Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Seminars in Immunology 55 (2021) 101508

Contents lists available at ScienceDirect

Seminars in Immunology

journal homepage: www.elsevier.com/locate/ysmim

Review

Hallmarks of immune response in COVID-19: Exploring dysregulation and exhaustion

Alessio Mazzoni, Lorenzo Salvati, Laura Maggi, Francesco Annunziato *, Lorenzo Cosmi

Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy

ARTICLE INFO

Keywords:
SARS-CoV-2
Immune dysregulation
Exhaustion
Lymphocytes
Cytokines

ABSTRACT

One and half year following the occurrence of COVID-19 pandemic, significant efforts from laboratories all over the world generated a huge amount of data describing the prototypical features of immunity in the course of SARS-CoV-2 infection. In this Review, we rationalize and organize the main observations, trying to define a "core" signature of immunity in COVID-19. We identified six hallmarks describing the main alterations occurring in the early infection phase and in the course of the disease, which predispose to severe illness. The six hallmarks are dysregulated type I IFN activity, hyperinflammation, lymphopenia, lymphocyte impairment, dysregulated myeloid response, and heterogeneous adaptive immunity to SARS-CoV-2. Dysregulation and exhaustion came out as the trait d'union, connecting abnormalities affecting both innate and adaptive immunity, humoral and cellular responses.

1. Introduction

"*After all, do not fear difficult times. The best comes from there.*" - Rita Levi Montalcini

The COVID-19 pandemic has dramatically revealed the impact of emerging infections in the 21st century world. Less than a year after SARS-CoV-2 isolation, vaccines have been developed using new platforms and administered on a large scale. Globally, as of October 2021, there have been more than 236 million confirmed cases of COVID-19, including more than 4 million deaths, and more than 6 billion vaccine doses have been administered [1]. Innate and adaptive immune responses are essential in protection against viral infections and in successful vaccination. We present a comprehensive overview of the main characteristics of immune response in different phases of COVID-19.

Taking inspiration from the classification of the major properties of cancer [2], we tried to identify the hallmarks defining the immune response in COVID-19 (Fig. 1). Indeed, we know that SARS-CoV-2 infection can profoundly affect the functionality of the immune system, leading to profound dysregulation and immune cell exhaustion. We identified six hallmarks that collectively define the major immunological abnormalities in COVID-19. The first hallmark, occurring early after the infection, is the dysregulated type I IFN response, which blunts the establishment of an efficacious rapid antiviral response. The inability to restrict viral replication promotes the production of high levels of pro-inflammatory cytokines, favoring the occurrence of systemic hyper-inflammation (second hallmark). Cytokine storm is accompanied by a dramatic lymphocyte depletion (third hallmark) in both blood and secondary lymphoid organs. We now know that lymphocytes are not only affected in terms of absolute numbers, but also from a functional point of view. Indeed, lymphocyte impairment (fourth hallmark) is another typical feature of severe COVID-19. Myeloid cell response dysregulation also occurs (fifth hallmark), affecting all cell subsets. The sixth hallmark concerns SARS-CoV-2 specific adaptive immune response that is highly heterogeneous in terms of magnitude, with a strong correlation with clinical outcome.

2. Dysregulated type I IFN activity

Following SARS-CoV-2 infection in the upper respiratory tract, type I IFN release is a major mechanism involved in limiting viral replication [3]. Accordingly, type I IFN is highly effective also on SARS-CoV-2 replication, as demonstrated by *in vitro* experiments that showed its suppressive ability when exogenously administered [4]. In addition, type I IFN promotes the development of effective innate and adaptive immune responses. Indeed, it favors maturation of antigen presenting cells, activation of NK cells and both $CD4^+$ and $CD8^+$ T cell responses [5]. Given the pivotal role of type I IFN pathway in the antiviral

* Corresponding author at: Department of Experimental and Clinical Medicine, University of Florence, Viale Pieraccini, 6, 50134, Firenze, Italy.
E-mail address: francesco.annunziato@unifi.it (F. Annunziato).

https://doi.org/10.1016/j.smim.2021.101508
Received 30 July 2021; Received in revised form 11 October 2021; Accepted 15 October 2021
Available online 26 October 2021

response, viruses have evolved to counteract or delay the production of this cytokine. SARS-CoV-2 does not make an exception, and it has been shown that non-structural proteins (nsp) 1 and nsp6 are particularly effective in suppressing type I IFN response [6]. Furthermore, ORF3b and ORF6 are also potent antagonists of interferon activity [7,8]. In agreement with this, severe COVID-19 patients are characterized by an impaired type I IFN response, with no IFN-β and low IFN-α production [9,10]. However, other studies reported instead an increased type I IFN signature in severe patients, with high expression of IFN-stimulated genes (ISG) in bronchoalveolar lavage fluid cells [11] and circulating monocytes [12]. In agreement, single-cell RNA sequencing (scRNAseq) data showed that PBMNC from moderate COVID-19 patients had an inflammatory signature driven by TNF-α and IL-1, while in severe patients type I IFN response was also present [13]. The differences observed in human studies may be related to different time of sampling. Indeed, the importance of an appropriate early response is confirmed by *in vivo* murine studies showing that delayed type I IFN production orchestrates an inappropriate proinflammatory response with lung immunopathology in the context of SARS-CoV-1 infection [14]. On the contrary, early administration of type I IFN in this model has a protective effect with reduced viral load and controlled inflammation [14]. Additional studies obtained in mice demonstrated a role for type I IFN in the recruitment of proinflammatory cells into the lungs, thus contributing to pathology [15]. Other mouse models of viral infections have shown that impaired type I IFN response is associated with increased pathology due to the concomitant production of high levels of proinflammatory cytokines [16]. Supporting this concept, a genetic study has shown that loss of function variants affecting type I IFN response are significantly enriched in patients with life threatening SARS-CoV-2 pneumonia [17]. The same group also reported the presence of autoantibodies neutralizing type I IFN, predisposing to the development of severe COVID-19 [18]. Altogether, the data suggest that viral-mediated delayed production of type I IFN is the first step towards COVID-19 worsening.

3. Hyperinflammation

Some patients with COVID-19 develop a hyperinflammatory syndrome that is characterized by elevations in proinflammatory markers and multiorgan failure resembling the cytokine release syndrome that may complicate chimeric antigen receptor (CAR)-T cell therapy [19–21,23–25]. Cytokine release syndrome is a systemic inflammatory response that can be triggered by various therapies, infections, cancers, autoimmune diseases, and monogenic disorders [26,35]. Active evaluation of efficacy and safety of immunomodulatory therapies in COVID-19 patients through extensive approaches integrating clinical, laboratory, pathologic, and imaging features has played a crucial role in the management of COVID-19 [27,28]. Nonetheless, case-series, clinical trials enrolling small numbers of patients, and observational cohort studies are not sufficient for good clinical practice and suffer from potential biases. Large randomized clinical trials are necessary to improve patients' outcomes and provide reliable data to guide evidence-based clinical decisions [29].

Recovery from viral infections requires an effective host immune response that eliminates the virus, or at least controls viral replication. Basically, the effector activity of the immune response is counterbalanced by mechanisms of suppression and/or regulation. Sustained viral replication resulting from impaired type I IFN-γ production and persistent activation of the immune response result in a continuous inflammatory process whose consequences are detrimental [30]. A dysregulated response is indeed ineffective in clearing the virus and causes epithelial and endothelial damage, vascular leakage, up to organ failure [31–33]. SARS-CoV-2 infection recapitulates the critical role of an effective immune response and the devastating effects of immune dysregulation. After an initial response with generally mild to moderate symptoms, some patients show a progression to an excessive and dysregulated inflammatory response [34] (Fig. 2). This is a hyperinflammatory response that equals a "cytokine storm", a potentially life-threatening systemic inflammatory syndrome involving elevated plasma cytokine levels and immune-cell hyperactivation with consequent acute systemic inflammatory symptoms and organ dysfunction [35].

A complex, interconnected network of innate and adaptive cell types, signaling pathways, and cytokines is involved in COVID-19 associated cytokine storm. Inflammatory markers (C-reactive protein, serum amyloid A, fibrinogen, ferritin) are highly increased and correspond to elevated serum cytokine levels including IL-1β, IL-1RA, IL-2, IL-4, IL-6, IL-7, IL-10, IL-19, G-CSF, TNF-α, IFN-γ, but also chemokine levels including monocyte chemoattractant protein (MCP)-1 (CCL2), MCP-2 (CCL8), MCP-3 (CCL7), CCL3, CXCL8 (IL-8), CXCL9, CXCL10 (IP-10), CXCL5 [25,36–38,40–44,46,47]. Circulating levels of IL-6 are significantly higher in severe disease than mild to moderate disease and predict COVID-19 severity and survival [49–51]. It is yet unknown the exact pathophysiology underlying COVID-19 associated cytokine storm. Immune hyperactivation could result from inappropriate triggering or danger sensing, impaired magnitude of response (either inappropriate or

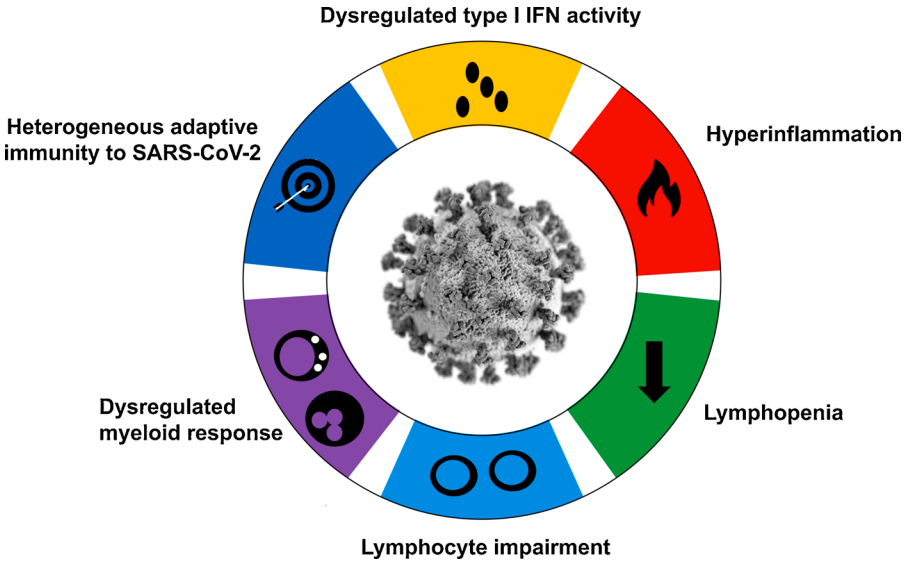

Fig. 1. The Hallmarks of immune response in COVID-19.
In severe COVID-19 patients, six main immunological abnormalities can be observed. 1) Dysregulated type I IFN activity occurs early after the infection, impairing viral replication control. 2) The unrestrained viral replication promotes the production of high levels of pro-inflammatory cytokines (hyperinflammation). 3) Cytokine storm is commonly accompanied by decreased absolute numbers of circulating lymphocytes (lymphopenia). 4) Lymphocytes display also functional impairment in terms of cytokine production, cytotoxic activity and exhibit increased expression of exhaustion markers. 5) Myeloid cell response is also affected, with profound alterations towards an immature and hyperactivated phenotype. 6) Heterogeneous cellular and humoral adaptive immune response to SARS-CoV-2 associates to severe disease. [SARS-CoV-2 ultrastructure is reproduced from Public Health Image Library (PHIL ID #23312)]

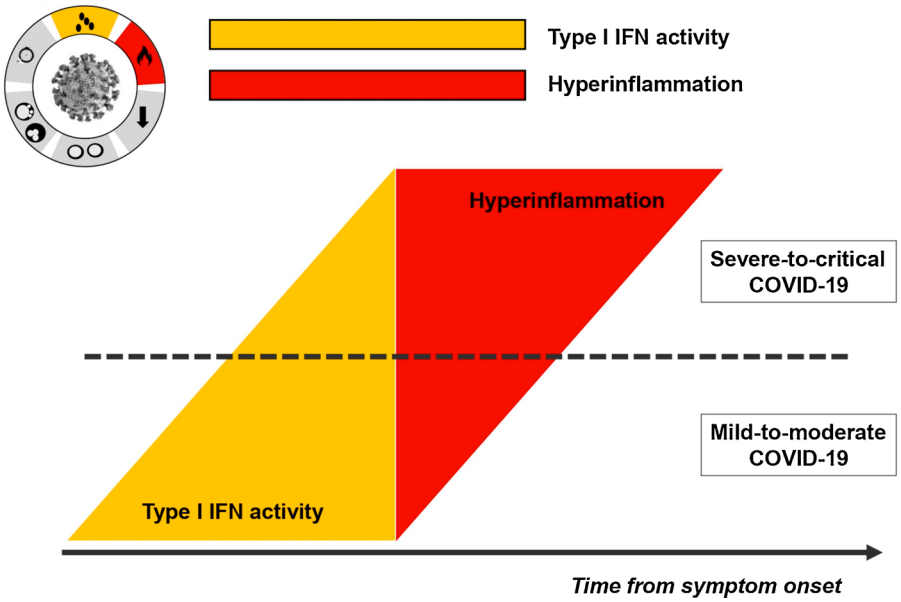

Fig. 2. Dysregulated type I IFN activity and hyperinflammation.
In the early phases of mild-moderate COVID-19, an efficacious type I IFN response restrains viral propagation, allowing proper control of the infection with the activation of a balanced immune response and moderate production of pro-inflammatory cytokines. However, in some patients several mechanisms can impair the early type IFN activity, including viral evasion systems, the presence of anti-IFN autoantibodies or genetic predisposition with mutations of molecules involved in IFN-signaling pathway. In any case, the delayed and reduced activity of type I IFN response cannot control viral replication, which leads to the compensatory, aberrant production of pro-inflammatory cytokines. This is the basis of cytokine storm occurring in severe COVID-19 patients.

ineffective), and/or failure to resolve inflammation because of ongoing viral replication or immune dysregulation [35,52]. Multisystem inflammatory syndrome in children (MIS-C) is a rare but serious complication of COVID-19 in the pediatric population; MIS-C is a hyperinflammatory syndrome with delayed presentation, generally occurring 2–6 weeks after SARS-CoV-2 infection [53–56]. In MIS-C associated cytokine storm, cytokines as IL-7, IL-8 and IFN-γ have been described to play a crucial role, differently from what is observed in adults with severe acute COVID-19 disease [47,57,58].

Many monoclonal antibodies targeting pro-inflammatory cytokines involved in COVID-19 cytokine storm have been used as immunomodulators to dampen the hyperinflammation. On March 2020, tocilizumab, a humanized anti-IL-6 receptor monoclonal antibody, approved in 2017 for the treatment of CAR-T cell-induced cytokine storm and used in many rheumatologic diseases, was proposed as immunomodulatory therapy in patients with severe COVID-19 [59–61]. However, studies on the efficacy of tocilizumab in patients with COVID-19 have been controversial, particularly considering differently enrolled populations and study designs [62–65,67–70,245]. IL-6 levels have been correlated with SARS-CoV-2 viral load, disease severity, and prognosis [49,50,71]. Blocking the IL-6 axis might account for improved pulmonary vascular perfusion: vascular radiologic score and alveolar-arterial oxygen gradient significantly improved after tocilizumab administration [68]. Among hospitalized adults with progressive severe or critical COVID-19 who have elevated markers of systemic inflammation, tocilizumab is suggested in addition to standard of care rather than standard of care alone [67]. It has been shown that in COVID-19 patients circulating IL-6 levels inversely and significantly correlate with granzyme-A producing NK cells [49]. In fact, increased levels of IL-6 inhibit NK cytotoxicity and downregulate the expression of perforin and granzyme [72–75]. Remarkably, in a small cohort of COVID-19 patients requiring intensive care, tocilizumab resulted in restoring of the cytotoxic potential of NK cells, as well as in reversion of metabolic alterations [49,76]. Sarilumab a monoclonal antibody with higher affinity for the IL-6 receptor than tocilizumab has been used in severe-critical COVID-19 patients showing conflicting results [64,77–79]. Anakinra, a recombinant human IL-1 receptor antagonist, approved for use in several autoinflammatory syndromes, has been studied for the treatment of severe COVID-19 with promising results [80–82,251,258]; however, no evidence of clinical benefit was observed in adults hospitalized with COVID-19 mild-moderate pneumonia [83]. Canakinumab, a human anti-IL-1β monoclonal antibody has been proposed in COVID-19 treatment, but efficacy needs to be fully demonostrated [84–86]. In the context of COVID-19-associated cytokine storm, targeting the JAK-STAT signaling pathway via JAK-inhibitors has emerged as a possible key in controlling the downstream signal mediated by cytokine receptors [87,88]. Ruxolitinib (JAK1/JAK2 inhibitor), baricitinib (JAK1/JAK2 inhibitor) and tofacitinib (pan-JAK1 inhibitor) have been used in COVID-19 hospitalized patients with good results [42,89–91,243]. In a randomized clinical trial, tofacitinib was superior to placebo in reducing the incidence of death or respiratory failure through day 28 [91]. Combination treatment of baricitinib plus remdesivir resulted superior to remdesivir alone in reducing recovery time and accelerating improvement in clinical status among patients with COVID-19, particularly among those receiving high-flow oxygen or noninvasive ventilation [92,93]. In hospitalized adults with severe COVID-19 and increased inflammatory markers but not on invasive mechanical ventilation, baricitinib rather than no baricitinib is recommended [67]. Evaluation of safety profile of JAK-inhibitors in COVID-19 must be addressed [94,95].

In 2003 in a correspondence to the NEJM Sung and Lee explained the rationale of the use of corticosteroids in SARS: “we used corticosteroid treatment to suppress the cytokine storm, hoping that would stop the progression of pulmonary disease. And, in fact, in many cases, it did. Lung shadows started to resolve and oxygenation improved after corticosteroid treatment. We must emphasize that corticosteroids were not used to treat acute respiratory distress syndrome (ARDS)” [96]. Immunosuppressive treatment had already been a major point for discussion in SARS-CoV infection [97–101]. Given the hyperinflammatory state associated with COVID-19, immunomodulatory treatments have been evaluated and are under evaluation in the management of patients with COVID-19. In hospitalized patients, the use of dexamethasone for up to 10 days resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone but not among those receiving no respiratory support [102]. In a prospective meta-analysis of clinical trials of critically ill patients with COVID-19, administration of systemic corticosteroids (dexamethasone, hydrocortisone, or methylprednisolone), compared with usual care or placebo, was associated with lower 28-day mortality, even if there are clinical trials showing conflicting results [45,103–105]. To date the use of corticosteroids in COVID-19 is recommended only in critical cases, suggested in hospitalized patients with severe disease, while discouraged in mild-moderate disease not requiring supplemental oxygen; no indications are available for those patients with mild-moderate COVID-19 in the outpatient setting [67,240]. In a cohort of children and

adolescents with suspected MIS-C, no evidence was found that recovery from disease differed after primary treatment with intravenous immunoglobulins (IVIG) alone, IVIG plus corticosteroids, or corticosteroids alone [106]. Restricting the analyses to those children who met the WHO criteria for MIS-C, a modest evidence of benefit for recovery with corticosteroids alone compared to IVIG alone was observed [106]. Another study demonstrated that among children and adolescents with MIS-C, initial treatment with IVIG plus corticosteroids was associated with a lower risk of new or persistent cardiovascular dysfunction compared to IVIG alone [107]. These data support the rapid initiation of immunomodulatory therapy in patients with MIS-C, as it can be life-saving [108].

In conclusion, more studies focusing on the mechanisms of hyperinflammation in COVID-19 are necessary to support the use of immunomodulatory therapies, particularly in different subsets of patients and at different times of disease course.

4. Lymphopenia

A common laboratory feature of SARS-CoV-2 infection is lymphopenia (i.e. an absolute lymphocyte count < 1000 cell/μl). Patients with COVID-19 show significant decrease of absolute numbers of circulating T cells (T $CD3^+$, T $CD4^+$, T $CD8^+$), B cells ($CD19^+$), NK cells ($CD56^+$), and NKT cells ($CD3^+CD56^+$) [38,49,109,111,113]. The CD4/CD8 ratio is generally higher than 1.5, as a result of a greater reduction of $CD8^+$ T cells than $CD4^+$ T cells [49,249] (Fig. 3). Loss of the NKT cell subset has been reported as one of the prominent features of COVID-19, which became apparent already within the first week of hospital admission and could predict disease evolution [114]. On the contrary, no significant alterations were described in peripheral blood [49,116] for T follicular helper cells (Tfh). Data on T regulatory cells are highly heterogeneous, with some reports showing an increase while some others showing a decrease in the circulation of severe COVID-19 patients [117,118]. Lymphopenia occurring in severe COVID-19 affects also the B cell compartment. A marked reduction in B cell absolute numbers has been described [49,177], although the percentages of total and naïve B cells did not show differences between patients and healthy controls [49, 119]. Lymphopenia is not limited to circulating cells, indeed it also occurs in secondary lymphoid organs: lymphocyte depletion of spleen and of lymph nodes has been observed in autoptic studies, similarly to SARS infection [120–123]. In the spleen, atrophy of the white pulp with even complete loss in some fatal cases has been described, while the red pulp appears to be congested and hemorrhagic [121,124]. In lethal COVID-19 cases, lymph nodes from the cervical, mediastinal and hilar regions revealed moderate-severe capillary stasis and edema, proliferation of extrafollicular plasmablasts (particularly, IgG^+ and IgM^+ plasmablasts), mild-moderate plasmacytosis, predominance of $CD8^+$ T cells, sinus histiocytosis with hemophagocytosis [125,246]. Moreover, lymph nodes and spleen are characterized by hypoplasia or absence of germinal centers with decreased follicular dendritic cells and Tfh cells, as well as striking reduction in Bcl-6^+ germinal center B cells paralleled by loss of circulating transitional and follicular B cells [126,246]. Tfh reduction in secondary lymphoid organs has been associated with severe inflammation, indeed high TNF-α levels were detected inside and outside follicles [126]. The increased presence of extrafollicular plasmablasts in the absence of follicular hyperplasia suggests rapid or primarily transient B cell immune response bypassing the germinal center response [127,128, 246]. The negative correlation between the presence of secondary follicles and SARS-CoV-2 viral load in the lungs might be consistent with delayed germinal center response [246]. It is known that most patients with sepsis develop signs of profound and long-term immunosuppression either concomitantly with initial inflammation or delayed [129–134]. Mechanisms contributing to sepsis-induced immunosuppression include cellular apoptosis, autophagy, endotoxin tolerance, metabolic and transcriptional reprogramming [129,135]. Sepsis induces a tolerogenic state that contributes to immunosuppression and explains the increased susceptibility to secondary infections after a severe primary infection [136]. Severe-critical COVID-19 has similarities with sepsis [134,137,138] and immunosuppression is indeed a pathological feature [94,95,139]. Starting with the first descriptions of COVID-19 case-series in 2019 at the beginning of the pandemic, a correlation between disease severity and lymphopenia had readily been demonstrated. Severe COVID-19 patients requiring intensive care have indeed significantly lower absolute number of circulating lymphocytes compared to patients with moderate disease [22,140–143,145,146] (Fig. 3). Lymphopenia on admission has then been correlated with poor outcomes in COVID-19 patients [147,148,247]. Lower lymphocyte count is associated with increased mortality, acute respiratory distress syndrome, need for intensive care, and severe disease, particularly in younger patients [247]. During hospitalization, lymphocytes count is more reduced in

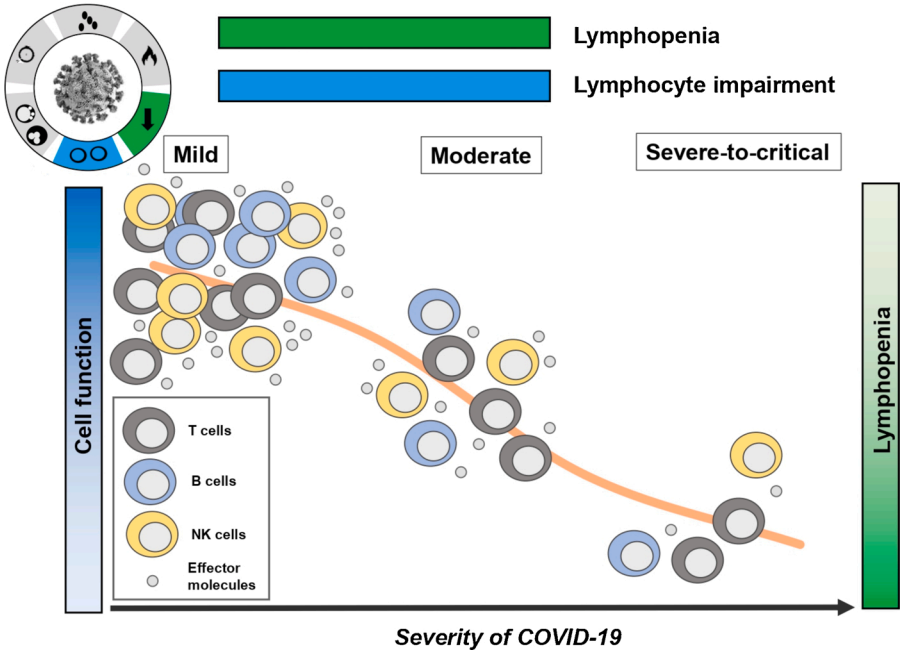

Fig. 3. Lymphopenia and lymphocyte impairment. COVID-19 progression towards severe phase is characterized by marked reduction of circulating lymphocytes. This defect affects all lymphocyte subsets i.e., T cells, B cells, NK cells. Lymphocyte absolute numbers are decreased also in secondary lymphoid organs, as demonstrated by post-mortem studies. Lymphocytes are profoundly affected in terms of functionality, as they are characterized by reduced production of pro-inflammatory cytokines and cytotoxic potential. Accordingly, lymphopenia and lymphocyte function impairment positively correlate with disease severity and all lymphocyte subsets display an exhausted phenotype.

patients who do not survive and have a more severe disease compared to patients who recover or have milder disease [22,149]. In survivors there is, indeed, a progressive increase of lymphocyte counts over time [22]. Lymphopenia is generally lower 4–7 days after symptoms onset and is concomitant with increase of pro-inflammatory cytokines [150,151]. It should be noted that other respiratory viral infections are associated with transient lymphopenia, from influenza to SARS [152–155]. It was initially speculated that peripheral lymphopenia in patients with COVID-19 could be a consequence of local recruitment into the lung tissue or lymphocyte adhesion to the endothelium [156,242]. Autopsy lung specimens have shown interstitial and perivascular lymphocytic infiltration of varying extent [157,158]. However, in severe-critical COVID-19, lymphopenia could be a consequence of elevated levels of IL-6, IL-10 and TNF-α through a direct effect on T cell subsets, but also as an indirect effect on dendritic cells and neutrophils [38,110]. In addition, hyper-activated T cells or elevated expression of pro-apoptotic molecules such as FAS (CD95), TRAIL (TNF-related apoptosis-inducing ligand) or caspase 3 could also contribute to lymphocyte reduction [38,116,159]. Increased levels of circulating apoptotic T cells, defined by expression of cleaved caspase-3 and/or cleaved PARP, were indeed observed in COVID-19 patients [161]. Various mechanisms have been hypothesized as implicated in the occurrence of lymphopenia in COVID-19, nonetheless no definite pathogenesis has been described yet [162]. Longitudinal analyses of TCR and BCR repertoire in COVID-19 patients could reveal important findings on the causes and effects of lymphocyte depletion [163–165].

