiple evidence supports the notion that TNFα is a key driver of cachexia in humans and in animal models[88] and data in TNF-receptors knockout mice (high-fat diet fed p75−/− C57bl76 mice (type II receptor)) showed the lowest body weight, while p55−/− and double knockout mice p55 −/− and p75 −/− gained weight over 16 weeks. Overall, these data suggest that TNF**α** acting via its receptors is not a contributor to obesity and associated insulin resistance.[89-90] In this context, while anti-IL1β did not prevent the occurrence of diabetes in the CANTOS trial,[91] IL-1α/β antagonist (Anakinra) had a beneficial effect on glucose handling in patients with type 2 diabetes mellitus.[65] Furthermore, experimental data show that IL6 deficiency in mice leads to mature-onset obesity,[92] but that also knockout IL1RA gene mice of both sexes developed mature-onset obesity.[93] Based on these assumptions, IL6 more than IL1α/β, might be the therapeutic target in obese patients. In fact, in the REMAP-CAP trial in which COVID-19 patients were randomized to anti-IL6 or anti-IL1α/β, being the main comorbidities obesity, diabetes and COPD, the best results were obtained with anti-IL6.[94]

## 5.6 | COPD and asthma

A high mortality rate has been observed in SARS-CoV-2-infected patients hospitalized for lung disease.[95] Unfortunately, inflammation in COPD lungs poorly responds to corticosteroid treatment. Several cytokines, such as IL1β, IL4, IL5, IL6, IL8, IL13, IL18, IL23, IL33, eotaxin-1 (CCL-11), thymic stromal lymphopoietin (TSLP) and TGFβ, have been targeted in order to achieve a more specific anti-inflammatory action, yet none did improve the outcome of the more severe cases.[96-97] In steroid refractory nonatopic asthma, anti-IL6 allowed to rescue resistant patients.[98] Even though, in a double-blind randomized controlled trial, etanercept had no beneficial effect for the treatment of acute exacerbations of COPD, patients with <2% eosinophils at baseline treated with etanercept showed a better response than those treated with prednisone,[99] restoring the broad attenuation effects of corticosteroids on inflammation and airway remodelling.[100] In asthma, anti-IgE therapy (omalizumab) improved outcomes in allergic asthma, and three anti-IL5 biologics (i.e. mepolizumab and others) and one anti-IL4R biologic (dupilumab) recently emerged as promising treatments for endotype driven by type 2 asthma inflammation.[101] Therefore, despite none of these drugs have been tested in SARS-CoV-2-infected patients, a fully characterized cytokine taxonomy, such patients' category, is mandatory to optimize treatment management and disease outcome.

## 5.7 | Central nervous system diseases

Brain diseases after SARS-CoV-2 infection have been reported as a consequence of the severe infection,[102] developing as inflammatory encephalomyelitis, necrotic lesion, thrombotic lesions, Guillain–Barrè or brachial plexopathy and suggesting the multi-systemic nature of SARS-CoV-2 infection. When dealing with CNS disease, inflammatory or thrombotic, all associated with central neuroinflammation, and the possible intervention with biologics arose to be limited only to anti-IL1α/β whose effectiveness in animal models as well as in humans has been demonstrated.[103-104]

### 5.8 | Clinical efficacy of biologics in the treatment of lung damage in SARS-COV-2-infected patients

We made a review of all published studies and articles were chosen for inclusion based on their relevance to biologics therapy (anti-IL6, anti-IL1, anti-GM-CSF/CSF-R and JAK inhibition) and major outcome (death). Death in fact represents the major outcome either in hospitalized SARS-CoV-2-infected patients[105] and in those admitted to ICUs.[6] Overall, hospital mortality from COVID-19 is estimated to be approximately 15%–20%, rising up to 34%–72% among patients requiring ICU admission after SARS-CoV-2 infection.[47]

Given the inhomogeneity of the reports, presenting different parameters in different settings, we chose to consider and analyse only studies dealing with patients with lung failure as demonstrated by at least one of the two altered parameters as entry criteria (PaO2/FiO2 < 300, SpO2 < 93% at room air and categorized according to the NIAID Ordinal Scale defining the severity of COVID illness and having death as the major outcome (Figure 3). In the analysis, we deliberately selected randomized controlled trials with at least one of these parameters and discarded studies with less than 100 enrolled patients.

Multiple studies assessed the efficacy of distinct biologics on lung failure in SARS-CoV-2-infected patients. Eligible criteria for biologic start were at least $PaO_2/FiO_2 < 300$ or $SpO_2 < 93\%$ at room air and death was defined as the major outcome. Moreover, several uncontrolled studies reported conflicting results about the effectiveness of anti-IL6R in the treatment of COVID-19 disease until the release of the REMAP-CAP[94] and the RECOVERY[82] trials. Afterwards, the meta-analysis conducted by the World Health Organization (WHO)[106] finally gave clear-cut support to the adoption of anti-IL6R in severe-critical SARS-CoV-2-infected patients (NIAID Ordinal Scale 6 and 7) (Figure 3) in addition to dexamethasone. Targeting IL1 showed contrasting results in uncontrolled studies, until a phase 3 trial conducted on 594 patients with an entry median PaO2/FiO2 of 237 (Ordinal scale 5/6) was released. This study showed that anti-IL1α/β can significantly decrease mortality,[67] while anti-IL1β did not show any meaningful clinical result.[107] Interestingly, when considering only critical cases (NIAID Ordinal Scale 6/7) in the REMAP-CAP study, in which the effectiveness of tocilizumab, sarilumab and anakinra was analysed, and tocilizumab (odds ratio 1.42) and sarilumab (odds ratio 1.51) but not anakinra (odds ratio 0.97) improved survival and duration of organ support of SARS-CoV-2 infected critically sick patients.[108]

