

**MINI REVIEW****T cell immunobiology and cytokine storm of COVID-19**Xiao-Hua Luo<sup>1</sup>  | Yan Zhu<sup>2</sup> | Jian Mao<sup>1</sup> | Rui-Chan Du<sup>1</sup>

<sup>1</sup>Department of Hematology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China

<sup>2</sup>Department of Hematology, Southwest Hospital, Third Military Medical University (Army Medical University), Chongqing, China

**Correspondence**

Xiao-Hua Luo, Department of Hematology, The First Affiliated Hospital of Chongqing Medical University, Youyi Road 1, Chongqing, 400016, P.R. China.  
Email: xiaohua.luo@gmail.com

**Abstract**

2019 coronavirus disease (COVID-19) presents as a newly recognized pneumonia and could rapidly progress into acute respiratory distress syndrome which has brought about a global pandemic. Until now, no curative therapy has been strongly recommended for COVID-19 except for personalized supportive care. T cells and virus-specific T cells are essential to protect against virus infection, including COVID-19. Delayed immune reconstitution (IR) and cytokine storm (CS) remain serious obstacles for the cure of COVID-19. Most COVID-19 patients, especially among elderly patients, had marked lymphopenia and increased neutrophils, but T cell counts in severe COVID-19 patients surviving the disease gradually restored later. Elevated pro-inflammatory cytokines, particularly IL-6, IL-10, IL-2 and IL-17, and exhausted T cells are found in peripheral blood and the lungs. It suggests that Thymosin  $\alpha$ 1 and adoptive COVID-19-specific T cells could improve IR, while convalescent plasma, IL-6 blockade, mesenchymal stem cells and corticosteroids could suppress CS. More clinical studies in this field worldwide are urgently warranted to pave the way for therapy of COVID-19 in the future.

**1 | INTRODUCTION**

Since December 2019, the 2019 coronavirus (COVID-19)-infected pneumonia has brought about a global pandemic,<sup>1,2</sup> which could progress into acute respiratory distress syndrome (ARDS). As of 14 October 2020, 37 704 153 patients were globally infected with 1 079 029 deaths reported to WHO.<sup>3</sup> The natural reservoir and intermediate host of COVID-19 have not been definitely settled, but bats<sup>4</sup> and pangolins<sup>5</sup> have evidenced infection with a related coronavirus in the laboratory. Until now, no curative therapy has been strongly recommended for COVID-19 except for personalized supportive care. T cell immune responses are essential for at least partial protection from many coronavirus infections, including COVID-19, and participate in abating the strong innate immune responses involved in cytokine syndrome. Rhesus macaques, indeed, induced cellular and humoral immune responses after SARS-CoV-2 infection and provided protection against a second infection.<sup>6</sup> These data raise the possibility

that immunological strategies to the prevention and treatment of SARS-CoV-2 infection may in fact be feasible.

**2 | CURRENT KNOWLEDGE OF T CELL IMMUNOLOGY OF COVID-19**

Similar to severe acute respiratory syndrome coronavirus (SARS) or Middle East respiratory syndrome coronavirus (MERS) patients,<sup>7,8</sup> most COVID-19 patients had marked lymphopenia, and non-survivors developed more severe lymphopenia over time.<sup>9-12</sup> Lymphopenia is a typical profile in patients with COVID-19, particularly among the elderly (older than 60 years)<sup>13,14</sup> and might be a pivotal element related to disease severity and mortality. Further analysis indicates a distinct reduction of T cell counts, especially CD8+ T cells during COVID-19.<sup>12,13,15-19</sup> Specifically, both intensive care unit (ICU) and non-ICU patients had significantly lower levels of monocytes as compared to healthy controls.<sup>15</sup> The

numbers of white blood cells and neutrophils were higher in non-survivors than those in survivors. In the non-survivors, the neutrophil counts continuously increased, while the lymphocyte counts progressively decreased until death. The neutrophil-to-lymphocyte ratio was regarded as the independent predictor for severe COVID-19 patients (Table 1).<sup>10,17</sup>