5. Lymphocyte impairment

Another hallmark that characterizes the lymphocyte compartment in COVID-19 is the altered functionality. We know indeed that both innate and adaptive lymphocytes are significantly impaired in severe SARS-CoV-2 infection, as a result of delayed type I IFN production, consequent cytokine storm and viral clearance inability. Although a direct relationship between these parameters and lymphocyte exhaustion has not been proved yet, we may speculate that persistent severe inflammation may impact on lymphocyte functionality. Indeed, it has been proved that inflammation and oxidative stress may impact main T cell effector functions and differentiation [166]. In addition, it has been demonstrated that increased levels of both soluble and membrane-bound PD-L1 positively correlate with COVID-19 severity [167,241,250]. This may result in increased ligation of cognate PD-1 receptors on lymphocytes thus resulting in their impaired functionality. Herein we describe the major abnormalities observed in both innate and adaptive lymphocytes (Fig. 3).

5.1. NK cells

NK cells have a primary role in viral clearance and, accordingly, it has been described their accumulation in the lungs of COVID-19 patients [144,168]. However, alterations in NK cell response have been reported in COVID-19 patients, especially in those with severe disease [114]. NK cells display reduced IFN-γ and TNF-α production, together with reduced expression of cytotoxic molecules such as granzymes and perforin [49,169–174]. These alterations are particularly evident in patients requiring intensive care therapy. Impaired NK cell functionality is directly dependent on the hyperinflammation occurring at later stages of COVID-19. Indeed, granzyme A expression inversely correlated with IL-6 serum levels [49]. Targeting IL-6 signaling with tocilizumab restored granzyme expression in a cohort of critically ill patients, while the JAK-STAT inhibitor ruxolitinib increased TNF-α production [42,49]. NK cells from SARS-CoV-2 infected subjects not only show reduced expression of cytotoxic molecules, but also reduced degranulation as assessed by CD107 expression when tested ex vivo [170–173]. In agreement with the reduced NK cell functionality, these cells exhibited an increased expression of inhibitory checkpoint molecules such as PD1, TIGIT and Tim-3 [173,175]. Supporting these data, scRNAseq showed that $CD56^{dim}$ NK cells, classically considered cytotoxic cells, are primarily depleted in severe COVID-19 patients, while $CD56^{bright}$ NK cells, known to produce high levels of IFN-γ and TNF-α, are depleted in all COVID-19 patients [12]. Single cell transcriptome data further reinforced the idea that NK cells in COVID-19 express inhibitory receptors as PD1, LAG-3 and Tim-3 [12]. A selective expansion of "adaptive" $NKG2C^+$ $CD57^+$ NK cells has been demonstrated in COVID-19. This NK cell subset is commonly associated with CMV infection [176], but it can also expand during other viral infections in CMV seropositive subjects. Of note, adaptive NK cell expansion was primarily demonstrated in CMV-seropositive severe COVID-19 patients, but in absence of an ongoing anti-CMV immune response [175]. This finding suggests that the expansion of $NKG2C^+$ $CD57^+$ NK cells may be directly induced by SARS-CoV-2 infection. Additional studies are needed to clarify the role of this cell subset in COVID-19.

5.2. T cells

T cell compartment is significantly affected in severe SARS-CoV-2 infection. Phenotypic analysis demonstrated that $CD4^+$ T cells from COVID-19 patients do not show alterations in the frequency of naïve and effector/central memory populations. Instead, $CD8^+$ T cells display a marked reduction in the frequency of naïve cells, with a parallel expansion of terminally differentiated $CCR7^-CD45RA^+$ TEMRA cells [49,119]. High expression of the surface marker CD57 further suggests the increased senescence of $CD8^+$ T cells in COVID-19 [49,119]. Furthermore, $CD8^+$ TEMRA cells from COVID-19 patients show a reduced proliferative capacity [119]. Additional studies have also demonstrated the upregulation of inhibitory checkpoints by both $CD4^+$ and $CD8^+$ T cells in COVID-19 patients, especially in the "non-naïve" compartment [114,116,119,159,171]. Of note, PD1 expression by $CD4^+$ T cells significantly increased during the first 5 days post hospital admission, but then it normalized in moderate patients while remaining elevated in severe ones [114]. In agreement with the increased expression of exhaustion markers, both $CD4^+$ and $CD8^+$ T cells from COVID-19 patients showed a significantly reduced production of pro-inflammatory cytokines when restimulated ex vivo [38,49]. Moreover, an altered cytotoxic capacity has been proposed for $CD8^+$ T cells from severe patients [174]. Although characterized by reduced functionality, both $CD4^+$ and $CD8^+$ T cells showed increased expression of HLA-DR and CD38, markers of cell activation, and of Ki-67, marker of T cell proliferation [116,119,178], and these parameters correlated to disease severity [178,114]. Unconventional T cells, including γδ T, mucosa-associated invariant T and invariant NKT cells in the peripheral blood of COVID-19 patients showed increased PD1 expression and, in agreement with their exhausted phenotype, produced less IFN-γ than cells from healthy donors [179].

Analysis of bronchoalveolar lavage (BAL) samples from COVID-19 patients demonstrated an enrichment of both $CD4^+$ and $CD8^+$ T cells in lungs [180] exhibiting clonal expansion [181]. Increased PD1 expression was observed in T cells from BAL than PB [182]. Two subsets of Th17 cells have been detected in COVID-19 BAL samples, one exhibiting a tissue-residency phenotype and characterized by GM-CSF production [181]. Of note, this subset shared clones with Th1 cells [181], suggesting that Th17 cells undergo inflammation-driven polarization into Th1 at sites of infection [183]. $CD8^+$ T cells were less represented in BAL of severe patients than in patients with moderate infection [144] suggesting an important role for these cells in SARS-CoV-2 eradication.

5.3. B cells

Regarding memory B cells, it was reported an increase in the $CD21^-$ $CD27^-$ population in moderate and severe COVID-19 patients. This subset represents exhausted B cells, characterized by reduced

proliferative capacity and its expansion has been already described in other viral infections [184–186]. Moreover, plasmablasts are significantly expanded in severe COVID-19 subjects [159,177,178] and show high Ki-67 expression [178]. Plasmablasts from severe COVID-19 patients display also a profound oligoclonal expansion [178] and reduced expression of genes involved in glycolysis, when compared to asymptomatic individuals [188]. Similarly to T cells, also B cells from severe patients show upregulation of apoptosis-related genes [174], thus providing a rationale for their reduction. Transcriptome data show that B cell activation pathways are more suppressed in severe than in moderate patients, suggesting a dysfunctional response that may limit the activity of these cells [174]. In agreement, another report showed that B cell transcriptomes in asymptomatic individuals have traits of increased type I IFN response, increased NF-kB signaling and increased BCR triggering [188].

6. Dysregulated myeloid response

Accumulating evidence has shown that the myeloid compartment is significantly affected in severe COVID-19 patients (Fig. 4).

6.1. Dendritic cells

Dendritic cells (DC) are a heterogeneous population of antigen presenting cells (APC), commonly divided in $CD123^{+}$ plasmacytoid DC and conventional (myeloid) DC [189]. Conventional DC can be additionally distinguished in $CD141^{+}$ cDC1 and $CD1c^{+}$ cDC2 [189]. Collectively, DC are crucial players in priming $CD4^{+}$ and $CD8^{+}$ T cells responses. In addition, pDC are a primary source of type I IFN following viral infections. All DC subsets are markedly reduced in the circulation of COVID-19 subjects when compared to healthy donors [159,189–191]. Interestingly, while pDC and cDC1 are reduced in all SARS-CoV-2 infected subjects irrespective of disease severity, cDC2 deficiency is more pronounced in critically ill patients [191]. In agreement, an enrichment of cDC2 in the lungs of severe COVID-19 patients was demonstrated [191]. This observation suggests that the loss of pDC and cDC1 is not caused by tissue redistribution. In agreement, increased expression of pro-apoptotic genes has been demonstrated in pDC from COVID-19 patients [192], suggesting that cell death may be a cause for the reduced absolute numbers. pDC also demonstrated functional impairment, with reduced expression of viral sensors TLR7 and DHX36 [192]. Accordingly, pDC from COVID-19 subjects demonstrated impaired IFNα production [193]. Moreover, pDCs from severe patients showed a reduced expression of genes related to IFN signaling, while increased activation of pathways related to TNF-α, IL-6 and NfKb [192]. This observation suggests that the suppression of type I IFN response in severe patients leads to the compensatory production of high levels of proinflammatory cytokines. The same imbalance was observed also in cDC subsets, together with a functional impairment also in cDC2 which exhibited decreased activity of several transcription factors [192]. SARS-CoV-2 cannot productively infect dendritic cells *in vitro* but can activate these cells to express costimulatory molecules and produce high IFNα levels [194]. This finding suggests the possibility that the reduced absolute numbers and functionality of circulating pDC observed in COVID-19 patients are not the result of a direct cytopathic viral effect, rather the result of systemic hyperinflammation occurring in severe COVID-19.

6.2. Monocytes

Monocytes are a subset of large mononuclear cells, historically considered an intermediate subset between bone marrow precursors and tissue macrophages. Monocytes have a crucial role in inflammation and pathogen fighting. Three subsets of circulating monocytes can be defined in humans: $CD14^{++}$ $CD16^{-}$ classical, $CD14^{++}$ $CD16^{+}$ intermediate and $CD14^{+}$ $CD16^{++}$ non-classical monocytes. Classical and intermediate monocytes are recruited at sites of infection or injury and can differentiate in macrophages or monocyte-derived dendritic cells. These monocyte subsets produce high levels of TNF-α, nitric oxide and reactive oxygen species (ROS), fundamental components of an efficient pathogen-fighting activity. Non-classical monocytes instead have a patrolling activity but are also involved in antiviral activity [195]. The three monocyte subsets are present in the blood in precise ratios, however significant changes can occur during infections [196]. Although the absolute number of circulating monocytes is not different in COVID-19 patients from that in healthy subjects [189], profound alterations in monocytes' phenotype and functionality have been described. Indeed, the percentage of non-classical monocytes is markedly reduced in the circulation of COVID-19 patients, particularly those requiring intensive care therapies, with a parallel increase in the frequency of classical monocytes [189,191,197]. The redistribution of monocyte subsets in the circulation is paralleled by an accumulation of non-classical monocytes

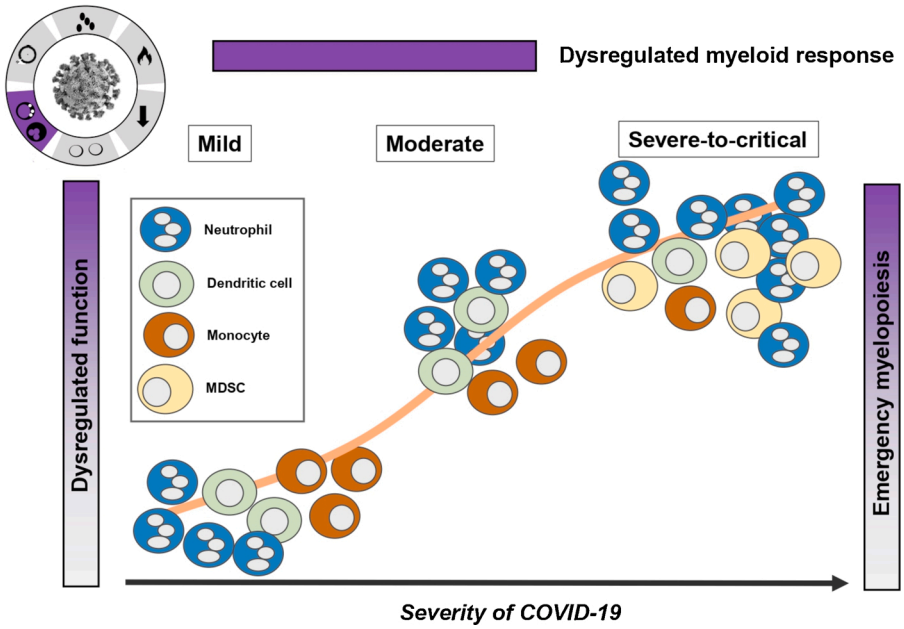

Fig. 4. Dysregulated myeloid response.
COVID-19 progression towards the severe phase is characterized by quantitative and qualitative alterations in the myeloid cell compartment. Immature cells appear in the circulation, as a sign of inflammation-driven emergency myelopoiesis. Neutrophils accumulate in severe COVID-19 but display an aberrant production of NETs, expression of activation markers and PD-L1. Monocytes show altered composition, with depletion of the non-classical subset from the circulation, and functionality, with increased production of pro-inflammatory cytokines and reduced surface expression of HLA-DR. DC are significantly depleted in severe patients and produce low IFN-α levels. Severe COVID-19 is characterized also by the appearance of myeloid derived suppressor cells (MDSC) with immune suppressive properties.

in the lungs, suggesting a selective recruitment of this population at site of inflammation [191]. Monocytes in COVID-19 patients also display altered phenotypic and functional properties. Indeed, these cells display significantly reduced levels of HLA-DR expression and an aberrant increase in activation markers such as CD64, CD11b and CD163 [189,198]. These phenotypic alterations are influenced by systemic inflammation, given that CRP levels are negatively correlated with HLA-DR expression [189,191]. In agreement, *in vitro* administration of the anti-IL-6R mAb tocilizumab restored monocyte HLA-DR expression [199], while *in vivo* suppression of cytokine signaling with JAK-STAT inhibitor ruxolitinib led to a normalization of activation markers expression [42]. Monocytes in COVID-19 patients also display an altered functionality, with increased TNF-α and IFN-γ but reduced IL-1β production, and an altered expression of cyclooxygenase 2 (COX-2), a rate-limiting enzyme in prostaglandin production [190]. Moreover, monocytes from COVID-19 patients display an impaired metabolism, with defective oxidative phosphorylation, glycolysis and oxidative burst [187], suggesting bioenergetics alterations in late stage disease. Dynamic alterations in the myeloid compartment have been described in the course of COVID-19, with the presence of HLA-DR^{hi}CD11c^{hi}/HLA-DR^{hi}CD83^{hi} monocytes with a strong antiviral IFN-signature in mild patients, substituted by the occurrence of HLA-DR^{low} monocytes in the severe phase of the disease [200].

The profound alteration of circulating monocytes can be the result of inflammation-driven emergency myelopoiesis, with an increased myeloid output from the bone marrow to fight the viral infection [201]. High expression of the proliferation marker Ki67 by circulating monocytes has been correlated to emergency myelopoiesis in other viral infections [202]. In agreement, monocytes from severe COVID-19 patients displayed high Ki67 expression, which correlated to levels of systemic inflammation [190]. Circulating monocytes in COVID-19 subjects also express high levels of the chemokine receptor CCR2, while its cognate chemokine is highly produced in the airways, suggesting a route for monocyte recruitment in the respiratory tract.

6.3. Neutrophils

Circulating neutrophils display quantitative and qualitative alterations in the course of SARS-CoV-2 infection. Although the absolute number of total white blood cells is generally normal in severe COVID-19, the leukocyte composition is profoundly affected. Indeed, the marked reduction of circulating lymphocytes is paralleled by a significant increase in the neutrophil count. Increased neutrophil to lymphocyte ratio is thus a typical feature of severe COVID-19 [49,178]. The composition of neutrophil subset is also heterogeneous, with the appearance of immature cells due to inflammation-driven myelopoiesis that can be related to high G-CSF levels in the plasma of critical patients [200,203]. Neutrophils from severe COVID-19 patients downregulate CD62 L expression while increasing the expression of CD64 and CD274 (PD-L1), as a sign of activation, dysfunction and immunosuppression [200]. In addition, neutrophils in severe COVID-19 are characterized by the hyper-expression of the activation marker CD66b [189]. In agreement, a transcriptional signature suggesting neutrophil hyper-activation has been correlated to critical illness, and neutrophil activation status on the day of hospitalization can predict the transfer to the intensive care unit [204,203]. From a functional point of view, phagocytosis capacity does not differ in mild versus severe COVID-19 patients, although a significantly reduced production of ROS was demonstrated in the latter group [200]. Neutrophil extracellular traps (NETs) production is also dysregulated in COVID-19. NETs are extracellular fibers made of DNA assembled with histones and granule-derived enzymes such as myeloperoxidase, with both anti-microbial and tissue destroying activities. Increased levels of NETs were reported in the plasma of COVID-19 patients and correlated with disease severity [205]. Post-mortem studies revealed NETs accumulation also in the lungs of patients who died from SARS-CoV-2 infection [206]. SARS-CoV-2 can infect neutrophils and activate NETs release, which in turn promote lung epithelial cell death, thus contributing to COVID-19 pathology [206].

6.4. Myeloid derived suppressor cells

Myeloid derived suppressor cells (MDSC) are a subset of bone-marrow derived, immature innate cells that increase in the circulation in cancer, inflammatory diseases, or infections [207,208]. Two subsets can be typically distinguished, monocytic (M-MDSC) or neutrophilic (PMN-MDSC), both involved in the suppression of innate and adaptive immune responses, with the contemporary promotion of regulatory cell development [208]. PMN-MDSC are typically enriched in the low-density neutrophil (LDN) fraction and suppress immune cells mainly via the release of ROS and arginase I. M-MDSC instead act mainly via iNOS and arginase I. Other immune suppressive mechanisms have also been described, including the release of IL-10, TGF-β and the enzyme IDO1. Increased levels of circulating MDSC in severe COVID-19 are a sign of immune dysregulation. Both subsets of MDSC are particularly increased in patients requiring intensive care, and their frequency correlates with proinflammatory cytokines in the serum [200,209,210]. PMN-MDSC from COVID-19 patients suppress T cell response and IFN-γ production through iNOS and TGF-β mediated mechanisms [209], while M-MDSC were found to suppress T cell response in an arginase I-mediated mechanism [211]. Given their immunosuppressive properties and their accumulation in severely ill patients, MDSC can contribute to the immune dysregulation that occurs at late stages of COVID-19 [210]. LDNs show intermediate levels of CD16 expression and their levels directly correlate with parameters of inflammation. Moreover, LDNs are highly enriched in the bronchoalveolar lavage fluid of COVID-19 patients [212]. LDNs have a pro-inflammatory gene signature, display enhanced NETs formation and interact with platelets, thus promoting the blood hypercoagulability that is typical of COVID-19 [212].

7. Heterogeneous adaptive immune response to SARS-CoV-2

Antigen-specific immune response against viruses is essential both at first encounter with pathogens for successful control of the infection, and in the long-term by development of immune memory and prevention of re-infection. The identification of antigen-specific T cells, B cells and antibodies against SARS-CoV-2 antigens represents an important tool to monitor the features of adaptive immune response in the course of acute COVID-19, in the recovery phase and months/years after infection. Seminal works published in the last year have demonstrated that a specific adaptive immune response occurs following SARS-CoV-2 infection [213–216]. Data on humoral response in COVID-19 patients are predominant, because the evaluation of serum levels of SARS-CoV-2-specific antibodies is easier and more rapid than the identification of antigen-specific circulating T cells. However, it was reported a significant direct correlation between the frequency of SARS-CoV-2 specific CD4$^+$, CD8$^+$ T cells and the levels of virus-specific antibodies [48,252,253], suggesting a coordinated activity of all branches of adaptive immunity. SARS-CoV-2 infection induces a wide spectrum of clinical manifestations ranging from no symptoms to pauci-, mild- or severe symptoms culminating in ARDS and multi-organ failure up to death. Many authors reported that the entity of SARS-CoV-2-specific immune response, both humoral and cell-mediated is lower in the asymptomatic patients than in the symptomatic ones [48,255,256]. However, T cells from asymptomatic individuals produced higher levels of IFN-γ and IL-2, while those from symptomatic subjects secreted more proinflammatory cytokines TNF-α, IL-1β and IL-6 [218]. In addition, people with severe COVID-19 displayed a dysregulated adaptive immunity to the virus, with altered CD4$^+$ and CD8$^+$ T cell responses and, in some cases, delayed or absent production of neutralizing antibodies [252] (Fig. 5). Higher disease severity occurring in aged individuals is associated to scarcity of naïve CD4$^+$ and CD8$^+$ T cells, thus confirming that a limited repertoire of naïve lymphocytes impairs the

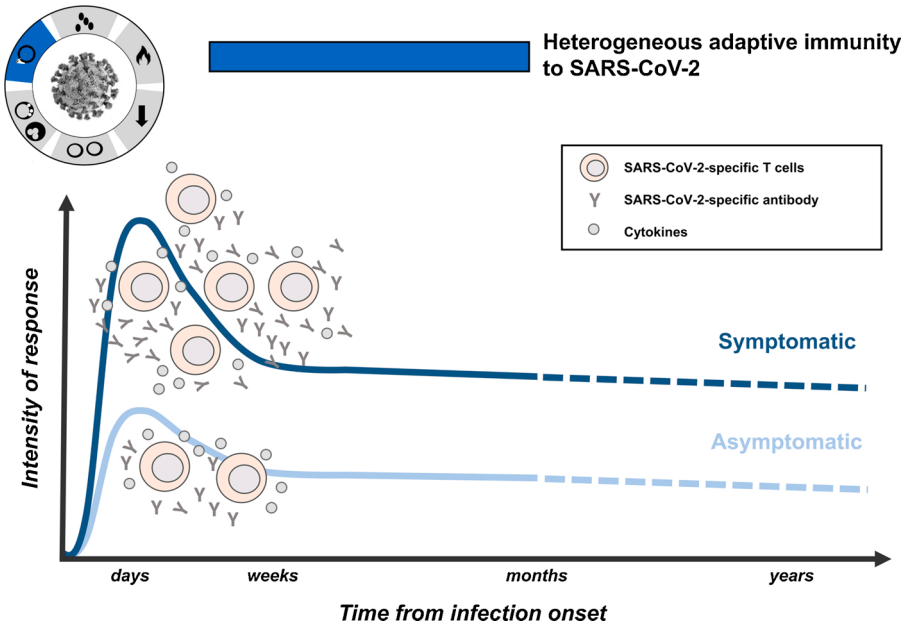

Fig. 5. Heterogeneous adaptive immunity to SARS-CoV-2.
In asymptomatic individuals, rapid activation of adaptive immunity to SARS-CoV-2 allows to rapidly control the infection, with limited production of virus-specific antibodies and T cells. T cells are functionally superior, in asymptomatic than symptomatic patients, with higher production of pro-inflammatory cytokines. Continuous lines represent the observed trend of SARS-CoV-2 specific immune response in symptomatic and asymptomatic individuals, whereas the dotted lines are hypothetical long-term memory immune responses.

capacity to mount a rapid and effective antiviral response [252]. These findings are in agreement with the observation that rapid induction of SARS-CoV-2-specific T cells associates with mild disease, while delayed response occurs in critically ill patients [219]. Altogether, these data suggest that a more severe disease is a consequence of a dysregulated priming of anti-SARS-CoV-2-specific immunity, which leads to a hyperactive and uncoordinated response. Moreover, SARS-CoV-2-specific T cell responses are lower in children when compared to adults [221]. This heterogeneity could also be due to the presence of pre-existing cross-reactive antigen-specific T cells or antibodies in SARS-CoV-2 unexposed individuals [213,216,222]. In addition to the frequency, the deep phenotypic characterization of antigen-specific T cells is critical to understand their specific function, such as the kind of cytokine production and the expression of activation/inhibition markers. It has been reported that SARS-CoV-2-reactive T cells are polyfunctional due to the production of more than one effector cytokine (IL-2, IFN-γ and TNF-α) and highly express immune-checkpoints PD-1 and TIGIT [48] as sign of their recent stimulation. Interestingly, both these features are more evident in symptomatic than asymptomatic patients. Prolonged T cells activation due to disease and virus persistence can induce T cells exhaustion as supported by high level of TIGIT, PD-1 and Tim-3 on $CD4^+$ and $CD8^+$ T cells, despite their TCR specificity, correlating with disease severity [113,223,224]. Moreover, PD-L1 is upregulated in SARS-CoV-2 infected cells and in COVID-19 patients' lung biopsies and increased serum levels of soluble PD-L1 are considered a negative prognostic marker [250]. One of the most frequent questions at the moment is how long will the antigen-specific immune response be maintained, which is fundamental to guarantee long-lasting protection. During the last year, several reports have been accumulated demonstrating the persistence of SARS-CoV-2-specific immune response, both humoral and cell-mediated, at different time points after recovery from natural infection [225–228,234].