The demonstration that targeting the JAK–STAT pathway leads to very similar results with tofacitinib (JAK1-3 inhibitor) in patients in NIAID Ordinal Scale 5–6[109] and baricitinib (JAK1-2 inhibitor) in patients in NIAID Ordinal Scale 4–6 and 7[110-111] support the rationale that the main driver of poor outcomes is certainly the underlying inflammation. In fact, dexamethazone represents now the milestone to treat severe (NIAID Ordinal Scale 6/7) pneumonia because of its strong and wide anti-inflammatory action.[112-113] Due to their broad anti-inflammatory action, JAK inhibitors might be chosen early on after the 'primary molecular target' failed (NIAID Ordinal Scale 5), or 'in rapid progressors' since the early phase (NIAID Ordinal Scale 6–7) of the disease. In recent months, as clinicians, we have realized that the clinical decision must be as rapid

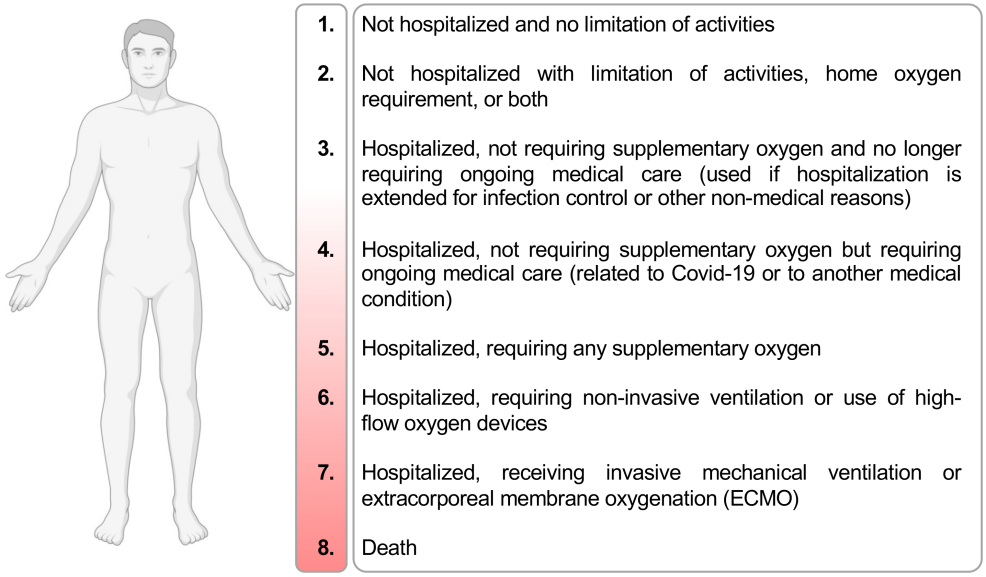


FIGURE 3 NIAID Ordinal Scale Score.

and personalized as possible to achieve the best clinical outcome, and that the biology of the disease at specific time points should drive the therapeutic choices.[114] Why did we come to use drugs adopted first in chronic inflammatory autoimmune arthritis? This is because the inflammation occurring within the lungs of SARS-CoV-2-infected patients arose to be very similar to what is seen in the synovial tissue of a severe chronic inflammatory disease (i.e. rheumatoid arthritis—RA), in terms of macrophage subpopulations. It was hypothesized that the mechanisms enhancing tissue inflammation were similar[115] due to the similarity found between alveolar and synovial tissue infiltrating macrophages (STMs). In particular, bronchoalveolar lavage fluid (BALF) macrophage cluster $FCN1^{pos}SPP1^{pos}$ is predominant in severe COVID-19 pneumonitis and is transcriptionally similar to $CD48^{high}S100A12^{pos}$ and $CD48^{pos}SPP1^{pos}$ STM clusters that drive RA synovitis.[116-117] Therefore, given that sudden progressive systemic inflammation might develop in a variable percentage of SARS-CoV-2-infected patients, here we raise the issue that patients with different coexistent comorbidities may selectively respond to distinct targets, thus explaining the lack of complete control of many severe-critical SARS-CoV-2 infections. Importantly, we learnt from several studies that viral cultures are generally negative for SARS-CoV-2, 8 days after symptoms onset.[118-120] Therefore, a specific antiviral treatment may play a major role initially (i.e. molnupiravir, paxlovid, monoclonals)[121-122] and less afterwards when it is mainly the COVID-19 systemic disease that causes organ damage at various levels which might be amplified by co-existing comorbidities (Figure 1).

## 6 | CONCLUSIONS

SARS-CoV-2 infection might lead to different disease course from asymptomatic to severe multi-organ failure based on the degree of the host-immune response against the virus. Distinct comorbidities are known to influence the individual signature based on specific deregulation of inflammatory molecules taxonomy which are involved in the host-immune response against SARS-CoV-2. Therefore, therapeutic interventions should be tailored, as much as possible, considering single or multiple comorbidities impacting the concomitant biological background, aimed to reduce the severity of host-inflammatory response-related tissue and organ damage.

## AUTHOR CONTRIBUTIONS

EG and GF made substantial contributions to the study conception and design, acquisition of data, and analysis and interpretation of data, drafted the paper for its intellectual content and finally approved the version of the submitted article. SA, DB, AMP, SP and BT made substantial contributions to the acquisition of data, and analysis and interpretation of data, revised the paper for its intellectual content and finally approved the version of the submitted article.

## CONFLICT OF INTEREST STATEMENT

We state here that no conflicts of interest for this manuscript exist.

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