Notably, T cells in surviving patients with severe COVID-19 gradually restored to levels comparable to those of the mild cases.<sup>16,17</sup> The COVID-19 patients that cleared the virus infection had reconstituted CD3+, CD4+, CD8+ T cells and B cells in contrast to the virus-positive patients, while the recovered patients had a declined percentage of NKG2A+ CTLs cells.<sup>16</sup> Activated CD38+ HLA-DR+ T cells, especially CD8+ T cells, emerged and rapidly increased at day 7-9 prior to the resolution of symptoms.<sup>20</sup> Activated CD4+ and CD8+ T cells, follicular T helper cells, elevated antibody-secreting cells and IgM/IgG COVID-19-binding antibodies persisted in the peripheral blood for at least seven days after complete remission of symptoms, suggesting substantial antiviral immunity in one case with non-severe COVID-19.<sup>20</sup> Excitingly, Ling Ni et al recently observed COVID-19-specific humoral and cellular immunity in recovered individuals infected by COVID-19.<sup>21</sup> These convalescent-phase SARS-CoV-2-specific T cells were polyfunctional and displayed a stem-like memory phenotype.<sup>22</sup> Alba Grifoni et al then found that circulating SARS-CoV-2-specific CD8+ and CD4+ T cells were identified in ~70% and 100% of COVID-19 convalescent patients, respectively.<sup>23</sup> CD4 and CD8 T cell immune responses can be further detected to diverse regions of the viral proteome including the M, spike and N proteins.<sup>23</sup> The strongest T cell responses were directed to the spike (S) surface glycoprotein, and SARS-CoV-2-specific T cells predominantly produced effector and T helper 1 (TH1) cytokines, although TH2 and TH17 cytokines were also detected.<sup>24</sup> The breadth and magnitude of T cell responses were significantly greater in severe as compared with mild cases, but higher proportions of SARS-CoV-2-specific CD8+ T cells were observed in mild cases.<sup>25</sup> The majority of COVID-19 pentamer-binding CD8+ T cells were effector memory and central memory with early and intermediate differentiation phenotypes, with functional potential on antigen re-exposure.<sup>25</sup> Early phase clinical trials of candidate vaccines developed in China and UK show antiviral T cells and neutralizing antibodies in vaccinated healthy volunteers,<sup>26,27</sup> indicating promising for protective immunity. Interestingly, antigen-specific T cell studies reported that 20%-50% of people who had not been exposed to SARS-CoV-2 had a range of pre-existing memory T cells that are cross-reactive with comparable affinity to SARS-CoV-2 and the common cold coronaviruses HCoV-OC43, HCoV-229E, HCoV-NL63 or HCoV-HKU1.<sup>24,28,29</sup> It shows that SARS-CoV-2 pre-existing immunity exists to some extent in the general population.<sup>30</sup>

### Highlights

- Delayed immune reconstitution (IR) and cytokine storm (CS) remain serious obstacles for the cure of COVID-19.
- It suggests that Thymosin  $\alpha$ 1 and adoptive COVID-19-specific T cells could improve IR, while convalescent plasma, IL-6 blockade, mesenchymal stem cells and corticosteroids could suppress CS.