The kinetics of development and maintenance of immunological memory against SARS-CoV-2 shows that specific memory B cells arise over 3–5 months reaching a plateau phase at 6–8 months, supporting the long-lasting antibody production in that period. On the other hand, SARS-CoV-2-specific $CD4^+$ and $CD8^+$ memory T cells peak within the first month and then slowly decline in the following months [220,225]. In addition, it has been described the development of SARS-CoV-2-specific stem cell like memory T cells regardless of disease severity [229]. Similar findings were reported also for humoral specific immune response, since the gradual decrease of total SARS-CoV-2 Ig levels was associated with a high neutralising antibody titres and a robust specific memory B cell response in both moderate and severe COVID-19 recovered patients, irrespective of disease severity at hospitalisation [254]. Although the majority of previously infected individuals maintain high levels of circulating specific $CD4^+$ T cells and antibodies, about 10–20 % of recovered subjects showed a borderline specific adaptive immune response, suggesting they could be more susceptible to reinfection and thus may benefit from vaccination [225,227,234]. All these data indicate that the balance between functionality and dysregulation of the components of the specific immune response (B cells, T cells and antibodies) determine the effective anti-SARS-CoV-2 protection over time. Of note, for future investigation on the functional features and on the durability of SARS-CoV-2-specific adaptive immune response it is important to note that longitudinal evaluation of persistence of infection-induced Spike-specific immunity will be influenced by vaccination. Moreover, it should be considered that additional SARS-CoV-2 antigens, different from the "classic" Spike, Nucleoprotein and Membrane may be of importance to track SARS-CoV-2-specific memory durability. This is further supported by the recent identification of antibodies against non-structural/accessory proteins in COVID-19 patients, as well as of HLA-I peptides derived from both canonical open reading frames (ORFs) and internal out-of-frame ORFs of S and N proteins [217,230]. These data open the way to further investigation and strategic approach in monitoring SARS-CoV-2 specific immune response.

Since the publication of SARS-CoV-2 genome sequence at the beginning of 2020, the scientific community has produced an unprecedented effort to develop efficacious vaccines against COVID-19. Given the central role of Spike in the infectious process, this protein has become the main target for vaccine development. Different platforms have been approached, but those that entered earlier in clinical trials are based on mRNA or non-replicating viral vectors. mRNA vaccines from Pfizer-BioNTech (BNT162b2) and Moderna (mRNA-1273) are now currently used in Europe and the USA; viral-vector based vaccines from AstraZeneca and Janssen are both used in Europe, while only Janssen in the USA. Ad26.COV2.S from Janssen is the only vaccine that requires one shot, while the others are being administered with a two doses schedule. All vaccines displayed good immunogenicity, eliciting both humoral and cellular immune responses [231,232]. In particular, it has been shown that the second dose administration can significantly boost

the levels of specific neutralizing antibodies, T cells and B cells [233,238]. The second dose is also important to increase the levels of $CD4^+$ T cells and antibodies with neutralizing activity against SARS-CoV-2 variants of concern [235,259]. Given the efficacy and the safety profiles of currently approved vaccines, in most countries they have been offered to the whole population, regardless of prior SARS-CoV-2 infection. However, it should be noted that none of the currently approved vaccines has been tested in clinical trials in people who recovered from COVID-19. Emerging data have demonstrated that one vaccine administration is sufficient to achieve high levels of anti-Spike immunity in people with a past SARS-CoV-2 infection. Indeed, it has been shown that following the first dose of mRNA vaccine, COVID-19 recovered subjects display high levels of anti-Spike IgG, including those with neutralizing activity [233,236,237]. Moreover, in recovered COVID-19 subjects the first vaccine dose maximizes the levels of circulating, Spike-specific, T and B cells [233,238]. On the contrary, the administration of the second vaccine dose in ex−COVID-19 individuals is associated with a contraction of neutralizing antibody levels, as well as Spike-specific T and B cell frequencies [233,239]. Thus, the second scheduled inoculation seems detrimental, rather than beneficial, in this population, suggesting that over-boosting Spike-specific immunity may lead to anergy and exhaustion. This hypothesis should be seriously taken into consideration and tested. Evaluation of exhaustion markers expressed by Spike-specific $CD4^+$ T cells in naïve and COVID-19 recovered subjects following the complete vaccination cycle did not show differences among the two groups [233]. However, it should be noted that functional assays requiring cell stimulation *in vitro* might not allow the identification of exhausted T cells, given that these cells may not be activated following antigenic stimulation. Thus, additional studies using different experimental approaches are needed to understand if the second vaccine dose in COVID-19 recovered subjects is associated with immune cell exhaustion.

8. Conclusion and future perspectives

The six hallmarks presented in this Review summarize the main features of the immune response in the course of COVID-19. SARS-CoV-2 infection represents a major challenge for the immune system, and the deriving immune response has a significant impact on the patient's outcome. A balanced, well-coordinated and early-established response involving both innate and adaptive immunity can promote a rapid eradication of viral infection, with minimal symptoms. On the contrary, a late-occurring and uncoordinated response opens the way towards disease worsening, promoting abnormalities that affect all compartments of the immune system and that reinforce each other in a positive feedback loop. Immune dysregulation is the causative event for the organ dysfunction that occurs in late-stage disease, thus representing an important target for therapeutic intervention. For this reason, further deepening the knowledge of the complex mechanisms controlling immune dysfunction in COVID-19 will be crucial to design appropriate interventions.

Funding

None.

Declaration of Competing Interest

None.

Acknowledgements

We acknowledge the Department of Experimental and Clinical Medicine, University of Florence for project Excellence Departments 2018-2022 (Ministero dell'Istruzione, dell'Università e della Ricerca, Italy); the University of Florence for project RICTD2122; the Tuscany Region for project TagSARS-CoV-2; the Ministero della Salute (Italy) for project COVID-2020-12371849.

References

[1] WHO, WHO Coronavirus (COVID-19) Dashboard at October 10, 2021. Available at https://covid19.who.int/. Accessed October 11, 2021.
[2] D. Hanahan, R.A. Weinberg, Hallmarks of cancer: the next generation, Cell 144 (5 March) (2011) 646–674, https://doi.org/10.1016/j.cell.2011.02.013, 4PMID: 21376230.
[3] O. Gallo, L.G. Locatello, A. Mazzoni, L. Novelli, F. Annunziato, The central role of the nasal microenvironment in the transmission, modulation, and clinical progression of SARS-CoV-2 infection, Mucosal Immunol. 14 (2 March) (2021) 305–316, https://doi.org/10.1038/s41385-020-00359-2. Epub 2020 Nov 26. PMID: 33244161; PMCID: PMC7690066.
[4] U. Felgenhauer, A. Schoen, H.H. Gad, R. Hartmann, A.R. Schaubmar, K. Failing, C. Drosten, F. Weber, Inhibition of SARS-CoV-2 by type I and type III interferons, J. Biol. Chem. 295 (41 October) (2020) 13958–13964, https://doi.org/10.1074/jbc.AC120.013788, 9Epub 2020 Jun 25. PMID: 32587093; PMCID: PMC7549028.
[5] C. King, J. Sprent, Dual nature of type I interferons in SARS-CoV-2-Induced inflammation, Trends Immunol. 42 (4 April) (2021) 312–322, https://doi.org/10.1016/j.it.2021.02.003. Epub 2021 Feb 12. PMID: 33622601; PMCID: PMC7879020.
[6] H. Xia, Z. Cao, X. Xie, X. Zhang, J.Y. Chen, H. Wang, V.D. Menachery, R. Rajsbaum, P.Y. Shi, Evasion of type I interferon by SARS-CoV-2, Cell Rep. 33 (1 October) (2020) 108234, https://doi.org/10.1016/j.celrep.2020.108234, 6Epub 2020 Sep 19. PMID: 32979938; PMCID: PMC7501843.
[7] Y. Konno, I. Kimura, K. Uriu, M. Fukushi, T. Irie, Y. Koyanagi, D. Sauter, R. J. Gifford, USFQ-COVID19 Consortium, S. Nakagawa, K. Sato, SARS-CoV-2 ORF3b is a potent interferon antagonist whose activity is increased by a naturally occurring elongation variant, Cell Rep. 32 (12 September) (2020) 108185, https://doi.org/10.1016/j.celrep.2020.108185, 22Epub 2020 Sep 4. PMID: 32941788; PMCID: PMC7473339.
[8] I. Kimura, Y. Konno, K. Uriu, K. Hopfensperger, D. Sauter, S. Nakagawa, K. Sato, Sarbecovirus ORF6 proteins hamper induction of interferon signaling, Cell Rep. 34 (13 March) (2021) 108916, https://doi.org/10.1016/j.celrep.2021.108916, 30Epub 2021 Mar 12. PMID: 33765414; PMCID: PMC7953434.
[9] D. Blanco-Melo, B.E. Nilsson-Payant, W.C. Liu, S. Uhl, D. Hoagland, R. Møller, T. X. Jordan, K. Oishi, M. Panis, D. Sachs, T.T. Wang, R.E. Schwartz, J.K. Lim, R. A. Albrecht, B.R. tenOever, Imbalanced host response to SARS-CoV-2 drives development of COVID-19, Cell 181 (5 May) (2020) 1036–1045, https://doi.org/10.1016/j.cell.2020.04.026, e928Epub 2020 May 15. PMID: 32416070; PMCID: PMC7227586.
[10] J. Hadjadj, N. Yatim, L. Barnabei, A. Corneau, J. Boussier, N. Smith, H. Péré, B. Charbit, V. Bondet, C. Chenevier-Gobeaux, P. Breillat, N. Carlier, R. Gauzit, C. Morbieu, F. Pène, N. Marin, N. Roche, T.A. Szwebel, S.H. Merkling, J. M. Treluyer, D. Veyer, L. Mouthon, C. Blanc, P.L. Tharaux, F. Rozenberg, A. Fischer, D. Duffy, F. Rieux-Laucat, S. Kernéis, B. Terrier, Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients, Science 369 (6504 August) (2020) 718–724, https://doi.org/10.1126/science.abc6027, 7Epub 2020 Jul 13. PMID: 32661059; PMCID: PMC7402632.
[11] Z. Zhou, L. Ren, L. Zhang, J. Zhong, Y. Xiao, Z. Jia, L. Guo, J. Yang, C. Wang, S. Jiang, D. Yang, G. Zhang, H. Li, F. Chen, Y. Xu, M. Chen, Z. Gao, J. Yang, J. Dong, B. Liu, X. Zhang, W. Wang, K. He, Q. Jin, M. Li, J. Wang, Heightened innate immune responses in the respiratory tract of COVID-19 patients, Cell Host Microbe 27 (6 June) (2020) 883–890, https://doi.org/10.1016/j.chom.2020.04.017, 10e2Epub 2020 May 4. PMID: 32407669; PMCID: PMC7196896.
[12] A.J. Wilk, A. Rustagi, N.Q. Zhao, J. Roque, G.J. Martínez-Colón, J.L. McKechnie, G.T. Ivison, T. Ranganath, R. Vergara, T. Hollis, L.J. Simpson, P. Grant, A. Subramanian, A.J. Rogers, C.A. Blish, A single-cell atlas of the peripheral immune response in patients with severe COVID-19, Nat. Med. 26 (7 July) (2020) 1070–1076, https://doi.org/10.1038/s41591-020-0944-y. Epub 2020 Jun 8. PMID: 32514174; PMCID: PMC7382903.
[13] J.S. Lee, S. Park, H.W. Jeong, J.Y. Ahn, S.J. Choi, H. Lee, B. Choi, S.K. Nam, M. Sa, J.S. Kwon, S.J. Jeong, H.K. Lee, S.H. Park, S.H. Park, J.Y. Choi, S.H. Kim, I. Jung, E.C. Shin, Immunophenotyping of COVID-19 and influenza highlights the role of type I interferons in development of severe COVID-19, Sci. Immunol. 5 (49 July) (2020) eabd1554, https://doi.org/10.1126/sciimmunol.abd1554, 10PMID: 32651212; PMCID: PMC7402635.
[14] R. Channappanavar, A.R. Fehr, R. Vijay, M. Mack, J. Zhao, D.K. Meyerholz, S. Perlman, Dysregulated type I interferon and inflammatory monocyte-macrophage responses cause lethal pneumonia in SARS-CoV-Infected mice, Cell Host Microbe 19 (2 Febuary) (2016) 181–193, https://doi.org/10.1016/j.chom.2016.01.007, 10PMID: 26867177; PMCID: PMC4752723.
[15] B. Israelow, E. Song, T. Mao, P. Lu, A. Meir, F. Liu, M.M. Alfajaro, J. Wei, H. Dong, R.J. Homer, A. Ring, C.B. Wilen, A. Iwasaki, Mouse model of SARS-CoV-2 reveals inflammatory role of type I interferon signaling, J. Exp. Med. 217 (12 December) (2020) e20201241, https://doi.org/10.1084/jem.20201241, 7PMID: 32750141; PMCID: PMC7401025.
[16] J.B. Westover, B.T. Hickerson, A.J. Van Wettere, B.L. Hurst, J.P. Kurz, A. Dagley, P. Wülfroth, T. Komeno, Y. Furuta, T. Steiner, B.B. Gowen, Vascular leak and hypercytokinemia associated with severe fever with thrombocytopenia syndrome virus infection in mice, Pathogens 8 (4 September) (2019) 158, https://doi.org/10.3390/pathogens8040158, 21PMID: 31546590; PMCID: PMC6963364.

[17] Q. Zhang, P. Bastard, Z. Liu, J. Le Pen, M. Moncada-Velez, J. Chen, M. Ogishi, I.K. D. Sabli, S. Hodeib, C. Korol, J. Rosain, K. Bilguvar, J. Ye, A. Bolze, B. Bigio, R. Yang, A.A. Arias, Q. Zhou, Y. Zhang, F. Onodi, S. Korniotis, L. Karpf, Q. Philippot, M. Chbihi, L. Bonnet-Madin, K. Dorgham, N. Smith, W.M. Schneider, B.S. Razooky, H.H. Hoffmann, E. Michailidis, L. Moens, J.E. Han, L. Lorenzo, L. Bizien, P. Meade, A.L. Neehus, A.C. Ugurbil, A. Corneau, G. Kerner, P. Zhang, F. Rapaport, Y. Seeleuthner, J. Manry, C. Masson, Y. Schmitt, A. Schlüter, T. Le Voyer, T. Khan, J. Li, J. Fellay, L. Roussel, M. Shahrooei, M.F. Alosaimi, D. Mansouri, H. Al-Saud, F. Al-Mulla, F. Almourfi, S.Z. Al-Muhsen, F. Alsohime, S. Al Turki, R. Hasanato, D. van de Beek, A. Biondi, L.R. Bettini, M. D'Angio', P. Bonfanti, L. Imberti, A. Sottini, S. Paghera, E. Quiros-Roldan, C. Rossi, A. J. Oler, M.F. Tompkins, C. Alba, I. Vandernoot, J.C. Goffard, G. Smits, I. Migeotte, F. Haerynck, P. Soler-Palacin, A. Martin-Nalda, R. Colobran, P.E. Morange, S. Keles, F. Çölkesen, T. Ozcelik, K.K. Yasar, S. Senoglu, ŞN. Karabela, C. Rodríguez-Gallego, G. Novelli, S. Hraiech, Y. Tandjaoui-Lambiotte, X. Duval, C. Laouénan, COVID-STORM Clinicians, COVID Clinicians; Imagine COVID Group, French COVID Cohort Study Group, CoV-Contact Cohort, Amsterdam UMC Covid-19 Biobank, COVID Human Genetic Effort, NIAID-USUHS/TAGC COVID Immunity Group, A.L. Snow, C.L. Dalgard, J.D. Milner, D.C. Vinh, T. H. Mogensen, N. Marr, A.N. Spaan, B. Boisson, S. Boisson-Dupuis, J. Bustamante, A. Puel, M.J. Ciancanelli, I. Meyts, T. Maniatis, V. Soumelis, A. Amara, M. Nussenzweig, A. García-Sastre, F. Krammer, A. Pujol, D. Duffy, R.P. Lifton, S. Y. Zhang, G. Gorochov, V. Béziat, E. Jouanguy, V. Sancho-Shimizu, C.M. Rice, L. Abel, L.D. Notarangelo, A. Cobat, H.C. Su, J.L. Casanova, Inborn errors of type I IFN immunity in patients with life-threatening COVID-19, Science 370 (6515 October) (2020) eabd4570, https://doi.org/10.1126/science.abd4570, 23Epub 2020 Sep 24. PMID: 32972995; PMCID: PMC7857407.

[18] P. Bastard, L.B. Rosen, Q. Zhang, E. Michailidis, H.H. Hoffmann, Y. Zhang, K. Dorgham, Q. Philippot, J. Rosain, V. Béziat, J. Manry, E. Shaw, L. Haljasmägi, P. Peterson, L. Lorenzo, L. Bizien, S. Trouillet-Assant, K. Dobbs, A.A. de Jesus, A. Belot, A. Kallaste, E. Catherinot, Y. Tandjaoui-Lambiotte, J. Le Pen, G. Kerner, B. Bigio, Y. Seeleuthner, R. Yang, A. Bolze, A.N. Spaan, O.M. Delmonte, M. S. Abers, A. Aiuti, G. Casari, V. Lampasona, L. Piemonti, F. Ciceri, K. Bilguvar, R. P. Lifton, M. Vasse, D.M. Smadja, M. Migaud, J. Hadjadj, B. Terrier, D. Duffy, L. Quintana-Murci, D. van de Beek, L. Roussel, D.C. Vinh, S.G. Tangye, F. Haerynck, D. Dalmau, J. Martinez-Picado, P. Brodin, M.C. Nussenzweig, S. Boisson-Dupuis, C. Rodríguez-Gallego, G. Vogt, T.H. Mogensen, A.J. Oler, J. Gu, P.D. Burbelo, J.I. Cohen, A. Biondi, L.R. Bettini, M. D'Angio, P. Bonfanti, P. Rossignol, J. Mayaux, F. Rieux-Laucat, E.S. Husebye, F. Fusco, M.V. Ursini, L. Imberti, A. Sottini, S. Paghera, E. Quiros-Roldan, C. Rossi, R. Castagnoli, D. Montagna, A. Licari, G.L. Marseglia, X. Duval, J. Ghosn, HGID Lab, NIAID-USUHS Immune Response to COVID Group; COVID Clinicians, COVID-STORM Clinicians, Imagine COVID Group, French COVID Cohort Study Group, Milieu Intérieur Consortium, CoV-Contact Cohort, Amsterdam UMC Covid-19 Biobank, COVID Human Genetic Effort, J.S. Tsang, R. Goldbach-Mansky, K. Kisand, M. S. Lionakis, A. Puel, S.Y. Zhang, S.M. Holland, G. Gorochov, E. Jouanguy, C. M. Rice, A. Cobat, L.D. Notarangelo, L. Abel, H.C. Su, J.L. Casanova, Autoantibodies against type I IFNs in patients with life-threatening COVID-19, Science 370 (6515 October) (2020), https://doi.org/10.1126/science.abd4585 eabd458523Epub 2020 Sep 24. PMID: 32972996; PMCID: PMC7857397.

[19] D.A. Berlin, R.M. Gulick, F.J. Martinez, Severe Covid-19, N. Engl. J. Med. 383 (25) (2020) 2451–2460, https://doi.org/10.1056/NEJMcp2009575.

[20] J.N. Gustine, D. Jones, Immunopathology of hyperinflammation in COVID-19, Am. J. Pathol. 191 (1) (2021) 4–17, https://doi.org/10.1016/j.ajpath.2020.08.009.

[21] R.A. Morgan, J.C. Yang, M. Kitano, M.E. Dudley, C.M. Laurencot, S.A. Rosenberg, Case report of a serious adverse event following the administration of T cells transduced with a chimeric antigen receptor recognizing ERBB2, Mol. Ther. 18 (4 April) (2010) 843–851, https://doi.org/10.1038/mt.2010.24. Epub 2010 Feb 23. PMID: 20179677; PMCID: PMC2862534.

[22] D. Wang, B. Hu, C. Hu, et al., Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China, JAMA 323 (11) (2020) 1061–1069, https://doi.org/10.1001/jama.2020.1585.

[23] W. Wang, X. Liu, S. Wu, S. Chen, Y. Li, L. Nong, P. Lie, L. Huang, L. Cheng, Y. Lin, J. He, Definition and risks of cytokine release syndrome in 11 critically ill COVID-19 patients with pneumonia: analysis of disease characteristics, J. Infect. Dis. 222 (9 October) (2020) 1444–1451, https://doi.org/10.1093/infdis/jiaa387, 1PMID: 32601708; PMCID: PMC7337810.

[24] C.W. Freyer, D.L. Porter, Cytokine release syndrome and neurotoxicity following CAR T-cell therapy for hematologic malignancies, J. Allergy Clin. Immunol. 146 (5 November) (2020) 940–948, https://doi.org/10.1016/j.jaci.2020.07.025. Epub 2020 Aug 6. PMID: 32771558.

[25] B.J. Webb, I.D. Peltan, P. Jensen, D. Hoda, B. Hunter, A. Silver, N. Starr, W. Buckel, N. Grisel, E. Hummel, G. Snow, D. Morris, E. Stenehjem, R. Srivastava, S.M. Brown, Clinical criteria for COVID-19-associated hyperinflammatory syndrome: a cohort study, Lancet Rheumatol. 2 (12 December) (2020) e754–e763, https://doi.org/10.1016/S2665-9913(20)30343-X. Epub 2020 Sep 29. PMID: 33015645; PMCID: PMC7524533.

[26] A. Shimabukuro-Vornhagen, P. Gödel, M. Subklewe, H.J. Stemmler, H. A. Schlößer, M. Schlaak, M. Kochanek, B. Böll, M.S. von Bergwelt-Baildon, Cytokine release syndrome, J. Immunother. Cancer 6 (1 June) (2018) 56, https://doi.org/10.1186/s40425-018-0343-9, 15PMID: 29907163; PMCID: PMC6003181.

[27] S. Agarwal, C.H. June, Harnessing CAR T-cell insights to develop treatments for hyperinflammatory responses in patients with COVID-19, Cancer Discov. 10 (6 June) (2020) 775–778, https://doi.org/10.1158/2159-8290.CD-20-0473. Epub 2020 Apr 17. PMID: 32303509; PMCID: PMC7249633.

[28] J.B. Moore, C.H. June, COVID-19 Cytokine release syndrome in severe COVID-19, Science 368 (6490) (2020) 473–474, https://doi.org/10.1126/science.abb8925.

[29] H.C. Lane, A.S. Fauci, Research in the context of a pandemic, N. Engl. J. Med. 384 (8 Febuary) (2021) 755–757, https://doi.org/10.1056/NEJMe2024638, 25Epub 2020 Jul 17. PMID: 32678528; PMCID: PMC7383591.

[30] S.A. Vardhana, J.D. Wolchok, The many faces of the anti-COVID immune response, J. Exp. Med. 217 (6 June) (2020) e20200678, https://doi.org/10.1084/jem.20200678, 1PMID: 32353870; PMCID: PMC7191310.

[31] M.Z. Tay, C.M. Poh, L. Rénia, P.A. MacAry, L.F.P. Ng, The trinity of COVID-19: immunity, inflammation and intervention, Nat. Rev. Immunol. 20 (6) (2020) 363–374, https://doi.org/10.1038/s41577-020-0311-8.

[32] S.F. Pedersen, Y.C. Ho, SARS-CoV-2: a storm is raging, J. Clin. Invest. 130 (5) (2020) 2202–2205, https://doi.org/10.1172/JCI137647.

[33] H.K. Siddiqi, M.R. Mehra, COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal, J. Heart Lung Transplant. 39 (5) (2020) 405–407, https://doi.org/10.1016/j.healun.2020.03.012.

[34] V. Castelli, A. Cimini, C. Ferri, Cytokine Storm in COVID-19: "When You Come Out of the Storm, You Won't Be the Same Person Who Walked in", Front. Immunol. 11 (2020) 2132, https://doi.org/10.3389/fimmu.2020.02132.

[35] D.C. Fajgenbaum, C.H. June, Cytokine storm, N. Engl. J. Med. 383 (23 December) (2020) 2255–2273, https://doi.org/10.1056/NEJMra2026131, 3.

[36] R.K. Mahat, S. Panda, V. Rathore, S. Swain, L. Yadav, S.P. Sah, The dynamics of inflammatory markers in coronavirus disease-2019 (COVID-19) patients: a systematic review and meta-analysis, Clin. Epidemiol. Glob. Health 11 (July-September) (2021) 100727, https://doi.org/10.1016/j.cegh.2021.100727. Epub 2021 Mar 20. PMID: 33778183; PMCID: PMC7979575.

[37] Z. Zhu, T. Cai, L. Fan, K. Lou, X. Hua, Z. Huang, G. Gao, Clinical value of immune-inflammatory parameters to assess the severity of coronavirus disease 2019, Int. J. Infect. Dis. 95 (June) (2020) 332–339, https://doi.org/10.1016/j.ijid.2020.04.041. Epub 2020 Apr 22. PMID: 32334118; PMCID: PMC7195003.

[38] G. Chen, D. Wu, W. Guo, Y. Cao, D. Huang, H. Wang, T. Wang, X. Zhang, H. Chen, H. Yu, X. Zhang, M. Zhang, S. Wu, J. Song, T. Chen, M. Han, S. Li, X. Luo, J. Zhao, Q. Ning, Clinical and immunological features of severe and moderate coronavirus disease 2019, J. Clin. Invest. 130 (5 May) (2020) 2620–2629, https://doi.org/10.1172/JCI137244, 1PMID: 32217835; PMCID: PMC7190990.

[40] L. Cheng, H. Li, L. Li, C. Liu, S. Yan, H. Chen, Y. Li, Ferritin in the coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis, J. Clin. Lab. Anal. 34 (10 October) (2020) e23618, https://doi.org/10.1002/jcla.23618. Epub 2020 Oct 19. PMID: 33078400; PMCID: PMC7595919.

[41] J.T. Sims, V. Krishnan, C.Y. Chang, S.M. Engle, G. Casalini, G.H. Rodgers, N. Bivi, B.J. Nickoloff, R.J. Konrad, S. de Bono, R.E. Higgs, R.J. Benschop, S. Ottaviani, A. Cardoso, A. Nirula, M. Corbellino, J. Stebbing, Characterization of the cytokine storm reflects hyperinflammatory endothelial dysfunction in COVID-19, J. Allergy Clin. Immunol. 147 (1 January) (2021) 107–111, https://doi.org/10.1016/j.jaci.2020.08.031. Epub 2020 Sep 10. PMID: 32920092; PMCID: PMC7488591.

[42] A.M. Vannucchi, B. Sordi, A. Morettini, C. Nozzoli, L. Poggesi, F. Pieralli, A. Bartoloni, A. Atanasio, F. Miselli, C. Paoli, G.G. Loscocco, A. Fanelli, O. Para, A. Berni, I. Tassinari, L. Zammarchi, L. Maggi, A. Mazzoni, V. Scotti, G. Falchetti, D. Malandrino, F. Luise, G. Millotti, S. Bencini, M. Capone, M.P. Piccinni, F. Annunziato, P. Guglielmelli, RUXO-COVID Study Group, Compassionate use of JAK1/2 inhibitor ruxolitinib for severe COVID-19: a prospective observational study, Leukemia 35 (4 April) (2021) 1121–1133, https://doi.org/10.1038/s41375-020-01018-y. Epub 2020 Aug 19. PMID: 32814839; PMCID: PMC7437386.

[43] Y. Yang, C. Shen, J. Li, J. Yuan, J. Wei, F. Huang, F. Wang, G. Li, Y. Li, L. Xing, L. Peng, M. Yang, M. Cao, H. Zheng, W. Wu, R. Zou, D. Li, Z. Xu, H. Wang, M. Zhang, Z. Zhang, G.F. Gao, C. Jiang, L. Liu, Y. Liu, Plasma IP-10 and MCP-3 levels are highly associated with disease severity and predict the progression of COVID-19, J. Allergy Clin. Immunol. 146 (1 July) (2020) 119–127, https://doi.org/10.1016/j.jaci.2020.04.027, e4Epub 2020 Apr 29. PMID: 32360286; PMCID: PMC7189843.

[44] L. Yang, S. Liu, J. Liu, et al., COVID-19: immunopathogenesis and immunotherapeutics, Signal Transduct. Target. Ther. 5 (1) (2020) 128, https://doi.org/10.1038/s41392-020-00243-2.

[45] Z. Yang, J. Liu, Y. Zhou, X. Zhao, Q. Zhao, J. Liu, The effect of corticosteroid treatment on patients with coronavirus infection: a systematic review and meta-analysis, J. Infect. 81 (1 July) (2020) e13–e20, https://doi.org/10.1016/j.jinf.2020.03.062. Epub 2020 Apr 10. PMID: 32283144; PMCID: PMC7195158.

[46] B.A. Khalil, N.M. Elemam, A.A. Maghazachi, Chemokines and chemokine receptors during COVID-19 infection, Comput. Struct. Biotechnol. J. 19 (2021) 976–988, https://doi.org/10.1016/j.csbj.2021.01.034. Epub 2021 Jan 27. PMID: 33558827; PMCID: PMC7859556.

[47] L. Rodriguez, P.T. Pekkarinen, T. Lakshmikanth, Z. Tan, C.R. Consiglio, C. Pou, Y. Chen, C.H. Mugabo, N.A. Nguyen, K. Nowlan, T. Strandin, L. Levanov, J. Mikes, J. Wang, A. Kantele, J. Hepojoki, O. Vapalahti, S. Heinonen, E. Kekäläinen, P. Brodin, Systems-level immunomonitoring from acute to recovery phase of severe COVID-19, Cell Rep Med. 1 (5 August) (2020) 100078, https://doi.org/10.1016/j.xcrm.2020.100078, 25Epub 2020 Aug 5. PMID: 32838342; PMCID: PMC7405891.

[48] A. Mazzoni, L. Maggi, M. Capone, M. Spinicci, L. Salvati, M.G. Colao, A. Vanni, S. T. Kiros, J. Mencarini, L. Zammarchi, E. Mantengoli, L. Menicacci, E. Caldini, S. Romagnani, F. Liotta, A. Morettini, G.M. Rossolini, A. Bartoloni, L. Cosmi, F. Annunziato, Cell-mediated and humoral adaptive immune responses to SARS-

CoV-2 are lower in asymptomatic than symptomatic COVID-19 patients, Eur. J. Immunol. 50 (12 December) (2020) 2013–2024, https://doi.org/10.1002/eji.202048915. Epub 2020 Nov 9. PMID: 33080068.

[49] A. Mazzoni, L. Salvati, L. Maggi, M. Capone, A. Vanni, M. Spinicci, J. Mencarini, R. Caporale, B. Peruzzi, A. Antonelli, M. Trotta, L. Zammarchi, L. Ciani, L. Gori, C. Lazzeri, A. Matucci, A. Vultaggio, O. Rossi, F. Almerigogna, P. Parronchi, P. Fontanari, F. Lavorini, A. Peris, G.M. Rossolini, A. Bartoloni, S. Romagnani, F. Liotta, F. Annunziato, L. Cosmi, Impaired immune cell cytotoxicity in severe COVID-19 is IL-6 dependent, J. Clin. Invest. 130 (9 September) (2020) 4694–4703, https://doi.org/10.1172/JCI138554, 1PMID: 32463803; PMCID: PMC7456250.

[50] A. Vultaggio, E. Vivarelli, G. Virgili, E. Lucenteforte, A. Bartoloni, C. Nozzoli, A. Morettini, A. Berni, D. Malandrino, O. Rossi, F. Nencini, F. Pieralli, A. Peris, F. Lagi, G. Scocchera, M. Spinicci, M. Trotta, M. Mazzetti, P. Parronchi, L. Cosmi, F. Liotta, P. Fontanari, A. Mazzoni, L. Salvati, E. Maggi, F. Annunziato, F. Almerigogna, A. Matucci, Prompt predicting of early clinical deterioration of moderate-to-Severe COVID-19 patients: usefulness of a combined score using IL-6 in a preliminary study, J. Allergy Clin. Immunol. Pract. 8 (8) (2020) 2575–2581, https://doi.org/10.1016/j.jaip.2020.06.013, e2.

[51] D.M. Del Valle, S. Kim-Schulze, H.H. Huang, N.D. Beckmann, S. Nirenberg, B. Wang, Y. Lavin, T.H. Swartz, D. Madduri, A. Stock, T.U. Marron, H. Xie, M. Patel, K. Tuballes, O. Van Oekelen, A. Rahman, P. Kovatch, J.A. Aberg, E. Schadt, S. Jagannath, M. Mazumdar, A.W. Charney, A. Firpo-Betancourt, D. R. Mendu, J. Jhang, D. Reich, K. Sigel, C. Cordon-Cardo, M. Feldmann, S. Parekh, M. Merad, S. Gnjatic, An inflammatory cytokine signature predicts COVID-19 severity and survival, Nat. Med. 26 (10 October) (2020) 1636–1643, https://doi.org/10.1038/s41591-020-1051-9. Epub 2020 Aug 24. PMID: 32839624; PMCID: PMC7869028.

[52] E. Maggi, G.W. Canonica, L. Moretta, COVID-19: unanswered questions on immune response and pathogenesis, J. Allergy Clin. Immunol. 146 (1 July) (2020) 18–22, https://doi.org/10.1016/j.jaci.2020.05.001. Epub 2020 May 8. Erratum in: J Allergy Clin Immunol. 2020 Nov;146(5):1215. PMID: 32389590; PMCID: PMC7205667.

[53] L.R. Feldstein, E.B. Rose, S.M. Horwitz, J.P. Collins, M.M. Newhams, M.B.F. Son, J.W. Newburger, L.C. Kleinman, S.M. Heidemann, A.A. Martin, A.R. Singh, S. Li, K.M. Tarquinio, P. Jaggi, M.E. Oster, S.P. Zackai, J. Gillen, A.J. Ratner, R. F. Walsh, J.C. Fitzgerald, M.A. Keenaghan, H. Alharash, S. Doymaz, K.N. Clouser, J.S. Giuliano Jr., A. Gupta, R.M. Parker, A.B. Maddux, V. Havalad, S. Ramsingh, H. Bukulmez, T.T. Bradford, L.S. Smith, M.W. Tenforde, C.L. Carroll, B.J. Riggs, S. J. Gertz, A. Daube, A. Lansell, A. Coronado Munoz, C.V. Hobbs, K.L. Marohn, N. B. Halasa, M.M. Patel, A.G. Randolph, Overcoming COVID-19 Investigators, CDC COVID-19 Response Team, Multisystem inflammatory syndrome in U.S. Children and adolescents, N. Engl. J. Med. 383 (4 July) (2020) 334–346, https://doi.org/10.1056/NEJMoa2021680, 23Epub 2020 Jun 29. PMID: 32598831; PMCID: PMC7346765.

[54] L.R. Feldstein, M.W. Tenforde, K.G. Friedman, M. Newhams, E.B. Rose, H. Dapul, V.L. Soma, A.B. Maddux, P.M. Mourani, C. Bowens, M. Maamari, M.W. Hall, B. J. Riggs, J.S. Giuliano Jr., A.R. Singh, S. Li, M. Kong, J.E. Schuster, G. E. McLaughlin, S.P. Schwartz, T.C. Walker, L.L. Loftis, C.V. Hobbs, N.B. Halasa, S. Doymaz, C.J. Babbitt, J.R. Hume, S.J. Gertz, K. Irby, K.N. Clouser, N. Z. Cvijanovich, T.T. Bradford, L.S. Smith, S.M. Heidemann, S.P. Zackai, K. Wellnitz, R.A. Nofziger, S.M. Horwitz, R.W. Carroll, C.M. Rowan, K. M. Tarquinio, E.H. Mack, J.C. Fitzgerald, B.M. Coates, A.M. Jackson, C.C. Young, M.B.F. Son, M.M. Patel, J.W. Newburger, A.G. Randolph, Overcoming COVID-19 Investigators, Characteristics and outcomes of US children and adolescents with multisystem inflammatory syndrome in children (MIS-C) compared with severe acute COVID-19, JAMA 325 (11 March) (2021) 1074–1087, https://doi.org/10.1001/jama.2021.2091, 16PMID: 33625505; PMCID: PMC7905703.

[55] M. Levin, Childhood multisystem inflammatory syndrome - a new challenge in the pandemic, N. Engl. J. Med. 383 (4 July) (2020) 393–395, https://doi.org/10.1056/NEJMe2023158, 23Epub 2020 Jun 29. PMID: 32598829; PMCID: PMC7346677.

[56] S. Esposito, N. Principi, Multisystem inflammatory syndrome in children related to SARS-CoV-2, Paediatr. Drugs 23 (2 March) (2021) 119–129, https://doi.org/10.1007/s40272-020-00435-x. Epub 2021 Jan 22. PMID: 33479801; PMCID: PMC7819738.

[57] C.R. Consiglio, N. Cotugno, F. Sardh, C. Pou, D. Amodio, L. Rodriguez, Z. Tan, S. Zicari, A. Ruggiero, G.R. Pascucci, V. Santilli, T. Campbell, Y. Bryceson, D. Eriksson, J. Wang, A. Marchesi, T. Lakshmikanth, A. Campana, A. Villani, P. Rossi, CACTUS study team, landegren N, Palma p, Brodin P. The immunology of multisystem inflammatory syndrome in children with COVID-19, Cell 183 (4 November) (2020) 968–981, https://doi.org/10.1016/j.cell.2020.09.016, 12e7Epub 2020 Sep 6. PMID: 32966765; PMCID: PMC7474869.

[58] A. Esteve-Sole, J. Anton, R.M. Pino-Ramirez, J. Sanchez-Manubens, V. Fumadó, C. Fortuny, M. Rios-Barnes, J. Sanchez-de-Toledo, M. Girona-Alarcón, J. M. Mosquera, S. Ricart, C. Launes, M.F. de Sevilla, C. Jou, C. Muñoz-Almagro, E. González-Roca, A. Vergara, J. Carrillo, M. Juan, D. Cuadras, A. Noguera-Julian, I. Jordan, L. Alsina, Similarities and differences between the immunopathogenesis of COVID-19-related pediatric multisystem inflammatory syndrome and Kawasaki disease, J. Clin. Invest. 131 (6 March) (2021) e144554, https://doi.org/10.1172/JCI144554, 15PMID: 33497356; PMCID: PMC7954607.

[59] X. Xu, M. Han, T. Li, W. Sun, D. Wang, B. Fu, Y. Zhou, X. Zheng, Y. Yang, X. Li, X. Zhang, A. Pan, H. Wei, Effective treatment of severe COVID-19 patients with tocilizumab, Proc. Natl. Acad. Sci. U. S. A. 117 (20) (2020) 10970–10975, https://doi.org/10.1073/pnas.2005615117.

[60] C. Kotch, D. Barrett, D.T. Teachey, Tocilizumab for the treatment of chimeric antigen receptor T cell-induced cytokine release syndrome, Expert Rev. Clin. Immunol. 15 (8 August) (2019) 813–822, https://doi.org/10.1080/1744666X.2019.1629904. Epub 2019 Jun 20. PMID: 31219357; PMCID: PMC7936577.

[61] A. Rubbert-Roth, D.E. Furst, J.M. Nebesky, A. Jin, E. Berber, A review of recent advances using tocilizumab in the treatment of rheumatic diseases, Rheumatol. Ther. 5 (1 June) (2018) 21–42, https://doi.org/10.1007/s40744-018-0102-x. Epub 2018 Mar 3. PMID: 29502236; PMCID: PMC5935615.

[62] E.J. Rubin, D.L. Longo, L.R. Baden, Interleukin-6 receptor inhibition in Covid-19 - cooling the inflammatory soup, N. Engl. J. Med. 384 (16 April) (2021) 1564–1565, https://doi.org/10.1056/NEJMe2103108, 22Epub 2021 Feb 25. PMID: 33631064; PMCID: PMC7944949.

[63] I.O. Rosas, N. Bräu, M. Waters, R.C. Go, B.D. Hunter, S. Bhagani, D. Skiest, M. S. Aziz, N. Cooper, I.S. Douglas, S. Savic, T. Youngstein, L. Del Sorbo, A. Cubillo Gracian, D.J. De La Zerda, A. Ustianowski, M. Bao, S. Dimonaco, E. Graham, B. Matharu, H. Spotswood, L. Tsai, A. Malhotra, Tocilizumab in hospitalized patients with severe Covid-19 pneumonia, N. Engl. J. Med. 384 (16 April) (2021) 1503–1516, https://doi.org/10.1056/NEJMoa2028700, 22Epub 2021 Feb 25. PMID: 33631066; PMCID: PMC7953459.

[64] REMAP-CAP Investigators, A.C. Gordon, P.R. Mouncey, F. Al-Beidh, K.M. Rowan, A.D. Nichol, Y.M. Arabi, D. Annane, A. Beane, W. van Bentum-Puijk, L.R. Berry, Z. Bhimani, M.J.M. Bonten, C.A. Bradbury, F.M. Brunkhorst, A. Buzgau, A. C. Cheng, M.A. Detry, E.J. Duffy, L.J. Estcourt, M. Fitzgerald, H. Goossens, R. Haniffa, A.M. Higgins, T.E. Hills, C.M. Horvat, F. Lamontagne, P.R. Lawler, H. L. Leavis, K.M. Linstrum, E. Litton, E. Lorenzi, J.C. Marshall, F.B. Mayr, D. F. McAuley, A. McGlothlin, S.P. McGuinness, B.J. McVerry, S.K. Montgomery, S. C. Morpeth, S. Murthy, K. Orr, R.L. Parke, J.C. Parker, A.E. Patanwala, V. Pettilä, E. Rademaker, M.S. Santos, C.T. Saunders, C.W. Seymour, M. Shankar-Hari, W. I. Sligl, A.F. Turgeon, A.M. Turner, F.L. van de Veerdonk, R. Zarychanski, C. Green, R.J. Lewis, D.C. Angus, C.J. McArthur, S. Berry, S.A. Webb, L.P. G. Derde, Interleukin-6 receptor antagonists in critically ill patients with Covid-19, N. Engl. J. Med. 384 (16 April) (2021) 1491–1502, https://doi.org/10.1056/NEJMoa2100433, 22Epub 2021 Feb 25. PMID: 33631065; PMCID: PMC7953461.

[65] J.H. Stone, M.J. Frigault, N.J. Serling-Boyd, A.D. Fernandes, L. Harvey, A. S. Foulkes, N.K. Horick, B.C. Healy, R. Shah, A.M. Bensaci, A.E. Woolley, S. Nikiforow, N. Lin, M. Sagar, H. Schrager, D.S. Huckins, M. Axelrod, M. D. Pincus, J. Fleisher, C.A. Sacks, M. Dougan, C.M. North, Y.D. Halvorsen, T. K. Thurber, Z. Dagher, A. Scherer, R.S. Wallwork, A.Y. Kim, S. Schoenfeld, P. Sen, T.G. Neilan, C.A. Perugino, S.H. Unizony, D.S. Collier, M.A. Matza, J.M. Yinh, K. A. Bowman, E. Meyerowitz, A. Zafar, Z.D. Drobni, M.B. Bolster, M. Kohler, K. M. D'Silva, J. Dau, M.M. Lockwood, C. Cubbison, B.N. Weber, M.K. Mansour, BACC Bay Tocilizumab Trial Investigators, Efficacy of Tocilizumab in patients hospitalized with Covid-19, N. Engl. J. Med. 383 (24 December) (2020) 2333–2344, https://doi.org/10.1056/NEJMoa2028836, 10Epub 2020 Oct 21. PMID: 33085857; PMCID: PMC7646626.

[67] A. Bhimraj, R.L. Morgan, A.H. Shumaker, V. Lavergne, L. Baden, V.C. Cheng, K. M. Edwards, R. Gandhi, J. Gallagher, W.J. Muller, J.C. O'Horo, S. Shoham, M. H. Murad, R.A. Mustafa, S. Sultan, Y. Falck-Ytter, Infectious diseases society of america guidelines on the treatment and management of patients with COVID-19, Infectious Dis. Soc. Am. (2021). Version 4.4.1. Available at https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Accessed 11 October 2021.

[68] L. Salvati, M. Occhipinti, L. Gori, L. Ciani, A. Mazzoni, L. Maggi, M. Capone, P. Parronchi, F. Liotta, V. Miele, F. Annunziato, F. Lavorini, L. Cosmi, Pulmonary vascular improvement in severe COVID-19 patients treated with tocilizumab, Immunol. Lett. 228 (December) (2020) 122–128, https://doi.org/10.1016/j.imlet.2020.10.009. Epub 2020 Nov 5. PMID: 33161002; PMCID: PMC7644186.

[69] W.T. Lin, Sh Hung, Cc Lai, Cy Wang, Ch. Chen, The effect of tocilizumab on COVID-19 patient mortality: a systematic review and meta-analysis of randomized controlled trials, Int. Immunopharmacol. 96 (July) (2021) 107602, https://doi.org/10.1016/j.intimp.2021.107602. Epub 2021 Mar 24. PMID: 33812260; PMCID: PMC7988468.

[70] C. Salvarani, G. Dolci, M. Massari, D.F. Merlo, S. Cavuto, L. Savoldi, P. Bruzzi, F. Boni, L. Braglia, C. Turrà, P.F. Ballerini, R. Sciascia, L. Zammarchi, O. Para, P. G. Scotton, W.O. Inojosa, V. Ravagnani, N.D. Salerno, P.P. Sainaghi, A. Brignone, M. Codeluppi, E. Teopompi, M. Milesi, P. Bertomoro, N. Claudio, M. Salio, M. Falcone, G. Cenderello, L. Donghi, V. Del Bono, P.L. Colombelli, A. Angheben, A. Passaro, G. Secondo, R. Pascale, I. Piazza, N. Facciolongo, M. Costantini, RCT-TCZ-COVID-19 Study Group, Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized with COVID-19 Pneumonia: A Randomized Clinical Trial, JAMA Intern. Med. 181 (1 January) (2021) 24–31, https://doi.org/10.1001/jamainternmed.2020.6615, 1PMID:33080005; PMCID: PMC7577199.

[71] E. Huang, S.C. Jordan, Tocilizumab for Covid-19 - the ongoing search for effective therapies, N. Engl. J. Med. 383 (24) (2020) 2387–2388, https://doi.org/10.1056/NEJMe2032071.

[72] L. Cifaldi, G. Prencipe, I. Caiello, C. Bracaglia, F. Locatelli, F. De Benedetti, R. Strippoli, Inhibition of natural killer cell cytotoxicity by interleukin-6: implications for the pathogenesis of macrophage activation syndrome, Arthritis Rheumatol 67 (11 November) (2015) 3037–3046, https://doi.org/10.1002/art.39295. PMID: 26251193.

[73] Y.J. Kang, I.C. Jeung, A. Park, Y.J. Park, H. Jung, T.D. Kim, H.G. Lee, I. Choi, S. R. Yoon, An increased level of IL-6 suppresses NK cell activity in peritoneal fluid of patients with endometriosis via regulation of SHP-2 expression, Hum. Reprod. 29 (10 October) (2014) 2176–2189, https://doi.org/10.1093/humrep/deu172, 10Epub 2014 Jul 17. PMID: 25035432.

[74] N. Vabret, G.J. Britton, C. Gruber, S. Hegde, J. Kim, M. Kuksin, R. Levantovsky, L. Malle, A. Moreira, M.D. Park, L. Pia, E. Risson, M. Saffern, B. Salomé, M. Esai Selvan, M.P. Spindler, J. Tan, V. van der Heide, J.K. Gregory, K. Alexandropoulos, N. Bhardwaj, B.D. Brown, B. Greenbaum, Z.H. Gümüş, D. Homann, A. Horowitz, A.O. Kamphorst, M.A. Curotto de Lafaille, S. Mehandru, M. Merad, R. M. Samstein, Sinai immunology review project. Immunology of COVID-19: current state of the science, Immunity 52 (6 June) (2020) 910–941, https://doi.org/10.1016/j.immuni.2020.05.002, 16Epub 2020 May 6. PMID: 32505227; PMCID: PMC7200337.

[75] J. Wu, F.X. Gao, C. Wang, M. Qin, F. Han, T. Xu, Z. Hu, Y. Long, X.M. He, X. Deng, D.L. Ren, T.Y. Dai, IL-6 and IL-8 secreted by tumour cells impair the function of NK cells via the STAT3 pathway in oesophageal squamous cell carcinoma, J. Exp. Clin. Cancer Res. 38 (1 July) (2019) 321, https://doi.org/10.1186/s13046-019-1310-0, 19PMID: 31324197; PMCID: PMC6642486.

[76] G. Meoni, V. Ghini, L. Maggi, A. Vignoli, A. Mazzoni, L. Salvati, M. Capone, A. Vanni, L. Tenori, P. Fontanari, F. Lavorini, A. Peris, A. Bartoloni, F. Liotta, L. Cosmi, C. Luchinat, F. Annunziato, P. Turano, Metabolomic/lipidomic profiling of COVID-19 and individual response to tocilizumab, PLoS Pathog. 17 (2 Febuary) (2021) e1009243, https://doi.org/10.1371/journal.ppat.1009243, 1PMID: 33524041; PMCID: PMC7877736.

[77] F.X. Lescure, H. Honda, R.A. Fowler, J.S. Lazar, G. Shi, P. Wung, N. Patel, O. Hagino, Sarilumab COVID-19 Global Study Group, Sarilumab in patients admitted to hospital with severe or critical COVID-19: a randomised, double-blind, placebo-controlled, phase 3 trial, Lancet Respir. Med. 9 (5 May) (2021) 522–532, https://doi.org/10.1016/S2213-2600(21)00099-0. Epub 2021 Mar 4. PMID: 33676590; PMCID: PMC8078879.

[78] E. Della-Torre, C. Campochiaro, G. Cavalli, G. De Luca, A. Napolitano, S. La Marca, N. Boffini, V. Da Prat, G. Di Terlizzi, M. Lanzillotta, P. Rovere Querini, A. Ruggeri, G. Landoni, M. Tresoldi, F. Ciceri, A. Zangrillo, F. De Cobelli, L. Dagna, SARI-RAF Study Group; SARI-RAF Study Group members. Interleukin-6 blockade with sarilumab in severe COVID-19 pneumonia with systemic hyperinflammation: an open-label cohort study, Ann. Rheum. Dis. 79 (10 October) (2020) 1277–1285, https://doi.org/10.1136/annrheumdis-2020-218122. Epub 2020 Jul 3. PMID: 32620597; PMCID: PMC7509526.