Responding T cells indicate a general activation phenotype in a subgroup patients with COVID-19, expressing Ki67, CD38 and human leucocyte antigen-DR (HLA-DR).<sup>22,31,32</sup> Peripheral CD4+ T cells in 2019-nCoV patients expressed higher levels of CD69, CD38, OX40 and CD44, while activated CD8+ T cells expressing higher levels of CD69, CD38 and CD44.<sup>15</sup> The percentage of naïve helper T cells (CD3+CD4+CD45RA+) increased, while memory helper T cells (CD3+CD4+CD45RO+), CD28 positive cytotoxic suppressor T cells (CD3+CD8+CD28+) and regulatory T cells (CD3+CD4+CD25+CD127low+) decreased in severe cases,<sup>10</sup> implying that the immune system in the severe COVID-19 patients was impaired more greatly. However, several reports revealed exhaustive status of T cells. A much higher percentage of Tim3+PD-1+ expressed on both CD4+ and CD8+ T cells from COVID-19 patients with severe diseases, indicating the exhaustive T cells in response to this virus infection.<sup>13,15,32-34</sup> Moreover, increased expression of PD-1 and Tim-3 on T cells could predict progression from prodromal to overtly symptomatic stages of COVID-19.<sup>13</sup> Compared with the healthy control and mild group, the frequency of multi-functional CD4+ T cells (positive for at least two of cytokines IFN- $\gamma$ , TNF- $\alpha$  and IL-2) decreased significantly in the severe cases, whereas the proportion of non-functional subsets (IFN- $\gamma$  – TNF- $\alpha$  – IL-2–) increased significantly.<sup>34</sup> The frequency of the non-exhausted (PD-1 – CTLA-4 – TIGIT–) CD8+ T cell subset in the severe group was significantly lower than that in the non-severe group.<sup>34</sup> Meijuan Zheng et al reported that NKG2A expression was heightened substantially on CD8+ T cells in COVID-19-infected patients with reduced percentages of CD107a+CD8+, IFN- $\gamma$ +CD8+ and IL-2+CD8+ T cells and MFI of granzyme B+CD8+ T cells,<sup>16</sup> suggesting the functionally exhausted cytotoxic T cells at an early stage of the disease. It showed a tendency of lower IFN- $\gamma$  production by CD4+ T cells in severe COVID-19 patients than moderate patients,<sup>11</sup> further indicative of T cell exhaustion, while other reports demonstrate a hyperactive signature of CD8+ T cells.<sup>16,33</sup>

**TABLE 1** T cell immunobiology and cytokine storm reported in COVID-19 patients

Cohort	Sample	Methods used	T cell immunobiology	Cytokine storm	References
452 patients with 286 having severe infection	PBMCs, serum or plasma samples	Flow cytometry	T cells number significantly decreased and were more impaired in severe cases. Both Th cells and suppressor T cells in patients were below normal levels, with lower levels of Th cells in the severe group. The percentage of naive Th cells increased and memory Th cells decreased in severe cases.	Most severe cases demonstrated elevated levels of infection-related biomarkers and inflammatory cytokines. (ie TNF- $\alpha$ , IL-2R and IL-6)	10
11 severe cases and 10 moderate cases	PBMCs, serum or plasma samples	Flow cytometry and chemiluminescence immunoassay	Absolute numbers of T lymphocytes, CD4+ T cells and CD8+ T cells decreased in nearly all the patients and were markedly lower in severe cases than moderate cases.	Markedly higher levels of IL-2R, IL-6, IL-10 and TNF- $\alpha$ .	11
60 patients	PBMCs	Flow cytometry	CD4+ T cells and CD8+ T cells decreased in patients, and severe cases had a lower level than mild cases.	NR	12
522 patients and 40 healthy controls	PBMCs, serum or plasma samples	Flow cytometry	CD4+ and CD8+ T cells were dramatically reduced in patients. T cells from patients had significantly higher levels of the exhausted marker PD-1.	T cell numbers were negatively correlated to serum IL-6, IL-10 and TNF- $\alpha$ concentration, with patients in the disease resolution period showing reduced IL-6, IL-10 and TNF- $\alpha$ concentrations and restored T cell counts.	13
65 patients having mild (n = 30), severe (n = 20) and extremely severe (n = 15) illness	PBMCs, serum or plasma samples	Flow cytometry and chemiluminescence immunoassay	The absolute numbers of CD4+ T cells and CD8+ T cells were gradually decreased with increased severity of illness. HLA-DR and CD45RO expressed on CD4+ and CD8+ T cells were increased in severe and extremely severe patients. The percentage of IFN- $\gamma$ -producing CD8+ T cells was increased in both severe and extremely severe patients compared with mild patients.	IL-2R, IL-6 and IL-10 were all increased in extremely severe patients.	14
patients in ICU(n = 12) and Non-ICU(n = 21), and healthy controls (n = 10)	PBMCs	Flow cytometry	The CD4+ T cells from both ICU and non-ICU patients had decreased remarkably, whereas CD8+ T cells decreased more significantly in ICU patients. CD4+ and CD8+ T cells in patients have higher expression of CD69, CD38 and CD44. A much higher percentage of co-expression Tim3+ PD-1+ T subsets existed in both CD4+ and CD8+ T cells from patients, especially in ICU patients. A high percentage of GM-CSF+ and IL-6+ expressions could be found in CD4+ T cells from patients in both ICU and non-ICU patients compared to healthy controls	NR	15