[79] E. Gremese, A. Cingolani, S.L. Bosello, S. Alivernini, B. Tolusso, S. Perniola, F. Landi, M. Pompili, R. Murri, A. Santoliquido, M. Garcovich, M. Sali, G. De Pascale, M. Gabrielli, F. Biscetti, M. Montalto, A. Tosoni, G. Gambassi, G. L. Rapaccini, A. Iaconelli, L. Zileri Del Verme, L. Petricca, A.L. Fedele, M. M. Lizzio, E. Tamburrini, G. Natalello, L. Gigante, D. Bruno, L. Verardi, E. Taddei, A. Calabrese, F. Lombardi, R. Bernabei, R. Cauda, F. Franceschi, R. Landolfi, L. Richeldi, M. Sanguinetti, M. Fantoni, M. Antonelli, A. Gasbarrini, GEMELLI AGAINST COVID-19 Group, Sarilumab use in severe SARS-CoV-2 pneumonia, EClin. Med. 27 (October) (2020) 100553, https://doi.org/10.1016/j.eclinm.2020.100553. Epub 2020 Oct 2. PMID: 33043284; PMCID: PMC7531933.

[80] G. Cavalli, L. Dagna, The right place for IL-1 inhibition in COVID-19, Lancet Respir. Med. 9 (3 March) (2021) 223–224, https://doi.org/10.1016/S2213-2600(21)00035-7. Epub 2021 Jan 22. PMID: 33493449; PMCID: PMC7826019.

[81] G. Cavalli, G. De Luca, C. Campochiaro, E. Della-Torre, M. Ripa, D. Canetti, C. Oltolini, B. Castiglioni, C. Tassan Din, N. Boffini, A. Tomelleri, N. Farina, A. Ruggeri, P. Rovere-Querini, G. Di Lucca, S. Martinenghi, R. Scotti, M. Tresoldi, F. Ciceri, G. Landoni, A. Zangrillo, P. Scarpellini, L. Dagna, Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study, Lancet Rheumatol. 2 (6 June) (2020) e325–e331, https://doi.org/10.1016/S2665-9913(20)30127-2. Epub 2020 May 7. PMID: 32501454; PMCID: PMC7252085.

[82] L. Pasin, G. Cavalli, P. Navalesi, N. Sella, G. Landoni, A.G. Yavorovskiy, V. V. Likhvantsev, A. Zangrillo, L. Dagna, G. Monti, Anakinra for patients with COVID-19: a meta-analysis of non-randomized cohort studies, Eur. J. Intern. Med. 86 (April) (2021) 34–40, https://doi.org/10.1016/j.ejim.2021.01.016. Epub 2021 Feb 5. PMID: 33581979; PMCID: PMC7862887.

[83] CORIMUNO-19 Collaborative group, Effect of anakinra versus usual care in adults in hospital with COVID-19 and mild-to-moderate pneumonia (CORIMUNO-ANA-1): a randomised controlled trial, Lancet Respir. Med. 9 (3 March) (2021) 295–304, https://doi.org/10.1016/S2213-2600(20)30556-7. Epub 2021 Jan 22. PMID: 33493450; PMCID: PMC7825875.

[84] L. Landi, C. Ravaglia, E. Russo, P. Cataleta, M. Fusari, A. Boschi, D. Giannarelli, F. Facondini, I. Valentini, I. Panzini, L. Lazzari-Agli, P. Bassi, E. Marchionni, R. Romagnoli, R. De Giovanni, M. Assirelli, F. Baldazzi, F. Pieraccini, G. Rametta, L. Rossi, L. Santini, I. Valenti, F. Cappuzzo, Blockage of interleukin-1β with canakinumab in patients with Covid-19, Sci. Rep. 10 (1 December) (2020) 21775, https://doi.org/10.1038/s41598-020-78492-y, 11PMID: 33311551; PMCID: PMC7733468.

[85] C. Ucciferri, A. Auricchio, M. Di Nicola, N. Potere, A. Abbate, F. Cipollone, J. Vecchiet, K. Falasca, Canakinumab in a subgroup of patients with COVID-19, Lancet Rheumatol. 2 (8 August) (2020) e457–ee458, https://doi.org/10.1016/S2665-9913(20)30167-3. Epub 2020 Jun 4. PMID: 32835251; PMCID: PMC7272172.

[86] R. Caricchio, A. Abbate, I. Gordeev, J. Meng, P.Y. Hsue, T. Neogi, R. Arduino, D. Fomina, R. Bogdanov, T. Stepanenko, P. Ruiz-Seco, A. Gónzalez-García, Y. Chen, Y. Li, S. Whelan, S. Noviello, CAN-COVID Investigators, Effect of Canakinumab vs Placebo on Survival Without Invasive Mechanical Ventilation in Patients Hospitalized With Severe COVID-19: A Randomized Clinical Trial, JAMA 326 (3 July) (2021) 230–239, https://doi.org/10.1001/jama.2021.9508, 20PMID: 34283183; PMCID: PMC8293025.

[87] W. Luo, Y.X. Li, L.J. Jiang, Q. Chen, T. Wang, D.W. Ye, Targeting JAK-STAT signaling to control cytokine release syndrome in COVID-19, Trends Pharmacol. Sci. 41 (8 August) (2020) 531–543, https://doi.org/10.1016/j.tips.2020.06.007. Epub 2020 Jun 17. PMID: 32580895; PMCID: PMC7298494.

[88] F.R. Spinelli, F. Conti, M. Gadina, HiJAKing SARS-CoV-2? The potential role of JAK inhibitors in the management of COVID-19, Sci. Immunol. 5 (47 May) (2020) eabc5367, https://doi.org/10.1126/sciimmunol.abc5367, 8PMID: 32385052.

[89] Y. Cao, J. Wei, L. Zou, T. Jiang, G. Wang, L. Chen, L. Huang, F. Meng, L. Huang, N. Wang, X. Zhou, H. Luo, Z. Mao, X. Chen, J. Xie, J. Liu, H. Cheng, J. Zhao, G. Huang, W. Wang, J. Zhou, Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): A multicenter, single-blind, randomized controlled trial, J. Allergy Clin. Immunol. 146 (1 July) (2020) 137–146, https://doi.org/10.1016/j.jaci.2020.05.019, e3Epub 2020 May 26. PMID: 32470486; PMCID: PMC7250105.

[90] C.X. Chen, J.J. Wang, H. Li, L.T. Yuan, R.P. Gale, Y. Liang, JAK-inhibitors for coronavirus disease-2019 (COVID-19): a meta-analysis, Leukemia 14 (May) (2021) 1–5, https://doi.org/10.1038/s41375-021-01266-6. Epub ahead of print. PMID: 33990684; PMCID: PMC8119232.

[91] P.O. Guimarães, D. Quirk, R.H. Furtado, L.N. Maia, J.F. Saraiva, M.O. Antunes, R. Kalil Filho, V.M. Junior, A.M. Soeiro, A.P. Tognon, V.C. Veiga, P.A. Martins, D. D.F. Moia, B.S. Sampaio, S.R.L. Assis, R.V.P. Soares, L.P.A. Piano, K. Castilho, R.G. R.A.P. Momesso, F. Monfardini, H.P. Guimarães, D. Ponce de Leon, M. Dulcine, M.R.T. Pinheiro, L.M. Gunay, J.J. Deuring, L.V. Rizzo, T. Koncz, O. Berwanger, STOP-COVID Trial Investigators, Tofacitinib in Patients Hospitalized with Covid-19 Pneumonia, N. Engl. J. Med. 16 (June) (2021), https://doi.org/10.1056/NEJMoa2101643. NEJMoa2101643Epub ahead of print. PMID: 34133856; PMCID: PMC8220898.

[92] A.C. Kalil, T.F. Patterson, A.K. Mehta, K.M. Tomashek, C.R. Wolfe, V. Ghazaryan, V.C. Marconi, G.M. Ruiz-Palacios, L. Hsieh, S. Kline, V. Tapson, N.M. Iovine, M. K. Jain, D.A. Sweeney, H.M. El Sahly, A.R. Branche, J. Regalado Pineda, D.C. Lye, U. Sandkovsky, A.F. Luetkemeyer, S.H. Cohen, R.W. Finberg, P.E.H. Jackson, B. Taiwo, C.I. Paules, H. Arguinchona, N. Erdmann, N. Ahuja, M. Frank, M.D. Oh, E.S. Kim, S.Y. Tan, R.A. Mularski, H. Nielsen, P.O. Ponce, B.S. Taylor, L. Larson, N.G. Rouphael, Y. Saklawi, V.D. Cantos, E.R. Ko, J.J. Engemann, A.N. Amin, M. Watanabe, J. Billings, M.C. Elie, R.T. Davey, T.H. Burgess, J. Ferreira, M. Green, M. Makowski, A. Cardoso, S. de Bono, T. Bonnett, M. Proschan, G. A. Deye, W. Dempsey, S.U. Nayak, L.E. Dodd, J.H. Beigel, ACTT-2 Study Group Members, Baricitinib plus remdesivir for hospitalized adults with Covid-19, N. Engl. J. Med. 384 (9 March) (2021) 795–807, https://doi.org/10.1056/NEJMoa2031994, 4Epub 2020 Dec 11. PMID: 33306283; PMCID: PMC7745180.

[93] D. Goletti, F. Cantini, Baricitinib therapy in Covid-19 pneumonia - an unmet need fulfilled, N. Engl. J. Med. 384 (9 March) (2021) 867–869, https://doi.org/10.1056/NEJMe2034982, 4PMID: 33657299; PMCID: PMC7944951.

[94] P. Mehta, C. Ciurtin, M. Scully, M. Levi, R.C. Chambers, JAK inhibitors in COVID-19: the need for vigilance regarding increased inherent thrombotic risk, Eur. Respir. J. 56 (3 September) (2020) 2001919, https://doi.org/10.1183/13993003.01919-2020, 24PMID: 32631841; PMCID: PMC7338400.

[95] P. Mehta, D.F. McAuley, M. Brown, E. Sanchez, R.S. Tattersall, J.J. Manson, HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression, Lancet 395 (10229 March) (2020) 1033–1034, https://doi.org/10.1016/S0140-6736(20)30628-0, 28Epub 2020 Mar 16. PMID: 32192578; PMCID: PMC7270045.

[96] Y. Oba, The use of corticosteroids in SARS, N. Engl. J. Med. 348 (20 May) (2003) 2034–2035, https://doi.org/10.1056/NEJM200305153482017, author reply, PMID: 12748321.

[97] N. Lee, D. Hui, A. Wu, P. Chan, P. Cameron, G.M. Joynt, A. Ahuja, M.Y. Yung, C. B. Leung, K.F. To, S.F. Lui, C.C. Szeto, S. Chung, J.J. Sung, A major outbreak of severe acute respiratory syndrome in Hong Kong, N. Engl. J. Med. 348 (20 May) (2003) 1986–1994, https://doi.org/10.1056/NEJMoa030685, 15Epub 2003 Apr 7. PMID: 12682352.

[98] N. Lee, K.C. Allen Chan, D.S. Hui, E.K. Ng, A. Wu, R.W. Chiu, V.W. Wong, P. K. Chan, K.T. Wong, E. Wong, C.S. Cockram, J.S. Tam, J.J. Sung, Y.M. Lo, Effects of early corticosteroid treatment on plasma SARS-associated Coronavirus RNA concentrations in adult patients, J. Clin. Virol. 31 (4 December) (2004) 304–309, https://doi.org/10.1016/j.jcv.2004.07.006. PMID: 15494274; PMCID: PMC7108318.

[99] C.K. Wong, C.W. Lam, A.K. Wu, W.K. Ip, N.L. Lee, I.H. Chan, L.C. Lit, D.S. Hui, M. H. Chan, S.S. Chung, J.J. Sung, Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome, Clin. Exp. Immunol. 136 (1 April) (2004) 95–103, https://doi.org/10.1111/j.1365-2249.2004.02415.x. PMID: 15030519; PMCID: PMC1808997.

[100] L.J. Stockman, R. Bellamy, P. Garner, SARS: systematic review of treatment effects, PLoS Med. 3 (9 September) (2006) e343, https://doi.org/10.1371/journal.pmed.0030343. PMID: 16968120; PMCID: PMC1564166.

[101] N. Veronese, J. Demurtas, L. Yang, R. Tonelli, M. Barbagallo, P. Lopalco, E. Lagolio, S. Celotto, D. Pizzol, L. Zou, M.A. Tully, P.C. Ilie, M. Trott, G. F. López-Sánchez, L. Smith, Use of corticosteroids in coronavirus disease 2019 pneumonia: a systematic review of the literature, Front. Med. (Lausanne) 7 (April) (2020) 170, https://doi.org/10.3389/fmed.2020.00170, 24PMID: 32391369; PMCID: PMC7193030.

[102] RECOVERY Collaborative Group, P. Horby, W.S. Lim, J.R. Emberson, M. Mafham, J.L. Bell, L. Linsell, N. Staplin, C. Brightling, A. Ustianowski, E. Elmahi, B. Prudon, C. Green, T. Felton, D. Chadwick, K. Rege, C. Fegan, L.C. Chappell, S.N. Faust, T. Jaki, K. Jeffery, A. Montgomery, K. Rowan, E. Juszczak, J.K. Baillie, R. Haynes, M.J. Landray, Dexamethasone in hospitalized patients with Covid-19, N. Engl. J. Med. 384 (8 Febuary) (2021) 693–704, https://doi.org/10.1056/NEJMoa2021436, 25Epub 2020 Jul 17. PMID: 32678530; PMCID: PMC7383595.

[103] WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, J.A.C. Sterne, S. Murthy, J.V. Diaz, A.S. Slutsky, J. Villar, D.C. Angus, D. Annane, L.C.P. Azevedo, O. Berwanger, A.B. Cavalcanti, P.F. Dequin, B. Du, J. Emberson, D. Fisher, B. Giraudeau, A.C. Gordon, A. Granholm, C. Green, R. Haynes, N. Heming, J.P.T. Higgins, P. Horby, P. Jüni, M.J. Landray, A. Le Gouge, M. Leclerc, W.S. Lim, F.R. Machado, C. McArthur, F. Meziani, M.H. Møller, A. Perner, M.W. Petersen, J. Savovic, B. Tomazini, V.C. Veiga, S. Webb, J. C. Marshall, Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis, JAMA 324 (13 October) (2020) 1330–1341, https://doi.org/10.1001/jama.2020.17023, 6PMID: 32876694; PMCID: PMC7489434.

[104] C.M.P. Jeronimo, M.E.L. Farias, F.F.A. Val, V.S. Sampaio, M.A.A. Alexandre, G. C. Melo, I.P. Safe, M.G.S. Borba, R.L.A. Netto, A.B.S. Maciel, J.R.S. Neto, L. B. Oliveira, E.F.G. Figueiredo, K.M. Oliveira Dinelly, M.G. de Almeida Rodrigues, M. Brito, M.P.G. Mourão, G.A. Pivoto João, L.A. Hajjar, Q. Bassat, G.A.S. Romero, F.G. Naveca, H.L. Vasconcelos, M. de Araújo Tavares, J.D. Brito-Sousa, F.T. M. Costa, M.L. Nogueira, D.C. Baía-da-Silva, M.S. Xavier, W.M. Monteiro, M.V. G. Lacerda, Metcovid Team, Methylprednisolone as adjunctive therapy for patients hospitalized with coronavirus disease 2019 (COVID-19; Metcovid): a randomized, double-blind, phase IIb, placebo-controlled trial, Clin. Infect. Dis. 72 (9 May) (2021) e373–e381, https://doi.org/10.1093/cid/ciaa1177, 4PMID: 32785710; PMCID: PMC7454320.

[105] J.L. Lennox, Methylprednisolone for coronavirus disease 2019 (COVID-19): was benjamin rush prescient? Clin. Infect. Dis. 72 (9 May) (2021) e382–e383, https://doi.org/10.1093/cid/ciaa1262, 4PMID: 32845289; PMCID: PMC7499563.

[106] A.J. McArdle, O. Vito, H. Patel, E.G. Seaby, P. Shah, C. Wilson, C. Broderick, R. Nijman, A.H. Tremoulet, D. Munblit, R. Ulloa-Gutierrez, M.J. Carter, T. De, C. Hoggart, E. Whittaker, J.A. Herberg, M. Kaforou, A.J. Cunnington, M. Levin, BATS Consortium, Treatment of multisystem inflammatory syndrome in children, N. Engl. J. Med. 385 (1 July) (2021) 11–22, https://doi.org/10.1056/NEJMoa2102968, 1Epub 2021 Jun 16. PMID: 34133854; PMCID: PMC8220965.

[107] M.B.F. Son, N. Murray, K. Friedman, C.C. Young, M.M. Newhams, L.R. Feldstein, L.L. Loftis, K.M. Tarquinio, A.R. Singh, S.M. Heidemann, V.L. Soma, B.J. Riggs, J. C. Fitzgerald, M. Kong, S. Doymaz, J.S. Giuliano Jr., M.A. Keenaghan, J.R. Hume, C.V. Hobbs, J.E. Schuster, K.N. Clouser, M.W. Hall, L.S. Smith, S.M. Horwitz, S. P. Schwartz, K. Irby, T.T. Bradford, A.B. Maddux, C.J. Babbitt, C.M. Rowan, G. E. McLaughlin, P.H. Yager, M. Maamari, E.H. Mack, C.L. Carroll, V. L. Montgomery, N.B. Halasa, N.Z. Cvijanovich, B.M. Coates, C.E. Rose, J. W. Newburger, M.M. Patel, A.G. Randolph, Overcoming COVID-19 Investigators, Multisystem inflammatory syndrome in children - initial therapy and outcomes, N. Engl. J. Med. 385 (1 July) (2021) 23–34, https://doi.org/10.1056/NEJMoa2102605, 1Epub 2021 Jun 16. PMID: 34133855; PMCID: PMC8220972.

[108] R.L. DeBiasi, Immunotherapy for MIS-C - IVIG, Glucocorticoids, and Biologics, N. Engl. J. Med. 385 (1 July) (2021) 74–75, https://doi.org/10.1056/NEJMe2108276, 1Epub 2021 Jun 16. PMID: 34133878.

[109] S. Tavakolpour, T. Rakhshandehroo, E.X. Wei, M. Rashidian, Lymphopenia during the COVID-19 infection: what it shows and what can be learned, Immunol. Lett. 225 (2020) 31–32, https://doi.org/10.1016/j.imlet.2020.06.013.

[110] X. Chen, B. Zhao, Y. Qu, et al., Detectable serum severe acute respiratory syndrome coronavirus 2 viral load (rnaemia) is closely correlated with drastically elevated interleukin 6 level in critically ill patients with coronavirus disease 2019, Clin. Infect. Dis. 71 (8) (2020) 1937–1942, https://doi.org/10.1093/cid/ciaa449.

[111] D. Weiskopf, K.S. Schmitz, M.P. Raadsen, A. Grifoni, N.M.A. Okba, H. Endeman, J.P.C. van den Akker, R. Molenkamp, M.P.G. Koopmans, E.C.M. van Gorp, B. L. Haagmans, R.L. de Swart, A. Sette, R.D. de Vries, Phenotype and kinetics of SARS-CoV-2-specific T cells in COVID-19 patients with acute respiratory distress syndrome, Sci. Immunol. 5 (48 June) (2020) eabd2071, https://doi.org/10.1126/sciimmunol.abd2071, 26PMID: 32591408; PMCID: PMC7319493.

[113] A. Bobcakova, J. Petriskova, R. Vysehradsky, I. Kocan, L. Kapustova, M. Barnova, Z. Diamant, M. Jesenak, Immune profile in patients with COVID-19: lymphocytes exhaustion markers in relationship to clinical outcome, Front. Cell. Infect. Microbiol. 11 (April) (2021) 646688, https://doi.org/10.3389/fcimb.2021.646688, 15PMID: 33937096; PMCID: PMC8082075.

[114] S. Kreutmair, S. Unger, N.G. Núñez, F. Ingelfinger, C. Alberti, D. De Feo, S. Krishnarajah, M. Kauffmann, E. Friebel, S. Babaei, B. Gaborit, M. Lutz, N. P. Jurado, N.P. Malek, S. Goepel, P. Rosenberger, H.A. Häberle, I. Ayoub, S. Al-Hajj, J. Nilsson, M. Claassen, R. Liblau, G. Martin-Blondel, M. Bitzer, A. Roquilly, B. Becher, Distinct immunological signatures discriminate severe COVID-19 from non-SARS-CoV-2-driven critical pneumonia, Immunity S1074-7613 (21 May) (2021) 00208–00209, https://doi.org/10.1016/j.immuni.2021.05.002, 9Epub ahead of print. PMID: 34051147; PMCID: PMC8106882.

[116] D. Mathew, J.R. Giles, A.E. Baxter, D.A. Oldridge, A.R. Greenplate, J.E. Wu, C. Alanio, L. Kuri-Cervantes, M.B. Pampena, K. D'Andrea, S. Manne, Z. Chen, Y. J. Huang, J.P. Reilly, A.R. Weisman, C.A.G. Ittner, O. Kuthuru, J. Dougherty, K. Nzingha, N. Han, J. Kim, A. Pattekar, E.C. Goodwin, E.M. Anderson, M. E. Weirick, S. Gouma, C.P. Arevalo, M.J. Bolton, F. Chen, S.F. Lacey, H. Ramage, S. Cherry, S.E. Hensley, S.A. Apostolidis, A.C. Huang, L.A. Vella, UPenn COVID Processing Unit, M.R. Betts, N.J. Meyer, E.J. Wherry, Deep immune profiling of COVID-19 patients reveals distinct immunotypes with therapeutic implications, Science 369 (6508 September) (2020) eabc8511, https://doi.org/10.1126/science.abc8511, 4Epub 2020 Jul 15. PMID: 32669297; PMCID: PMC7402624.

[117] D. Fenoglio, C. Dentone, A. Parodi, A. Di Biagio, F. Bozzano, A. Vena, M. Fabbi, F. Ferrera, T. Altosole, B. Bruzzone, M. Giacomini, P. Pelosi, A. De Maria, M. Bassetti, R. De Palma, G. Filaci, Characterization of T lymphocytes in severe COVID-19 patients, J. Med. Virol. 29 (April) (2021), https://doi.org/10.1002/jmv.27037, 10.1002/jmv.27037. Epub ahead of print. PMID: 33913544; PMCID: PMC8242373.

[118] Y. Wang, J. Zheng, M.S. Islam, Y. Yang, Y. Hu, X. Chen, The role of CD4+FoxP3+ regulatory T cells in the immunopathogenesis of COVID-19: implications for treatment, Int. J. Biol. Sci. 17 (6 April) (2021) 1507–1520, https://doi.org/10.7150/ijbs.59534, 10PMID: 33907514; PMCID: PMC8071774.

[119] S. De Biasi, M. Meschiari, L. Gibellini, C. Bellinazzi, R. Borella, L. Fidanza, L. Gozzi, A. Iannone, D. Lo Tartaro, M. Mattioli, A. Paolini, M. Menozzi, J. Milić, G. Franceschi, R. Fantini, R. Tonelli, M. Sita, M. Sarti, T. Trenti, L. Brugioni, L. Cicchetti, F. Facchinetti, A. Pietrangelo, E. Clini, M. Girardis, G. Guaraldi, C. Mussini, A. Cossarizza, Marked T cell activation, senescence, exhaustion and skewing towards TH17 in patients with COVID-19 pneumonia, Nat. Commun. 11 (1 July) (2020) 3434, https://doi.org/10.1038/s41467-020-17292-4, 6PMID: 32632085; PMCID: PMC7338513.

[120] S.F. Lax, K. Skok, P. Zechner, et al., Pulmonary arterial thrombosis in COVID-19 with fatal outcome : results from a prospective, single-center, clinicopathologic case series, Ann. Intern. Med. 173 (5) (2020) 350–361, https://doi.org/10.7326/M20-2566.

[121] Q. Xiang, Z. Feng, B. Diao, C. Tu, Q. Qiao, H. Yang, Y. Zhang, G. Wang, H. Wang, C. Wang, L. Liu, C. Wang, L. Liu, R. Chen, Y. Wu, Y. Chen, SARS-CoV-2 Induces Lymphocytopenia by Promoting Inflammation and Decimates Secondary Lymphoid Organs, Front. Immunol. 28 (12 April) (2021) 661052, https://doi.org/10.3389/fimmu.2021.661052. PMID: 33995382; PMCID: PMC8113960.

[122] Q. Liu, Y. Shi, J. Cai, et al., Pathological changes in the lungs and lymphatic organs of twelve COVID-19 autopsy cases, Sci. Rev. 7 (12) (2020) 1868–1878, https://doi.org/10.1093/nsr/nwaa247.

[123] N.S. Panesar, What caused lymphopenia in SARS and how reliable is the lymphokine status in glucocorticoid-treated patients? Med. Hypotheses 71 (2 August) (2008) 298–301, https://doi.org/10.1016/j.mehy.2008.03.019.

[124] L. Falasca, R. Nardacci, D. Colombo, E. Lalle, A. Di Caro, E. Nicastri, A. Antinori, N. Petrosillo, L. Marchioni, G. Biava, G. D'Offizi, F. Palmieri, D. Goletti, A. Zumla, G. Ippolito, M. Piacentini, F. Del Nonno, Postmortem findings in italian patients with COVID-19: a descriptive full autopsy study of cases with and without comorbidities, J. Infect. Dis. 222 (11 November) (2020) 1807–1815, https://doi.org/10.1093/infdis/jiaa578, 9PMID: 32914853; PMCID: PMC7543426.

[125] R.B. Martines, J.M. Ritter, E. Matkovic, J. Gary, B.C. Bollweg, H. Bullock, C. S. Goldsmith, L. Silva-Flannery, J.N. Seixas, S. Reagan-Steiner, T. Uyeki, A. Denison, J. Bhatnagar, W.J. Shieh, S.R. Zaki, COVID-19 Pathology Working Group, Pathology and pathogenesis of SARS-CoV-2 associated with fatal coronavirus disease, United States, Emerg Infect Dis. 26 (9 September) (2020) 2005–2015, https://doi.org/10.3201/eid2609.202095. Epub 2020 May 21. PMID: 32437316; PMCID: PMC7454055.

[126] N. Kaneko, H.H. Kuo, J. Boucau, J.R. Farmer, H. Allard-Chamard, V.S. Mahajan, A. Piechocka-Trocha, K. Lefteri, M. Osborn, J. Bals, Y.C. Bartsch, N. Bonheur, T. M. Caradonna, J. Chevalier, F. Chowdhury, T.J. Diefenbach, K. Einkauf, J. Fallon, J. Feldman, K.K. Finn, P. Garcia-Broncano, C.A. Hartana, B.M. Hauser, C. Jiang, P. Kaplonek, M. Karpell, E.C. Koscher, X. Lian, H. Liu, J. Liu, N.L. Ly, A.R. Michell, Y. Rassadkina, K. Seiger, L. Sessa, S. Shin, N. Singh, W. Sun, X. Sun, H.J. Ticheli, M.T. Waring, A.L. Zhu, G. Alter, J.Z. Li, D. Lingwood, A.G. Schmidt, M. Lichterfeld, B.D. Walker, X.G. Yu, R.F. Padera Jr., S. Pillai, Massachusetts Consortium on Pathogen Readiness Specimen Working Group, Loss of Bcl-6-Expressing t follicular helper cells and germinal centers in COVID-19, Cell 183 (1 October) (2020) 143–157, https://doi.org/10.1016/j.cell.2020.08.025, e131Epub 2020 Aug 19. PMID: 32877699; PMCID: PMC7437499.

[127] A. Brighenti, M. Andrulis, E. Geissinger, S. Roth, H.K. Müller-Hermelink, T. Rüdiger, Extrafollicular proliferation of B cells in the absence of follicular hyperplasia: a distinct reaction pattern in lymph nodes correlated with primary or recall type responses, Histopathology 47 (1 July) (2005) 90–100, https://doi.org/10.1111/j.1365-2559.2005.02173.x. PMID: 15982328.

[128] A. Tzankov, S. Dirnhofer, A pattern-based approach to reactive lymphadenopathies, Semin. Diagn. Pathol. 35 (1 January) (2018) 4–19, https://doi.org/10.1053/j.semdp.2017.05.002. Epub 2017 May 25. PMID: 28619469.

[129] F. Venet, G. Monneret, Advances in the understanding and treatment of sepsis-induced immunosuppression, Nat. Rev. Nephrol. 14 (2 Febuary) (2018) 121–137, https://doi.org/10.1038/nrneph.2017.165. Epub 2017 Dec 11. PMID: 29225343.

[130] F. Venet, T. Rimmelé, G. Monneret, Management of sepsis-induced immunosuppression, Crit. Care Clin. 34 (1 January) (2018) 97–106, https://doi.org/10.1016/j.ccc.2017.08.007. Epub 2017 Oct 6. PMID: 29149944.

[131] H. Yadav, R. Cartin-Ceba, Balance between hyperinflammation and immunosuppression in Sepsis, Semin. Respir. Crit. Care Med. 37 (1 Febuary) (2016) 42–50, https://doi.org/10.1055/s-0035-1570356. Epub 2016 Jan 28. PMID: 26820273.

[132] R.S. Hotchkiss, G. Monneret, D. Payen, Immunosuppression in sepsis: a novel understanding of the disorder and a new therapeutic approach, Lancet Infect. Dis. 13 (3) (2013) 260–268, https://doi.org/10.1016/S1473-3099(13)70001-X.

[133] G.L. Lin, J.P. McGinley, S.B. Drysdale, A.J. Pollard, Epidemiology and immune pathogenesis of viral Sepsis, Front. Immunol. 9 (September) (2018) 2147, https://doi.org/10.3389/fimmu.2018.02147, 27PMID: 30319615; PMCID: PMC6170629.

[134] J. Beltrán-García, R. Osca-Verdegal, F.V. Pallardó, J. Ferreres, M. Rodríguez, S. Mulet, C. Ferrando-Sánchez, N. Carbonell, J.L. García-Giménez, Sepsis and coronavirus disease 2019: common features and anti-inflammatory therapeutic approaches, Crit. Care Med. 48 (12 December) (2020) 1841–1844, https://doi.org/10.1097/CCM.0000000000004625. PMID: 32826431; PMCID: PMC7467034.

[135] A. Roquilly, H.E.G. McWilliam, C. Jacqueline, Z. Tian, R. Cinotti, M. Rimbert, L. Wakim, I. Caminschi, M.H. Lahoud, G.T. Belz, A. Kallies, J.D. Mintern,

K. Asehnoune, J.A. Villadangos, Local modulation of antigen-presenting cell development after resolution of pneumonia induces long-term susceptibility to secondary infections, Immunity 47 (1 July) (2017) 135–147, https://doi.org/10.1016/j.immuni.2017.06.021, 18e5PMID: 28723546.
[136] F. Fattahi, P.A. Ward, Understanding immunosuppression after Sepsis, Immunity 47 (1 July) (2017) 3–5, https://doi.org/10.1016/j.immuni.2017.07.007, 18PMID: 28723551.
[137] J.G. Wilson, L.J. Simpson, A.M. Ferreira, A. Rustagi, J. Roque, A. Asuni, T. Ranganath, P.M. Grant, A. Subramanian, Y. Rosenberg-Hasson, H.T. Maecker, S.P. Holmes, J.E. Levitt, C.A. Blish, A.J. Rogers, Cytokine profile in plasma of severe COVID-19 does not differ from ARDS and sepsis, JCI Insight 5 (17 September) (2020) e140289, https://doi.org/10.1172/jci.insight.140289, 3PMID: 32706339; PMCID: PMC7526438.
[138] J.L. Vincent, COVID-19: it's all about sepsis, Future Microbiol. 16 (Febuary) (2021) 131–133, https://doi.org/10.2217/fmb-2020-0312. Epub 2021 Jan 25. PMID: 33491491; PMCID: PMC7837372.
[139] K.E. Remy, M. Mazer, D.A. Striker, A.H. Ellebedy, A.H. Walton, J. Unsinger, T. M. Blood, P.A. Mudd, D.J. Yi, D.A. Mannion, D.F. Osborne, R.S. Martin, N. J. Anand, J.P. Bosanquet, J. Blood, A.M. Drewry, C.C. Caldwell, I.R. Turnbull, S. C. Brakenridge, L.L. Moldwawer, R.S. Hotchkiss, Severe immunosuppression and not a cytokine storm characterizes COVID-19 infections, JCI Insight 5 (17 September) (2020) e140329, https://doi.org/10.1172/jci.insight.140329, 3PMID: 32687484; PMCID: PMC7526441.
[140] C. Huang, Y. Wang, X. Li, et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet 395 (10223) (2020) 497–506, https://doi.org/10.1016/S0140-6736(20)30183-5.
[141] W.J. Guan, Z.Y. Ni, Y. Hu, et al., Clinical characteristics of coronavirus disease 2019 in China, N. Engl. J. Med. 382 (18) (2020) 1708–1720, https://doi.org/10.1056/NEJMoa2002032.
[142] F. Lagi, M. Piccica, L. Graziani, et al., Early experience of an infectious and tropical diseases unit during the coronavirus disease (COVID-19) pandemic, Florence, Italy, February to March 2020, Euro Surveill. 25 (17) (2020) 2000556, https://doi.org/10.2807/1560-7917.ES.2020.25.17.2000556.
[143] D. Liao, F. Zhou, L. Luo, M. Xu, H. Wang, J. Xia, Y. Gao, L. Cai, Z. Wang, P. Yin, Y. Wang, L. Tang, J. Deng, H. Mei, Y. Hu, Haematological characteristics and risk factors in the classification and prognosis evaluation of COVID-19: a retrospective cohort study, Lancet Haematol. 7 (9) (2020) e671–e678, https://doi.org/10.1016/S2352-3026(20)30217-9.
[144] M. Liao, Y. Liu, J. Yuan, Y. Wen, G. Xu, J. Zhao, L. Cheng, J. Li, X. Wang, F. Wang, L. Liu, I. Amit, S. Zhang, Z. Zhang, Single-cell landscape of bronchoalveolar immune cells in patients with COVID-19, Nat. Med. 26 (6 June) (2020) 842–844, https://doi.org/10.1038/s41591-020-0901-9. Epub 2020 May 12. PMID: 32398875.
[145] L. Tan, Q. Wang, D. Zhang, et al., Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study, Signal Transduct. Target. Ther. 5 (1) (2020) 33, https://doi.org/10.1038/s41392-020-0148-4.
[146] C. Qin, L. Zhou, Z. Hu, S. Zhang, S. Yang, Y. Tao, C. Xie, K. Ma, K. Shang, W. Wang, D.S. Tian, Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan, China, Clin. Infect. Dis. 71 (15 July) (2020) 762–768, https://doi.org/10.1093/cid/ciaa248, 28.
[147] J. Lee, S.S. Park, T.Y. Kim, D.G. Lee, D.W. Kim, Lymphopenia as a biological predictor of outcomes in COVID-19 patients: a nationwide cohort study, Cancers (Basel). 13 (3) (2021) 471, https://doi.org/10.3390/cancers13030471. Published 2021 Jan 26.
[148] J. Wagner, A. DuPont, S. Larson, B. Cash, A. Farooq, Absolute lymphocyte count is a prognostic marker in Covid-19: a retrospective cohort review, Int. J. Lab. Hematol. 42 (6) (2020) 761–765, https://doi.org/10.1111/ijlh.13288.
[149] J. Liu, S. Li, J. Liu, et al., Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients, EBioMedicine. 55 (2020), 102763, https://doi.org/10.1016/j.ebiom.2020.102763.
[150] Z. Liu, W. Long, M. Tu, et al., Lymphocyte subset (CD4+, CD8+) counts reflect the severity of infection and predict the clinical outcomes in patients with COVID-19, J. Infect. 81 (2) (2020) 318–356, https://doi.org/10.1016/j.jinf.2020.03.054.
[151] Z. Deng, M. Zhang, T. Zhu, et al., Dynamic changes in peripheral blood lymphocyte subsets in adult patients with COVID-19, Int. J. Infect. Dis. 98 (2020) 353–358, https://doi.org/10.1016/j.ijid.2020.07.003.
[152] B.A. Cunha, F.M. Pherez, P. Schoch, Diagnostic importance of relative lymphopenia as a marker of swine influenza (H1N1) in adults, Clin. Infect. Dis. 49 (9) (2009) 1454–1456, https://doi.org/10.1086/644496.
[153] Z. He, C. Zhao, Q. Dong, H. Zhuang, S. Song, G. Peng, D.E. Dwyer, Effects of severe acute respiratory syndrome (SARS) coronavirus infection on peripheral blood lymphocytes and their subsets, Int. J. Infect. Dis. 9 (6) (2005) 323–330, https://doi.org/10.1016/j.ijid.2004.07.014.
[154] M.T. McClain, L.P. Park, B. Nicholson, et al., Longitudinal analysis of leukocyte differentials in peripheral blood of patients with acute respiratory viral infections, J. Clin. Virol. 58 (4 December) (2013) 689–695, https://doi.org/10.1016/j.jcv.2013.09.015.
[155] V. Bellelli, G. d'Ettorre, L. Celani, C. Borrazzo, G. Ceccarelli, M. Venditti, Clinical significance of lymphocytopenia in patients hospitalized with pneumonia caused by influenza virus, Crit. Care 23 (1 October) (2019) 330, https://doi.org/10.1186/s13054-019-2608-1, 29PMID: 31665060; PMCID: PMC6819578.
[156] J.W. Song, C. Zhang, X. Fan, F.P. Meng, Z. Xu, P. Xia, W.J. Cao, T. Yang, X.P. Dai, S.Y. Wang, R.N. Xu, T.J. Jiang, W.G. Li, D.W. Zhang, P. Zhao, M. Shi, C. Agrati, G. Ippolito, M. Maeurer, A. Zumla, F.S. Wang, J.Y. Zhang, Immunological and inflammatory profiles in mild and severe cases of COVID-19, Nat. Commun. 11 (1 July) (2020) 3410, https://doi.org/10.1038/s41467-020-17240-2, 8PMID: 32641700; PMCID: PMC7343781.
[157] L. Carsana, A. Sonzogni, A. Nasr, et al., Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study, Lancet Infect. Dis. 20 (10) (2020) 1135–1140, https://doi.org/10.1016/S1473-3099(20)30434-5.
[158] M. Ackermann, S.E. Verleden, M. Kuehnel, et al., Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19, N. Engl. J. Med. 383 (2) (2020) 120–128, https://doi.org/10.1056/NEJMoa2015432.
[159] A.G. Laing, A. Lorenc, I. Del Molino Del Barrio, A. Das, M. Fish, L. Monin, M. Muñoz-Ruiz, D.R. McKenzie, T.S. Hayday, I. Francos-Quijorna, S. Kamdar, M. Joseph, D. Davies, R. Davis, A. Jennings, I. Zlatareva, P. Vantourout, Y. Wu, V. Sofra, F. Cano, M. Greco, E. Theodoridis, J.D. Freedman, S. Gee, J.N.E. Chan, S. Ryan, E. Bugallo-Blanco, P. Peterson, K. Kisand, L. Haljasmägi, L. Chadli, P. Moingeon, L. Martinez, B. Merrick, K. Bisnauthsing, K. Brooks, M.A.A. Ibrahim, J. Mason, F. Lopez Gomez, K. Babalola, S. Abdul-Jawad, J. Cason, C. Mant, J. Seow, C. Graham, K.J. Doores, F. Di Rosa, J. Edgeworth, M. Shankar-Hari, A. C. Hayday, A dynamic COVID-19 immune signature includes associations with poor prognosis, Nat. Med. 26 (10 October) (2020) 1623–1635, https://doi.org/10.1038/s41591-020-1038-6. Epub 2020 Aug 17. Erratum in: Nat Med. 2020 Sep 9;: Erratum in: Nat Med. 2020 Dec;26(12):1951. PMID: 32807934.
[161] S. Adamo, S. Chevrier, C. Cervia, Y. Zurbuchen, M.E. Raeber, L. Yang, S. Sivapatham, A. Jacobs, E. Baechli, A. Rudiger, M. Stüssi-Helbling, L.C. Huber, D.J. Schaer, B. Bodenmiller, O. Boyman, J. Nilsson, Profound dysregulation of T cell homeostasis and function in patients with severe COVID-19, Allergy (April) (2021), https://doi.org/10.1111/all.14866. Epub ahead of print. PMID: 33884644; PMCID: PMC8251365.
[162] A. Jafarzadeh, S. Jafarzadeh, P. Nozari, P. Mokhtari, M. Nemati, Lymphopenia an important immunological abnormality in patients with COVID-19: possible mechanisms, Scand. J. Immunol. 93 (2 Febuary) (2021) e12967, https://doi.org/10.1111/sji.12967. Epub 2020 Sep 14. PMID: 32875598.
[163] L. Gutierrez, J. Beckford, H. Alachkar, Deciphering the TCR repertoire to solve the COVID-19 mystery, Trends Pharmacol. Sci. 41 (8 August) (2020) 518–530, https://doi.org/10.1016/j.tips.2020.06.001. Epub 2020 Jun 20. PMID: 32576386; PMCID: PMC7305739.
[164] C. Schultheiß, L. Paschold, D. Simnica, M. Mohme, E. Willscher, L. von Wenserski, R. Scholz, I. Wieters, C. Dahlke, E. Tolosa, D.G. Sedding, S. Ciesek, M. Addo, M. Binder, Next-generation sequencing of t and B cell receptor repertoires from COVID-19 patients showed signatures associated with severity of disease, Immunity 53 (2 August) (2020) 442–455, https://doi.org/10.1016/j.immuni.2020.06.024, 18e4Epub 2020 Jun 30. PMID: 32668194; PMCID: PMC7324317.
[165] X. Niu, S. Li, P. Li, W. Pan, Q. Wang, Y. Feng, X. Mo, Q. Yan, X. Ye, J. Luo, L. Qu, D. Weber, M.L. Byrne-Steele, Z. Wang, F. Yu, F. Li, R.M. Myers, M.T. Lotze, N. Zhong, J. Han, L. Chen, Longitudinal analysis of t and B cell receptor repertoire transcripts reveal dynamic immune response in COVID-19 patients, Front. Immunol. 11 (September) (2020) 582010, https://doi.org/10.3389/fimmu.2020.582010, 30Erratum in: Front Immunol. 2020 Dec 21;11:633815. PMID: 33117392; PMCID: PMC7561365.
[166] M.A. Moro-García, J.C. Mayo, R.M. Sainz, R. Alonso-Arias, Influence of inflammation in the process of t lymphocyte differentiation: proliferative, metabolic, and oxidative changes, Front. Immunol. 339 (9 March) (2018), https://doi.org/10.3389/fimmu.2018.00339, 1PMID: 29545794; PMCID: PMC5839096.
[167] J. Vitte, A.B. Diallo, A. Boumaza, A. Lopez, M. Michel, J. Allardet-Servent, S. Mezouar, Y. Sereme, J.M. Busnel, T. Miloud, F. Malergue, P.E. Morange, P. Halfon, D. Olive, M. Leone, J.L. Mege, A granulocytic signature identifies COVID-19 and its severity, J. Infect. Dis. 222 (12 November) (2020) 1985–1996, https://doi.org/10.1093/infdis/jiaa591, 13PMID: 32941618; PMCID: PMC7543529.
[168] R.L. Chua, S. Lukassen, S. Trump, B.P. Hennig, D. Wendisch, F. Pott, O. Debnath, L. Thürmann, F. Kurth, M.T. Völker, J. Kazmierski, B. Timmermann, S. Twardziok, S. Schneider, F. Machleidt, H. Müller-Redetzky, M. Maier, A. Krannich, S. Schmidt, F. Balzer, J. Liebig, J. Loske, N. Suttorp, J. Eils, N. Ishaque, U.G. Liebert, C. von Kalle, A. Hocke, M. Witzenrath, C. Goffinet, C. Drosten, S. Laudi, I. Lehmann, C. Conrad, L.E. Sander, R. Eils, COVID-19 severity correlates with airway epithelium-immune cell interactions identified by single-cell analysis, Nat. Biotechnol. 38 (8 August) (2020) 970–979, https://doi.org/10.1038/s41587-020-0602-4. Epub 2020 Jun 26. PMID: 32591762.
[169] V. Bordoni, A. Sacchi, E. Cimini, S. Notari, G. Grassi, E. Tartaglia, R. Casetti, M. L. Giancola, N. Bevilacqua, M. Maeurer, A. Zumla, F. Locatelli, F. De Benedetti, F. Palmieri, L. Marchioni, M.R. Capobianchi, G. D'Offizi, N. Petrosillo, A. Antinori, E. Nicastri, G. Ippolito, C. Agrati, An inflammatory profile correlates with decreased frequency of cytotoxic cells in coronavirus disease 2019, Clin. Infect. Dis. 71 (16 November) (2020) 2272–2275, https://doi.org/10.1093/cid/ciaa577, 19PMID: 32407466; PMCID: PMC7239202.
[170] M. Osman, R.M. Faridi, W. Sligl, M.T. Shabani-Rad, P. Dharmani-Khan, A. Parker, A. Kalra, M.B. Tripathi, J. Storek, J.W. Cohen Tervaert, F.M. Khan, Impaired natural killer cell counts and cytolytic activity in patients with severe COVID-19, Blood Adv. 4 (20 October) (2020) 5035–5039, https://doi.org/10.1182/bloodadvances.2020002650, 27PMID: 33075136; PMCID: PMC7594380.
[171] M. Zheng, Y. Gao, G. Wang, G. Song, S. Liu, D. Sun, Y. Xu, Z. Tian, Functional exhaustion of antiviral lymphocytes in COVID-19 patients, Cell. Mol. Immunol. 17 (5 May) (2020) 533–535, https://doi.org/10.1038/s41423-020-0402-2. Epub 2020 Mar 19. PMID: 32203188; PMCID: PMC7091858.

[172] F. Bozzano, C. Dentone, C. Perrone, A. Di Biagio, D. Fenoglio, A. Parodi, M. Mikulska, B. Bruzzone, D.R. Giacobbe, A. Vena, L. Taramasso, L. Nicolini, N. Patroniti, P. Pelosi, A. Gratarola, R. De Palma, G. Filaci, M. Bassetti, De Maria A; GECOVID study group. Extensive activation, tissue trafficking, turnover and functional impairment of NK cells in COVID-19 patients at disease onset associates with subsequent disease severity, PLoS Pathog. 17 (4 April) (2021) e1009448, https://doi.org/10.1371/journal.ppat.1009448, 16PMID: 33861802; PMCID: PMC8081333.

[173] S. Varchetta, D. Mele, B. Oliviero, S. Mantovani, S. Ludovisi, A. Cerino, R. Bruno, A. Castelli, M. Mosconi, M. Vecchia, S. Roda, M. Sachs, C. Klersy, M.U. Mondelli, Unique immunological profile in patients with COVID-19, Cell. Mol. Immunol. 18 (3 March) (2021) 604–612, https://doi.org/10.1038/s41423-020-00557-9. Epub 2020 Oct 15. PMID: 33060840; PMCID: PMC7557230.

[174] C. Yao, S.A. Bora, T. Parimon, T. Zaman, O.A. Friedman, J.A. Palatinus, N. S. Surapaneni, Y.P. Matusov, G.C. Chiang, A.G. Kassar, N. Patel, C.E.R. Green, A. W. Aziz, H. Suri, J. Suda, A.A. Lopez, G.A. Martins, B.R. Stripp, S.A. Gharib, H. S. Goodridge, P. Chen, Cell-type-specific immune dysregulation in severely ill COVID-19 patients, Cell Rep. 34 (13 March) (2021) 108943, https://doi.org/10.1016/j.celrep.2021.108943, 30Erratum for: Cell Rep. 2021 Jan 5;34(1): 108590. PMID: 33789116; PMCID: PMC8009498.

[175] C. Maucourant, I. Filipovic, A. Ponzetta, S. Aleman, M. Cornillet, L. Hertwig, B. Strunz, A. Lentini, B. Reinius, D. Brownlie, A. Cuapio, E.H. Ask, R.M. Hull, A. Haroun-Izquierdo, M. Schaffer, J. Klingström, E. Folkesson, M. Buggert, J. K. Sandberg, L.I. Eriksson, O. Rooyackers, H.G. Ljunggren, K.J. Malmberg, J. Michaëlsson, N. Marquardt, Q. Hammer, K. Strålin, N.K. Björkström, Karolinska COVID-19 Study Group, Natural killer cell immunotypes related to COVID-19 disease severity, Sci. Immunol. 5 (50 August) (2020) eabd6832, https://doi.org/10.1126/sciimmunol.abd6832, 21PMID: 32826343; PMCID: PMC7665314.

[176] S. Lopez-Vergès, J.M. Milush, B.S. Schwartz, M.J. Pando, J. Jarjoura, V.A. York, J. P. Houchins, S. Miller, S.M. Kang, P.J. Norris, D.F. Nixon, L.L. Lanier, Expansion of a unique CD57^{+}NKG2Chi natural killer cell subset during acute human cytomegalovirus infection, Proc. Natl. Acad. Sci. U. S. A. 108 (36 September) (2011) 14725–14732, https://doi.org/10.1073/pnas.1110900108, 6Epub 2011 Aug 8. PMID: 21825173; PMCID: PMC3169160.

[177] S. De Biasi, D. Lo Tartaro, M. Meschiari, L. Gibellini, C. Bellinazzi, R. Borella, L. Fidanza, M. Mattioli, A. Paolini, L. Gozzi, D. Jaacoub, M. Faltoni, S. Volpi, J. Milić, M. Sita, M. Sarti, C. Pucillo, M. Girardis, G. Guaraldi, C. Mussini, A. Cossarizza, Expansion of plasmablasts and loss of memory B cells in peripheral blood from COVID-19 patients with pneumonia, Eur. J. Immunol. 50 (9 September) (2020) 1283–1294, https://doi.org/10.1002/eji.202048838. Epub 2020 Aug 13. PMID: 32910469.

[178] L. Kuri-Cervantes, M.B. Pampena, W. Meng, A.M. Rosenfeld, C.A.G. Ittner, A. R. Weisman, R.S. Agyekum, D. Mathew, A.E. Baxter, L.A. Vella, O. Kuthuru, S. A. Apostolidis, L. Bershaw, J. Dougherty, A.R. Greenplate, A. Pattekar, J. Kim, N. Han, S. Gouma, M.E. Weirick, C.P. Arevalo, M.J. Bolton, E.C. Goodwin, E. M. Anderson, S.E. Hensley, T.K. Jones, N.S. Mangalmurti, E.T. Luning Prak, E. J. Wherry, N.J. Meyer, M.R. Betts, Comprehensive mapping of immune perturbations associated with severe COVID-19, Sci. Immunol. 5 (49 July) (2020) eabd7114, https://doi.org/10.1126/sciimmunol.abd7114, 15PMID: 32669287; PMCID: PMC7402634.

[179] Y. Jouan, A. Guillon, L. Gonzalez, Y. Perez, C. Boisseau, S. Ehrmann, M. Ferreira, T. Daix, R. Jeannet, B. François, P.F. Dequin, M. Si-Tahar, T. Baranek, C. Paget, Phenotypical and functional alteration of unconventional T cells in severe COVID-19 patients, J. Exp. Med. 217 (12 December) (2020) e20200872, https://doi.org/10.1084/jem.20200872, 7PMID: 32886755; PMCID: PMC7472174.

[180] R.A. Grant, L. Morales-Nebreda, N.S. Markov, S. Swaminathan, M. Querrey, E. R. Guzman, D.A. Abbott, H.K. Donnelly, A. Donayre, I.A. Goldberg, Z.M. Klug, N. Borkowski, Z. Lu, H. Kihshen, Y. Politanska, L. Sichizya, M. Kang, A. Shilatifard, C. Qi, J.W. Lomasney, A.C. Argento, J.M. Kruser, E.S. Malsin, C. O. Pickens, S.B. Smith, J.M. Walter, A.E. Pawlowski, D. Schneider, P. Nannapaneni, H. Abdala-Valencia, A. Bharat, C.J. Gottardi, G.R.S. Budinger, A. V. Misharin, B.D. Singer, R.G. Wunderink, NU SCRIPT Study Investigators, Circuits between infected macrophages and T cells in SARS-CoV-2 pneumonia, Nature 590 (7847 Febuary) (2021) 635–641, https://doi.org/10.1038/s41586-020-03148-w. Epub 2021 Jan 11. PMID: 33429418; PMCID: PMC7987233.

[181] Y. Zhao, C. Kilian, J.E. Turner, L. Bosurgi, K. Roedl, P. Bartsch, A.C. Gnirck, F. Cortesi, C. Schultheiß, M. Hellmig, L.U.B. Enk, F. Hausmann, A. Borchers, M. N. Wong, H.J. Paust, F. Siracusa, N. Scheibel, M. Herrmann, E. Rosati, P. Bacher, D. Kylies, D. Jarczak, M. Lütgehetmann, S. Pfefferle, S. Steurer, J.S. Zur-Wiesch, V.G. Puelles, J.P. Sperhake, M.M. Addo, A.W. Lohse, M. Binder, S. Huber, T. B. Huber, S. Kluge, S. Bonn, U. Panzer, N. Gagliani, C.F. Krebs, Clonal expansion and activation of tissue-resident memory-like Th17 cells expressing GM-CSF in the lungs of severe COVID-19 patients, Sci. Immunol. 6 (56 Febuary) (2021) eabf6692, https://doi.org/10.1126/sciimmunol.abf6692, 23PMID: 33622974; PMCID: PMC8128299.

[182] A. Saris, T.D.Y. Reijnders, E.J. Nossent, A.R. Schuurman, J. Verhoeff, S.V. Asten, H. Bontkes, S. Blok, J. Duitman, H.J. Bogaard, L. Heunks, R. Lutter, T. van der Poll, J.J. Garcia Vallejo, ArtDECO consortium and the Amsterdam UMC COVID study group, Distinct cellular immune profiles in the airways and blood of critically ill patients with COVID-19, Thorax (April) (2021) 12, https://doi.org/10.1136/thoraxjnl-2020-216256, thoraxjnl-2020-216256Epub ahead of print. PMID:33846275;PMCID: PMC8050882.

[183] A. Mazzoni, L. Maggi, F. Liotta, L. Cosmi, F. Annunziato, Biological and clinical significance of T helper 17 cell plasticity, Immunology 158 (4 December) (2019) 287–295, https://doi.org/10.1111/imm.13124. Epub 2019 Oct 14. PMID: 31566706; PMCID: PMC6856928.

[184] S. Moir, A. Malaspina, K.M. Ogwaro, E.T. Donoghue, C.W. Hallahan, L.A. Ehler, S. Liu, J. Adelsberger, R. Lapointe, P. Hwu, M. Baseler, J.M. Orenstein, T. W. Chun, J.A. Mican, A.S. Fauci, HIV-1 induces phenotypic and functional perturbations of B cells in chronically infected individuals, Proc. Natl. Acad. Sci. U. S. A. 98 (18 August) (2001) 10362–10367, https://doi.org/10.1073/pnas.181347898, 28Epub 2001 Aug 14. PMID: 11504927; PMCID: PMC56966.

[185] G. Sciaranghella, N. Tong, A.E. Mahan, T.J. Suscovich, G. Alter, Decoupling activation and exhaustion of B cells in spontaneous controllers of HIV infection, AIDS 27 (2 January) (2013) 175–180, https://doi.org/10.1097/QAD.0b013e32835bd1f0, 14PMID: 23135171; PMCID: PMC3729211.

[186] H. Doi, S. Tanoue, D.E. Kaplan, Peripheral CD27-CD21- B-cells represent an exhausted lymphocyte population in hepatitis C cirrhosis, Clin. Immunol. 150 (2 Febuary) (2014) 184–191, https://doi.org/10.1016/j.clim.2013.12.001. Epub 2013 Dec 17. PMID: 24434272; PMCID: PMC4580910.

[187] L. Gibellini, S. De Biasi, A. Paolini, R. Borella, F. Boraldi, M. Mattioli, D. Lo Tartaro, L. Fidanza, A. Caro-Maldonado, M. Meschiari, V. Iadisernia, E. Bacca, G. Riva, L. Cicchetti, D. Quaglino, G. Guaraldi, S. Busani, M. Girardis, C. Mussini, A. Cossarizza, Altered bioenergetics and mitochondrial dysfunction of monocytes in patients with COVID-19 pneumonia, EMBO Mol. Med. 12 (12 December) (2020) e13001, https://doi.org/10.15252/emmm.202013001, 7Epub 2020 Nov 5. PMID: 33078545; PMCID: PMC7645870.

[188] E. Stephenson, G. Reynolds, R.A. Botting, F.J. Calero-Nieto, M.D. Morgan, Z. K. Tuong, K. Bach, W. Sungnak, K.B. Worlock, M. Yoshida, N. Kumasaka, K. Kania, J. Engelbert, B. Olabi, J.S. Spegarova, N.K. Wilson, N. Mende, L. Jardine, L.C.S. Gardner, I. Goh, D. Horsfall, J. McGrath, S. Webb, M.W. Mather, R.G.H. Lindeboom, E. Dann, N. Huang, K. Polanski, E. Prigmore, F. Gothe, J. Scott, R.P. Payne, K.F. Baker, A.T. Hanrath, I.C.D. Schim van der Loeff, A. S. Barr, A. Sanchez-Gonzalez, L. Bergamaschi, F. Mescia, J.L. Barnes, E. Kilich, A. de Wilton, A. Saigal, A. Saleh, S.M. Janes, C.M. Smith, N. Gopee, C. Wilson, P. Coupland, J.M. Coxhead, V.Y. Kiselev, S. van Dongen, J. Bacardit, H.W. King, Cambridge Institute of Therapeutic Immunology and Infectious Disease-National Institute of Health Research (CITIID-NIHR) COVID-19 BioResource Collaboration, A.J. Rostron, A.J. Simpson, S. Hambleton, E. Laurenti, P.A. Lyons, K.B. Meyer, M. Z. Nikolić, C.J.A. Duncan, K.G.C. Smith, S.A. Teichmann, M.R. Clatworthy, J. C. Marioni, B. Göttgens, M. Haniffa, Single-cell multi-omics analysis of the immune response in COVID-19, Nat. Med. 27 (5 May) (2021) 904–916, https://doi.org/10.1038/s41591-021-01329-2. Epub 2021 Apr 20. PMID: 33879890; PMCID: PMC8121667.

[189] B. Peruzzi, S. Bencini, M. Capone, A. Mazzoni, L. Maggi, L. Salvati, A. Vanni, C. Orazzini, C. Nozzoli, A. Morettini, L. Poggesi, F. Pieralli, A. Peris, A. Bartoloni, A.M. Vannucchi, F. Liotta, R. Caporale, L. Cosmi, F. Annunziato, Quantitative and qualitative alterations of circulating myeloid cells and plasmacytoid DC in SARS-CoV-2 infection, Immunology 161 (4 December) (2020) 345–353, https://doi.org/10.1111/imm.13254. Epub 2020 Oct 6. Erratum in: Immunology. 2021 Feb; 162(2):248. PMID: 32870529; PMCID: PMC7692244.

[190] E.R. Mann, M. Menon, S.B. Knight, J.E. Konkel, C. Jagger, T.N. Shaw, S. Krishnan, M. Rattray, A. Ustianowski, N.D. Bakerly, P. Dark, G. Lord, A. Simpson, T. Felton, L.P. Ho, NIHR Respiratory TRC, M. Feldmann, CIRCO, J.R. Grainger, T. Hussell, Longitudinal immune profiling reveals key myeloid signatures associated with COVID-19, Sci. Immunol. 5 (51 September) (2020) eabd6197, https://doi.org/10.1126/sciimmunol.abd6197, 17PMID: 32943497; PMCID: PMC7857390.

[191] I. Sánchez-Cerrillo, P. Landete, B. Aldave, S. Sánchez-Alonso, A. Sánchez-Azofra, A. Marcos-Jiménez, E. Ávalos, A. Alcaraz-Serna, I. de Los Santos, T. Mateu-Albero, L. Esparcia, C. López-Sanz, P. Martínez-Fleta, L. Gabrie, L. Del Campo Guerola, H. de la Fuente, M.J. Calzada, I. González-Álvaro, A. Alfranca, F. Sánchez-Madrid, C. Muñoz-Calleja, J.B. Soriano, J. Ancochea, E. Martín-Gayo, REINMUN-COVID and EDEPIMIC groups, COVID-19 severity associates with pulmonary redistribution of CD1c+ DCs and inflammatory transitional and nonclassical monocytes, J. Clin. Invest. 130 (12 December) (2020) 6290–6300, https://doi.org/10.1172/JCI140335, 1PMID: 32784290; PMCID: PMC7685723.

[192] M. Saichi, M.Z. Ladjemi, S. Korniotis, C. Rousseau, Z. Ait Hamou, L. Massenet-Regad, E. Amblard, F. Noel, Y. Marie, D. Bouteiller, J. Medvedovic, F. Pène, V. Soumelis, Single-cell RNA sequencing of blood antigen-presenting cells in severe COVID-19 reveals multi-process defects in antiviral immunity, Nat. Cell Biol. 23 (5 May) (2021) 538–551, https://doi.org/10.1038/s41556-021-00681-2. Epub 2021 May 10. PMID: 33972731.

[193] P.S. Arunachalam, F. Wimmers, C.K.P. Mok, R.A.P.M. Perera, M. Scott, T. Hagan, N. Sigal, Y. Feng, L. Bristow, O. Tak-Yin Tsang, D. Wagh, J. Coller, K.L. Pellegrini, D. Kazmin, G. Alaaeddine, W.S. Leung, J.M.C. Chan, T.S.H. Chik, C.Y.C. Choi, C. Huerta, M. Paine McCullough, H. Lv, E. Anderson, S. Edupuganti, A. A. Upadhyay, S.E. Bosinger, H.T. Maecker, P. Khatri, N. Rouphael, M. Peiris, B. Pulendran, Systems biological assessment of immunity to mild versus severe COVID-19 infection in humans, Science 369 (6508 September) (2020) 1210–1220, https://doi.org/10.1126/science.abc6261, 4Epub 2020 Aug 11. PMID: 32788292; PMCID: PMC7665312.

[194] F. Onodi, L. Bonnet-Madin, L. Meertens, L. Karpf, J. Poirot, S.Y. Zhang, C. Picard, A. Puel, E. Jouanguy, Q. Zhang, J. Le Goff, J.M. Molina, C. Delaugerre, J. L. Casanova, A. Amara, V. Soumelis, SARS-CoV-2 induces human plasmacytoid predendritic cell diversification via UNC93B and IRAK4, J. Exp. Med. 218 (4 April) (2021) e20201387, https://doi.org/10.1084/jem.20201387, 5PMID: 33533916; PMCID: PMC7849819.

[195] K.L. Wong, W.H. Yeap, J.J. Tai, S.M. Ong, T.M. Dang, S.C. Wong, The three human monocyte subsets: implications for health and disease, Immunol. Res. 53 (1–3 September) (2012) 41–57, https://doi.org/10.1007/s12026-012-8297-3. PMID: 22430559.

[196] H. Lund, P. Boysen, C.P. Åkesson, Lewandowska-Sabat 359 AM, A.K. Storset, Transient migration of large numbers of CD14(++) CD16(+) monocytes to the draining lymph node after onset of inflammation, Front. Immunol. 7 (2016) 322, https://doi.org/10.3389/fimmu.2016.00322. Published 2016 Aug 29.

[197] E. Kvedaraite, L. Hertwig, I. Sinha, A. Ponzetta, I. Hed Myrberg, M. Lourda, M. Dzidic, M. Akber, J. Klingström, E. Folkesson, J.R. Muvva, P. Chen, S. Gredmark-Russ, S. Brighenti, A. Norrby-Teglund, L.I. Eriksson, O. Rooyackers, S. Aleman, K. Strålin, H.G. Ljunggren, F. Ginhoux, N.K. Björkström, J.I. Henter, M. Svensson, Karolinska KI/K COVID-19 Study Group, Major alterations in the mononuclear phagocyte landscape associated with COVID-19 severity, Proc. Natl. Acad. Sci. U. S. A. 118 (6 Febuary) (2021), https://doi.org/10.1073/pnas.2018587118 e20185871189PMID: 33479167; PMCID: PMC8017719.

[198] P.A. Szabo, P. Dogra, J.I. Gray, S.B. Wells, T.J. Connors, S.P. Weisberg, I. Krupska, R. Matsumoto, M.M.L. Poon, E. Idzikowski, S.E. Morris, C. Pasin, A.J. Yates, A. Ku, M. Chait, J. Davis-Porada, X.V. Guo, J. Zhou, M. Steinle, S. Mackay, A. Saqi, M.R. Baldwin, P.A. Sims, D.L. Farber, Longitudinal profiling of respiratory and systemic immune responses reveals myeloid cell-driven lung inflammation in severe COVID-19, Immunity 54 (4 April) (2021) 797–814, https://doi.org/10.1016/j.immuni.2021.03.005, 13e6Epub 2021 Mar 11. PMID: 33765436; PMCID: PMC7951561.

[199] E.J. Giamarellos-Bourboulis, M.G. Netea, N. Rovina, K. Akinosoglou, A. Antoniadou, N. Antonakos, G. Damoraki, T. Gkavogianni, M.E. Adami, P. Katsaounou, M. Ntaganou, M. Kyriakopoulou, G. Dimopoulos, I. Koutsodimitropoulos, D. Velissaris, P. Koufargyris, A. Karageorgos, K. Katrini, V. Lekakis, M. Lupse, A. Kotsaki, G. Renieris, D. Theodoulou, V. Panou, E. Koukaki, N. Koulouris, C. Gogos, A. Koutsoukou, Complex immune dysregulation in COVID-19 patients with severe respiratory failure, Cell Host Microbe 27 (6 June) (2020) 992–1000, https://doi.org/10.1016/j.chom.2020.04.009, e310Epub 2020 Apr 21. PMID: 32320677; PMCID: PMC7172841.

[200] J. Schulte-Schrepping, N. Reusch, D. Paclik, K. Baßler, S. Schlickeiser, B. Zhang, B. Krämer, T. Krammer, S. Brumhard, L. Bonaguro, E. De Domenico, D. Wendisch, M. Grasshoff, T.S. Kapellos, M. Beckstette, T. Pecht, A. Saglam, O. Dietrich, H. E. Mei, A.R. Schulz, C. Conrad, D. Kunkel, E. Vafadarnejad, C.J. Xu, A. Horne, M. Herbert, A. Drews, C. Thibeault, M. Pfeiffer, S. Hippenstiel, A. Hocke, H. Müller-Redetzky, K.M. Heim, F. Machleidt, A. Uhrig, L. Bosquillon de Jarcy, L. Jürgens, M. Stegemann, C.R. Glösenkamp, H.D. Volk, C. Goffinet, M. Landthaler, E. Wyler, P. Georg, M. Schneider, C. Dang-Heine, N. Neuwinger, K. Kappert, R. Tauber, V. Corman, J. Raabe, K.M. Kaiser, M.T. Vinh, G. Rieke, C. Meisel, T. Ulas, M. Becker, R. Geffers, M. Witzenrath, C. Drosten, N. Suttorp, C. von Kalle, F. Kurth, K. Händler, J.L. Schultze, A.C. Aschenbrenner, Y. Li, J. Nattermann, B. Sawitzki, A.E. Saliba, L.E. Sander, Deutsche COVID-19 OMICS Initiative (DeCOI), Severe COVID-19 is marked by a dysregulated myeloid cell compartment, Cell 182 (6 September) (2020) 1419–1440, https://doi.org/10.1016/j.cell.2020.08.001, 17e23Epub 2020 Aug 5. PMID: 32810438; PMCID: PMC7405822.

[201] J.L. Schultze, E. Mass, A. Schlitzer, Emerging principles in Myelopoiesis at homeostasis and during infection and inflammation, Immunity 50 (2 Febuary) (2019) 288–301, https://doi.org/10.1016/j.immuni.2019.01.019, 19PMID: 30784577.

[202] A.K. McElroy, R.S. Akondy, D.R. Mcllwain, H. Chen, Z. Bjornson-Hooper, N. Mukherjee, A.K. Mehta, G. Nolan, S.T. Nichol, C.F. Spiropoulou, Immunologic timeline of Ebola virus disease and recovery in humans, JCI Insight 5 (10 May) (2020) e137260, https://doi.org/10.1172/jci.insight.137260, 21PMID: 32434986; PMCID: PMC7259516.

[203] M.L. Meizlish, A.B. Pine, J.D. Bishai, G. Goshua, E.R. Nadelmann, M. Simonov, C. H. Chang, H. Zhang, M. Shallow, P. Bahel, K. Owusu, Y. Yamamoto, T. Arora, D. S. Atri, A. Patel, R. Gbyli, J. Kwan, C.H. Won, C. Dela Cruz, C. Price, J. Koff, B. A. King, H.M. Rinder, F.P. Wilson, J. Hwa, S. Halene, W. Damsky, D. van Dijk, A. I. Lee, H.J. Chun, A neutrophil activation signature predicts critical illness and mortality in COVID-19, Blood Adv. 5 (5 March) (2021) 1164–1177, https://doi.org/10.1182/bloodadvances.2020003568, 9PMID: 33635335; PMCID: PMC7908851.

[204] A.C. Aschenbrenner, M. Mouktaroudi, B. Krämer, M. Oestreich, N. Antonakos, M. Nuesch-Germano, K. Gkizeli, L. Bonaguro, N. Reusch, K. Baßler, M. Saridaki, R. Knoll, T. Pecht, T.S. Kapellos, S. Doulou, C. Kröger, M. Herbert, L. Holsten, A. Horne, I.D. Gemünd, N. Rovina, S. Agrawal, K. Dahm, M. van Uelft, A. Drews, L. Lenkeit, N. Bruse, J. Gerretsen, J. Gierlich, M. Becker, K. Händler, M. Kraut, H. Theis, S. Mengiste, E. De Domenico, J. Schulte-Schrepping, L. Seep, J. Raabe, C. Hoffmeister, M. ToVinh, V. Keitel, G. Rieke, V. Talevi, D. Skowasch, N.A. Aziz, P. Pickkers, F.L. van de Veerdonk, M.G. Netea, J.L. Schultze, M. Kox, M.M. B. Breteler, J. Nattermann, A. Koutsoukou, E.J. Giamarellos-Bourboulis, T. Ulas, German COVID-19 Omics Initiative (DeCOI). Disease severity-specific neutrophil signatures in blood transcriptomes stratify COVID-19 patients, Genome Med. 13 (1 January) (2021) 7, https://doi.org/10.1186/s13073-020-00823-5, 13PMID: 33441124; PMCID: PMC7805430.

[205] E.A. Middleton, X.Y. He, F. Denorme, R.A. Campbell, D. Ng, S.P. Salvatore, M. Mostyka, A. Baxter-Stoltzfus, A.C. Borczuk, M. Loda, M.J. Cody, B.K. Manne, I. Portier, E.S. Harris, A.C. Petrey, E.J. Beswick, A.F. Caulin, A. Iovino, L. M. Abegglen, A.S. Weyrich, M.T. Rondina, M. Egeblad, J.D. Schiffman, C.C. Yost, Neutrophil extracellular traps contribute to immunothrombosis in COVID-19 acute respiratory distress syndrome, Blood 136 (10 September) (2020) 1169–1179, https://doi.org/10.1182/blood.2020007008, 3PMID: 32597954; PMCID: PMC7472714.

[206] F.P. Veras, M.C. Pontelli, C.M. Silva, J.E. Toller-Kawahisa, M. de Lima, D. C. Nascimento, A.H. Schneider, D. Caetité, L.A. Tavares, I.M. Paiva, R. Rosales, D. Colón, R. Martins, I.A. Castro, G.M. Almeida, M.I.F. Lopes, M.N. Benatti, L. P. Bonjorno, M.C. Giannini, R. Luppino-Assad, S.L. Almeida, F. Vilar, R. Santana, V.R. Bollela, M. Auxiliadora-Martins, M. Borges, C.H. Miranda, A. Pazin-Filho, L. L.P. da Silva, L.D. Cunha, D.S. Zamboni, F. Dal-Pizzol, L.O. Leiria, L. Siyuan, S. Batah, A. Fabro, T. Mauad, M. Dolhnikoff, A. Duarte-Neto, P. Saldiva, T. M. Cunha, J.C. Alves-Filho, E. Arruda, P. Louzada-Junior, R.D. Oliveira, F. Q. Cunha, SARS-CoV-2-triggered neutrophil extracellular traps mediate COVID-19 pathology, J. Exp. Med. 217 (12 December) (2020) e20201129, https://doi.org/10.1084/jem.20201129, 7PMID: 32926098; PMCID: PMC7488868.

[207] D.I. Gabrilovich, S. Nagaraj, Myeloid-derived suppressor cells as regulators of the immune system, Nat. Rev. Immunol. 9 (3 March) (2009) 162–174, https://doi.org/10.1038/nri2506. PMID: 19197294; PMCID: PMC2828349.

[208] M. Rowlands, F. Segal, D. Hartl, Myeloid-derived suppressor cells as a potential biomarker and therapeutic target in COVID-19, Front. Immunol. 18 (12 June) (2021) 697405, https://doi.org/10.3389/fimmu.2021.697405. PMID: 34220859; PMCID: PMC8250151.

[209] A. Sacchi, G. Grassi, V. Bordoni, P. Lorenzini, E. Cimini, R. Casetti, E. Tartaglia, L. Marchioni, N. Petrosillo, F. Palmieri, G. D'Offizi, S. Notari, M. Tempestilli, M. R. Capobianchi, E. Nicastri, M. Maeurer, A. Zumla, F. Locatelli, A. Antinori, G. Ippolito, C. Agrati, Early expansion of myeloid-derived suppressor cells inhibits SARS-CoV-2 specific T-cell response and may predict fatal COVID-19 outcome, Cell Death Dis. 11 (10 October) (2020) 921, https://doi.org/10.1038/s41419-020-03125-1, 27PMID: 33110074; PMCID: PMC7590570.

[210] P. Bost, F. De Sanctis, S. Canè, S. Ugel, K. Donadello, M. Castellucci, D. Eyal, A. Fiore, C. Anselmi, R.M. Barouni, R. Trovato, S. Caligola, A. Lamolinara, M. Iezzi, F. Facciotti, A. Mazzariol, D. Gibellini, P. De Nardo, E. Tacconelli, L. Gottin, E. Polati, B. Schwikowski, I. Amit, V. Bronte, Deciphering the state of immune silence in fatal COVID-19 patients, Nat. Commun. 12 (1 March) (2021) 1428, https://doi.org/10.1038/s41467-021-21702-6, 5PMID: 33674591; PMCID: PMC7935849.

[211] S. Falck-Jones, S. Vangeti, M. Yu, R. Falck-Jones, A. Cagigi, I. Badolati, B. Österberg, M.J. Lautenbach, E. Åhlberg, A. Lin, R. Lepzien, I. Szurgot, K. Lenart, F. Hellgren, H. Maecker, J. Sälde, J. Albert, N. Johansson, M. Bell, K. Loré, A. Färnert, A. Smed-Sörensen, Functional monocytic myeloid-derived suppressor cells increase in blood but not airways and predict COVID-19 severity, J. Clin. Invest. 131 (6 March) (2021) e144734, https://doi.org/10.1172/JCI144734, 15PMID: 33492309; PMCID: PMC7954608.

[212] S.M. Morrissey, A.E. Geller, X. Hu, D. Tieri, C. Ding, C.K. Klaes, E.A. Cooke, M. R. Woeste, Z.C. Martin, O. Chen, S.E. Bush, H.G. Zhang, R. Cavallazzi, S. P. Clifford, J. Chen, S. Ghare, S.S. Barve, L. Cai, M. Kong, E.C. Rouchka, K. R. McLeish, S.M. Uriarte, C.T. Watson, J. Huang, J. Yan, A specific low-density neutrophil population correlates with hypercoagulation and disease severity in hospitalized COVID-19 patients, JCI Insight 6 (9 May) (2021) 148435, https://doi.org/10.1172/jci.insight.148435, 10PMID: 33986193.

[213] P. Bacher, E. Rosati, D. Esser, G.R. Martini, C. Saggau, E. Schiminsky, J. Dargvainiene, I. Schröder, I. Wieters, Y. Khodamoradi, F. Eberhardt, M.J.G. T. Vehreschild, H. Neb, M. Sonntagbauer, C. Conrad, F. Tran, P. Rosenstiel, R. Markewitz, K.P. Wandinger, M. Augustin, J. Rybniker, M. Kochanek, F. Leypoldt, O.A. Cornely, P. Koehler, A. Franke, A. Scheffold, Low-avidity CD4+ t cell responses to SARS-CoV-2 in unexposed individuals and humans with severe COVID-19, Immunity 53 (6 December) (2020) 1258–1271, https://doi.org/10.1016/j.immuni.2020.11.016, e515Epub 2020 Nov 26. PMID: 33296686; PMCID: PMC7689350.

[214] J. Braun, L. Loyal, M. Frentsch, D. Wendisch, P. Georg, F. Kurth, S. Hippenstiel, M. Dingeldey, B. Kruse, F. Fauchere, E. Baysal, M. Mangold, L. Henze, R. Lauster, M.A. Mall, K. Beyer, J. Röhmel, S. Voigt, J. Schmitz, S. Miltenyi, I. Demuth, M. A. Müller, A. Hocke, M. Witzenrath, N. Suttorp, F. Kern, U. Reimer, H. Wenschuh, C. Drosten, V.M. Corman, C. Giesecke-Thiel, L.E. Sander, A. Thiel, SARS-CoV-2-reactive T cells in healthy donors and patients with COVID-19, Nature 587 (7833 November) (2020) 270–274, https://doi.org/10.1038/s41586-020-2598-9. Epub 2020 Jul 29. PMID: 32726801.

[215] N. Le Bert, A.T. Tan, K. Kunasegaran, C.Y.L. Tham, M. Hafezi, A. Chia, M.H. Y. Chng, M. Lin, N. Tan, M. Linster, W.N. Chia, M.I. Chen, L.F. Wang, E.E. Ooi, S. Kalimuddin, P.A. Tambyah, J.G. Low, Y.J. Tan, A. Bertoletti, SARS-CoV-2-specific T cell immunity in cases of COVID-19 and SARS, and uninfected controls, Nature 584 (7821 August) (2020) 457–462, https://doi.org/10.1038/s41586-020-2550-z. Epub 2020 Jul 15. PMID: 32668444.

[216] A. Grifoni, D. Weiskopf, S.I. Ramirez, J. Mateus, J.M. Dan, C.R. Moderbacher, S. A. Rawlings, A. Sutherland, L. Premkumar, R.S. Jadi, D. Marrama, A.M. de Silva, A. Frazier, A.F. Carlin, J.A. Greenbaum, B. Peters, F. Krammer, D.M. Smith, S. Crotty, A. Sette, Targets of t cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals, Cell 181 (7 June) (2020) 1489–1501, https://doi.org/10.1016/j.cell.2020.05.015, e1525Epub 2020 May 20. PMID: 32473127; PMCID: PMC7237901.

[217] S. Weingarten-Gabbay, S. Klaeger, S. Sarkizova, L.R. Pearlman, D.Y. Chen, K.M. E. Gallagher, M.R. Bauer, H.B. Taylor, W.A. Dunn, C. Tarr, J. Sidney, S. Rachimi, H.L. Conway, K. Katsis, Y. Wang, D. Leistritz-Edwards, M.R. Durkin, C. H. Tomkins-Tinch, Y. Finkel, A. Nachshon, M. Gentili, K.D. Rivera, I.P. Carulli, V. A. Chea, A. Chandrashekar, C.C. Bozkus, M. Carrington, MGH COVID-19 Collection & Processing Team, N. Bhardwaj, D.H. Barouch, A. Sette, M.V. Maus, C.M. Rice, K.R. Clauser, D.B. Keskin, D.C. Pregibon, N. Hacohen, S.A. Carr, J. G. Abelin, M. Saeed, P.C. Sabeti, Profiling SARS-CoV-2 HLA-I peptidome reveals T cell epitopes from out-of-frame ORFs, Cell S0092-8674 (21 June) (2021) 00701–00707, https://doi.org/10.1016/j.cell.2021.05.046, 3Epub ahead of print. PMID: 34171305; PMCID: PMC8173604.

[218] N. Le Bert, H.E. Clapham, A.T. Tan, W.N. Chia, C.Y.L. Tham, J.M. Lim, K. Kunasegaran, L.W.L. Tan, C.A. Dutertre, N. Shankar, J.M.E. Lim, L.J. Sun, M. Zahari, Z.M. Tun, V. Kumar, B.L. Lim, S.H. Lim, A. Chia, Y.J. Tan, P. A. Tambyah, S. Kalimuddin, D. Lye, J.G.H. Low, L.F. Wang, W.Y. Wan, L.Y. Hsu, A. Bertoletti, C.C. Tam, Highly functional virus-specific cellular immune response in asymptomatic SARS-CoV-2 infection, J. Exp. Med. 218 (5 May) (2021) e20202617, https://doi.org/10.1084/jem.20202617, 3PMID: 33646265; PMCID: PMC7927662.

[219] A.T. Tan, M. Linster, C.W. Tan, N. Le Bert, W.N. Chia, K. Kunasegaran, Y. Zhuang, C.Y.L. Tham, A. Chia, G.J.D. Smith, B. Young, S. Kalimuddin, J.G.H. Low, D. Lye, L.F. Wang, A. Bertoletti, Early induction of functional SARS-CoV-2-specific T cells associates with rapid viral clearance and mild disease in COVID-19 patients, Cell Rep. 34 (6 Febuary) (2021) 108728, https://doi.org/10.1016/j.celrep.2021.108728, 9Epub 2021 Jan 21. PMID: 33516277; PMCID: PMC7826084.

[220] K.W. Cohen, S.L. Linderman, Z. Moodie, J. Czartoski, L. Lai, G. Mantus, C. Norwood, L.E. Nyhoff, V.V. Edara, K. Floyd, S.C. De Rosa, H. Ahmed, R. Whaley, S.N. Patel, B. Prigmore, M.P. Lemos, C.W. Davis, S. Furth, J. O'Keefe, M.P. Gharpure, S. Gunisetty, K.A. Stephens, R. Antia, V.I. Zarnitsyna, D. S. Stephens, S. Edupuganti, N. Rouphael, E.J. Anderson, A.K. Mehta, J. Wrammert, M.S. Suthar, R. Ahmed, M.J. McElrath, Longitudinal analysis shows durable and broad immune memory after SARS-CoV-2 infection with persisting antibody responses and memory B and T cells, Cell Rep Med. 3 (July) (2021) 100354, https://doi.org/10.1016/j.xcrm.2021.100354. Epub ahead of print. PMID: 34250512; PMCID: PMC8253687.

[221] C.A. Cohen, A.P.Y. Li, A. Hachim, D.S.C. Hui, M.Y.W. Kwan, O.T.Y. Tsang, S. S. Chiu, W.H. Chan, Y.S. Yau, N. Kavian, F.N.L. Ma, E.H.Y. Lau, S.M.S. Cheng, L.L. M. Poon, M. Peiris, S.A. Valkenburg, SARS-CoV-2 specific T cell responses are lower in children and increase with age and time after infection, Nat. Commun. 12 (1 July) (2021) 4678, https://doi.org/10.1038/s41467-021-24938-4, 29PMID: 34326343.

[222] E.M. Anderson, E.C. Goodwin, A. Verma, C.P. Arevalo, M.J. Bolton, M.E. Weirick, S. Gouma, C.M. McAllister, S.R. Christensen, J. Weaver, P. Hicks, T.B. Manzoni, O. Oniyide, H. Ramage, D. Mathew, A.E. Baxter, D.A. Oldridge, A.R. Greenplate, J.E. Wu, C. Alanio, K. D'Andrea, O. Kuthuru, J. Dougherty, A. Pattekar, J. Kim, N. Han, S.A. Apostolidis, A.C. Huang, L.A. Vella, L. Kuri-Cervantes, M. B. Pampena, UPenn COVID Processing Unit, M.R. Betts, E.J. Wherry, N.J. Meyer, S. Cherry, P. Bates, D.J. Rader, S.E. Hensley, Seasonal human coronavirus antibodies are boosted upon SARS-CoV-2 infection but not associated with protection, Cell 184 (7 April) (2021) 1858–1864, https://doi.org/10.1016/j.cell.2021.02.010, e101Epub 2021 Feb 9. PMID: 33631096; PMCID: PMC7871851.

[223] B. Diao, C. Wang, Y. Tan, X. Chen, Y. Liu, L. Ning, et al., Reduction and functional exhaustion of t cells in patients with coronavirus disease 2019 (Covid-19), Front. Immunol. 11 (2020) 827, https://doi.org/10.3389/fimmu.2020.00827.

[224] M. Shahbazi, Z. Moulana, M. Sepidarkish, M. Bagherzadeh, M. Rezanejad, M. Mirzakhani, M. Jafari, M. Mohammadnia-Afrouzi, Pronounce expression of Tim-3 and CD39 but not PD1 defines CD8 T cells in critical Covid-19 patients, Microb. Pathog. 153 (April) (2021) 104779, https://doi.org/10.1016/j.micpath.2021.104779. Epub 2021 Feb 4. PMID: 33548481; PMCID: PMC7857983.

[225] J.M. Dan, J. Mateus, Y. Kato, K.M. Hastie, Faliti C.E. Yu ED, A. Grifoni, S. I. Ramirez, S. Haupt, A. Frazier, C. Nakao, V. Rayaprolu, S.A. Rawlings, B. Peters, F. Krammer, V. Simon, E.O. Saphire, D.M. Smith, D. Weiskopf, A. Sette, S. Crotty, Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection, Science 371 (6529 Febuary) (2021), https://doi.org/10.1126/science.abf4063 eabf40635Epub 2021 Jan 6. PMID: 33408181; PMCID: PMC7919858.

[226] A. Ansari, R. Arya, S. Sachan, S.N. Jha, A. Kalia, A. Lall, A. Sette, A. Grifoni, D. Weiskopf, P. Coshic, A. Sharma, N. Gupta, Immune memory in mild COVID-19 patients and unexposed donors reveals persistent t cell responses after SARS-CoV-2 infection, Front. Immunol. 11 (12 March) (2021) 636768, https://doi.org/10.3389/fimmu.2021.636768. PMID: 33777028; PMCID: PMC7991090.

[227] P.G. Choe, K.H. Kim, C.K. Kang, H.J. Suh, E. Kang, S.Y. Lee, N.J. Kim, J. Yi, W. B. Park, M.D. Oh, Antibody responses one year after mild SARS-CoV-2 infection, J. Korean Med. Sci. 36 (21 May) (2021) e157, https://doi.org/10.3346/jkms.2021.36.e157, 31PMID: 34060263; PMCID: PMC8167408.

[228] J. Zuo, A.C. Dowell, H. Pearce, K. Verma, H.M. Long, J. Begum, F. Aiano, Z. Amin-Chowdhury, K. Hoschler, T. Brooks, S. Taylor, J. Hewson, B. Hallis, L. Stapley, R. Borrow, E. Linley, S. Ahmad, B. Parker, A. Horsley, G. Amirthalingam, K. Brown, M.E. Ramsay, S. Ladhani, P. Moss, Robust SARS-CoV-2-specific T cell immunity is maintained at 6 months following primary infection, Nat. Immunol. 22 (5 May) (2021) 620–626, https://doi.org/10.1038/s41590-021-00902-8. Epub 2021 Mar 5. Erratum in: Nat Immunol. 2021 Jul;22(7):928. PMID: 33674800; PMCID: PMC7610739.

[229] J.H. Jung, M.S. Rha, M. Sa, H.K. Choi, J.H. Jeon, H. Seok, D.W. Park, S.H. Park, H. W. Jeong, W.S. Choi, E.C. Shin, SARS-CoV-2-specific T cell memory is sustained in COVID-19 convalescent patients for 10 months with successful development of stem cell-like memory T cells, Nat. Commun. 12 (1 June) (2021) 4043, https://doi.org/10.1038/s41467-021-24377-1, 30PMID: 34193870.

[230] Y. Li, Z. Xu, Q. Lei, D.Y. Lai, H. Hou, H.W. Jiang, Y.X. Zheng, X.N. Wang, J. Wu, M.L. Ma, B. Zhang, H. Chen, C. Yu, J.B. Xue, H.N. Zhang, H. Qi, S.J. Guo, Y. Zhang, X. Lin, Z. Yao, H. Sheng, Z. Sun, F. Wang, X. Fan, S.C. Tao, Antibody landscape against SARS-CoV-2 reveals significant differences between non-structural/accessory and structural proteins, Cell Rep. 26 (June) (2021) 109391, https://doi.org/10.1016/j.celrep.2021.109391. Epub ahead of print. PMID: 34242574; PMCID: PMC8233850.

[231] L. Dai, G.F. Gao, Viral targets for vaccines against COVID-19, Nat. Rev. Immunol. 21 (2 Febuary) (2021) 73–82, https://doi.org/10.1038/s41577-020-00480-0. Epub 2020 Dec 18. PMID: 33340022; PMCID: PMC7747004.

[232] G. Forni, A. Mantovani, COVID-19 Commission of Accademia Nazionale dei Lincei, Rome. COVID-19 vaccines: where we stand and challenges ahead, Cell Death Differ. 28 (2 Febuary) (2021) 626–639, https://doi.org/10.1038/s41418-020-00720-9. Epub 2021 Jan 21. PMID: 33479399; PMCID: PMC7818063.

[233] A. Mazzoni, N. Di Lauria, L. Maggi, L. Salvati, A. Vanni, M. Capone, G. Lamacchia, E. Mantengoli, M. Spinicci, L. Zammarchi, S.T. Kiros, A. Rocca, F. Lagi, M. G. Colao, P. Parronchi, C. Scaletti, L. Turco, F. Liotta, G.M. Rossolini, L. Cosmi, A. Bartoloni, F. Annunziato, COVID-19 Research Group, First-dose mRNA vaccination is sufficient to reactivate immunological memory to SARS-CoV-2 in subjects who have recovered from COVID-19, J. Clin. Invest. 131 (12 June) (2021) e149150, https://doi.org/10.1172/JCI149150, 15PMID: 33939647; PMCID: PMC8203460.

[234] A. Mazzoni, L. Maggi, M. Capone, A. Vanni, M. Spinicci, L. Salvati, S. Tekle Kiros, R. Semeraro, L. Pengue, M.G. Colao, A. Magi, G.M. Rossolini, F. Liotta, L. Cosmi, A. Bartoloni, F. Annunziato, Heterogeneous magnitude of immunological memory to SARS-CoV-2 in recovered individuals, Clin. Transl. Immunol. 10 (5 May) (2021) e1281, https://doi.org/10.1002/cti2.1281, 6PMID: 33976879; PMCID: PMC8101693.

[235] A. Tarke, J. Sidney, N. Methot, E.D. Yu, Y. Zhang, J.M. Dan, B. Goodwin, P. Rubiro, A. Sutherland, E. Wang, A. Frazier, S.I. Ramirez, S.A. Rawlings, D. M. Smith, R. da Silva Antunes, B. Peters, R.H. Scheuermann, D. Weiskopf, S. Crotty, A. Grifoni, A. Sette, Impact of SARS-CoV-2 variants on the total CD4+ and CD8+ T cell reactivity in infected or vaccinated individuals, Cell Rep Med. 2 (July) (2021) 100355, https://doi.org/10.1016/j.xcrm.2021.100355. Epub ahead of print. PMID: 34230917; PMCID: PMC8249675.

[236] R. Levi, E. Azzolini, C. Pozzi, L. Ubaldi, M. Lagioia, A. Mantovani, M. Rescigno, One dose of SARS-CoV-2 vaccine exponentially increases antibodies in individuals who have recovered from symptomatic COVID-19, J. Clin. Invest. 131 (12 June) (2021) e149154, https://doi.org/10.1172/JCI149154, 15PMID: 33956667; PMCID: PMC8203458.

[237] G.P. Marc, D. Alvarez-Paggi, F.P. Polack, Mounting evidence for immunizing previously infected subjects with a single dose of SARS-CoV-2 vaccine, J. Clin. Invest. 131 (12 June) (2021) e150135, https://doi.org/10.1172/JCI150135, 15PMID: 34018969; PMCID: PMC8203470.

[238] M.M. Painter, D. Mathew, R.R. Goel, S.A. Apostolidis, A. Pattekar, O. Kuthuru, A. E. Baxter, R.S. Herati, D.A. Oldridge, S. Gouma, P. Hicks, S. Dysinger, K. A. Lundgreen, L. Kuri-Cervantes, S. Adamski, A. Hicks, S. Korte, J.R. Giles, M. E. Weirick, C.M. McAllister, J. Dougherty, S. Long, K. D'Andrea, J.T. Hamilton, M. R. Betts, P. Bates, S.E. Hensley, A. Grifoni, D. Weiskopf, A. Sette, A.R. Greenplate, E.J. Wherry, Rapid induction of antigen-specific CD4+ T cells is associated with coordinated humoral and cellular immunity to SARS-CoV-2 mRNA vaccination, Immunity 54 (9 September) (2021) 2133–2142, https://doi.org/10.1016/j.immuni.2021.08.001, e314Epub 2021 Aug 13. PMID: 34453880; PMCID: PMC8361141.

[239] R.R. Goel, S.A. Apostolidis, M.M. Painter, D. Mathew, A. Pattekar, O. Kuthuru, S. Gouma, P. Hicks, W. Meng, A.M. Rosenfeld, S. Dysinger, K.A. Lundgreen, L. Kuri-Cervantes, S. Adamski, A. Hicks, S. Korte, D.A. Oldridge, A.E. Baxter, J. R. Giles, M.E. Weirick, C.M. McAllister, J. Dougherty, S. Long, K. D'Andrea, J. T. Hamilton, M.R. Betts, E.T. Luning Prak, P. Bates, S.E. Hensley, A.R. Greenplate, E.J. Wherry, Distinct antibody and memory B cell responses in SARS-CoV-2 naïve and recovered individuals following mRNA vaccination, Sci. Immunol. 6 (58 April) (2021) eabi6950, https://doi.org/10.1126/sciimmunol.abi6950, 15PMID: 33858945; PMCID: PMC8158969.

[240] L. Calzetta, M. Aiello, A. Frizzelli, P. Rogliani, A. Chetta, Dexamethasone in patients hospitalized with COVID-19: whether, when and to whom, J. Clin. Med. 10 (8 April) (2021) 1607, https://doi.org/10.3390/jcm10081607, 10PMID: 33920093; PMCID: PMC8069656.

[241] J. Chen, L. Vitetta, Increased PD-L1 expression may Be associated with the cytokine storm and CD8+ T-Cell exhaustion in severe COVID-19, J. Infect. Dis. 223 (9 May) (2021) 1659–1660, https://doi.org/10.1093/infdis/jiab061, 20PMID: 33524110; PMCID: PMC7928766.

[242] Z. Chen, E. John Wherry, T cell responses in patients with COVID-19, Nat. Rev. Immunol. 20 (9) (2020) 529–536, https://doi.org/10.1038/s41577-020-0402-6.

[243] ClinicalTrials.gov. Phase 3 Randomized, Double-blind, Placebo-controlled Multicenter Study to Assess the Efficacy and Safety of Ruxolitinib in Patients With COVID-19 Associated Cytokine Storm (RUXCOVID). NCT04362137. Available from: https://clinicaltrials.gov/ct2/show/NCT04362137.

[245] S. Gupta, W. Wang, S.S. Hayek, L. Chan, K.S. Mathews, M.L. Melamed, S. K. Brenner, A. Leonberg-Yoo, E.J. Schenck, J. Radbel, J. Reiser, A. Bansal, A. Srivastava, Y. Zhou, D. Finkel, A. Green, M. Mallappallil, A.J. Faugno, J. Zhang, J.C.Q. Velez, S. Shaefi, C.R. Parikh, D.M. Charytan, A.M. Athavale, A. N. Friedman, R.E. Redfern, S.A.P. Short, S. Correa, K.K. Pokharel, A.J. Admon, J. P. Donnelly, H.B. Gershengorn, D.J. Douin, M.W. Semler, M.A. Hernán, D.E. Leaf, STOP-COVID Investigators, Association between early treatment with tocilizumab and mortality among critically ill patients with COVID-19, JAMA Intern. Med. 181 (1) (2021) 41–51, https://doi.org/10.1001/jamainternmed.2020.6252.

[246] J.D. Haslbauer, M.S. Matter, A.K. Stalder, A. Tzankov, Histomorphological patterns of regional lymph nodes in COVID-19 lungs, Pathologe 5 (May) (2021) 1–9, https://doi.org/10.1007/s00292-021-00945-6. Epub ahead of print. PMID: 33950285; PMCID: PMC8098637.

[247] I. Huang, R. Pranata, Lymphopenia in severe coronavirus disease-2019 (COVID-19): systematic review and meta-analysis, J. Intensive Care 24 (8 May) (2020) 36, https://doi.org/10.1186/s40560-020-00453-4.

[249] H. Zhang, T. Wu, CD4+T, CD8+T counts and severe COVID-19: A meta-analysis, J. Infect. 81 (3) (2020) e82–e84, https://doi.org/10.1016/j.jinf.2020.06.036.
[250] F. Sabbatino, V. Conti, G. Franci, C. Sellitto, V. Manzo, P. Pagliano, E. De Bellis, A. Masullo, F.A. Salzano, A. Caputo, I. Peluso, P. Zeppa, G. Scognamiglio, G. Greco, C. Zannella, M. Ciccarelli, C. Cicala, C. Vecchione, A. Filippelli, S. Pepe, PD-L1 dysregulation in COVID-19 patients, Front. Immunol. 12 (2021) 695242, https://doi.org/10.3389/fimmu.2021.695242. PMID: 34163490; PMCID: PMC8215357.
[251] E. Kyriazopoulou, T. Huet, G. Cavalli, et al., Effect of anakinra on mortality in patients with COVID-19: a systematic review and patient-level meta-analysis, Lancet Rheumatol 3 (10) (2021) e690–e697, https://doi.org/10.1016/S2665-9913(21)00216-2.
[252] C. Rydyznski Moderbacher, S.I. Ramirez, J.M. Dan, et al., Antigen-Specific Adaptive Immunity to SARS-CoV-2 in Acute COVID-19 and Associations with Age and Disease Severity, Cell 183 (4) (2020) 996–1012.e19, https://doi.org/10.1016/j.cell.2020.09.038.
[253] T. Sekine, A. Perez-Potti, O. Rivera-Ballesteros, K. Strålin, J.B. Gorin, A. Olsson, S. Llewellyn-Lacey, H. Kamal, G. Bogdanovic, S. Muschiol, D.J. Wullimann, T. Kammann, J. Emgård, T. Parrot, E. Folkesson, Karolinska, Study Group, O. Rooyackers, L.I. Eriksson, J.I. Henter, A. Sönnerborg, M. Buggert, Robust T Cell Immunity in Convalescent Individuals with Asymptomatic or Mild COVID-19, Cell 183 (1) (2020) 158–168.e14. https://doi.org/10.1016/j.cell.2020.08.017.
[254] Karolinska COVID-19 Study Group, J.T. Sandberg, R. Varnaitė, W. Christ, P. Chen, J.R. Muvva, K.T. Maleki, M. García, M. Dzidic, E. Folkesson, M. Skagerberg, G. Ahlén, L. Frelin, M. Sällberg, L.I. Eriksson, O. Rooyackers, A. Sönnerborg, M. Buggert, N.K. Björkström, S. Aleman, K. Strålin, SARS-CoV-2-specific humoral and cellular immunity persists through 9 months irrespective of COVID-19 severity at hospitalisation, Clinical & translational immunology 10 (7) (2021) e1306. https://doi.org/10.1002/cti2.1306.
[255] A. Sattler, S. Angermair, H. Stockmann, K.M. Heim, D. Khadzhynov, S. Treskatsch, F. Halleck, M.E. Kreis, K. Kotsch, SARS-CoV-2-specific T cell responses and correlations with COVID-19 patient predisposition, The Journal of clinical investigation 130 (12) (2020) 6477–6489. https://doi.org/10.1172/JCI140965.
[256] Q.X. Long, X.J. Tang, Q.L. Shi, Q. Li, H.J. Deng, J. Yuan, J.L. Hu, W. Xu, Y. Zhang, F.J. Lv, K. Su, F. Zhang, J. Gong, B. Wu, X.M. Liu, J.J. Li, J.F. Qiu, J. Chen, A. L. Huang, Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections, Nature medicine 26 (8) (2020) 1200–1204. https://doi.org/10.1038/s41591-020-0965-6.
[258] E. Kyriazopoulou, G. Poulakou, H. Milionis, S. Metallidis, G. Adamis, K. Tsiakos, A. Fragkou, A. Rapti, C. Damoulari, M. Fantoni, I. Kalomenidis, G. Chrysos, A. Angheben, I. Kainis, Z. Alexiou, F. Castelli, F.S. Serino, M. Tsilika, P. Bakakos, E. Nicastri, E.J. Giamarellos-Bourboulis, Early treatment of COVID-19 with anakinra guided by soluble urokinase plasminogen receptor plasma levels: a double-blind, randomized controlled phase 3 trial, Nature medicine 27 (10) (2021) 1752–1760. https://doi.org/10.1038/s41591-021-01499-z.
[259] D. Geers, M.C. Shamier, S. Bogers, G. den Hartog, L. Gommers, N.N. Nieuwkoop, K.S. Schmitz, L.C. Rijsbergen, J. van Osch, E. Dijkhuizen, G. Smits, A. Comvalius, D. van Mourik, T.G. Caniels, van Gils, R.W. Sanders, Oude Munnink, R. Molenkamp, de Jager, B.L. Haagmans, C.H. GeurtsvanKessel, SARS-CoV-2 variants of concern partially escape humoral but not T-cell responses in COVID-19 convalescent donors and vaccinees, Science immunology 6 (59) (2021) eabj1750. https://doi.org/10.1126/sciimmunol.abj1750.