(Continues)

TABLE 1 (Continued)

Cohort	Sample	Methods used	T cell immunobiology	Cytokine storm	References
55 cases of mild disease (MD) and 13 cases of severe disease (SD).	PBMCs	Flow cytometry	The number of T cells and CD8+ T cells was significantly lower in SD patients than that in MD cases. In patients infected with SARS-CoV-2, NKG2A expression was increased significantly on CD8+ T cells compared with that in HCs. Patients showed decreased percentages of CD107a+ CD8+, IFN- $\gamma$ + CD8+ and IL-2+ CD8+ T cells and MFI of granzyme B+ CD8+ T cells, compared with those in healthy controls.	NR	16
13 severe cases and 27 mild cases	PBMCs, serum or plasma samples	Flow cytometry and cytokine profiles	Significant decreases in the counts of T cells, especially CD8+ T cells in the peripheral blood in the severe cases compared to those in the mild cases. T cell counts and cytokine levels in severe patients who survived the disease gradually recovered at later time points to levels that were comparable to those of the mild cases.	Increases in IL-6, IL-10, IL-2 and IFN- $\gamma$ levels in the peripheral blood in the severe cases compared to those in the mild cases.	17
86 were patients with mild-to-moderate illness and 17 were patients with severe illness	PBMCs	Flow cytometry	CD3+ T cells, CD4+ T cells and CD8+ T cells were significantly decreased in patients with COVID-19. These patients had a relatively slight decrease in CD4+ T cells but a severe decrease in CD8+ T cells. The significantly elevated CD4/CD8 ratio was observed in patients.	NR	18
19 patients with moderate or critical disease and five healthy controls	nasopharyngeal and bronchial samples	single-cell RNA sequencing	NR	Critical cases exhibited stronger interactions between epithelial and immune cells, as indicated by ligand-receptor expression profiles and activated immune cells, including inflammatory macrophages expressing CCL2, CCL3, CCL20, CXCL1, CXCL3, CXCL10, IL8, IL1B and TNF.	
A non-severe case	PBMCs, serum or plasma samples	Flow cytometry and the Human CBA Kit	The recruitment of immune cell populations (follicular helper T cells (TFH cells) and activated CD4+ and CD8+ T cells) in the patient's blood before the resolution of symptoms.	Minimal pro-inflammatory cytokines and chemokines were found in this patient with COVID-19, even while she was symptomatic at days 7-9.	20

(Continues)

TABLE 1 (Continued)

Cohort	Sample	Methods used	T cell immunobiology	Cytokine storm	References
14 patients who recently recovered	PBMCs	Flow cytometry and ELISPOT	A strong correlation between neutralization antibody titres and the numbers of virus-specific T cells.	NR	21
Unexposed individuals, exposed family members and individuals with acute or convalescent disease	PBMCs	High-dimensional flow cytometry and ELISPOT	Acute-phase SARS-CoV-2-specific T cells displayed a highly activated cytotoxic phenotype that correlated with various clinical markers of disease severity, whereas convalescent-phase SARS-CoV-2-specific T cells were polyfunctional and displayed a stem-like memory phenotype. SARS-CoV-2-specific T cells were detectable in antibody-seronegative exposed family members and convalescent individuals with a history of asymptomatic and mild COVID-19.	NR	22
20 adult patients who had recovered and 20 unexposed individuals	PBMCs	Flow cytometry and the Human CBA Kit	Circulating SARS-CoV-2-specific CD8+ and CD4+ T cells were identified in ~ 70% and 100% of COVID-19 convalescent patients, respectively. SARS-CoV-2-reactive CD4+ T cells were detected in ~ 40%–60% of unexposed individuals.	NR	23
10 patients who required admission to an intensive care unit and 10 healthy controls	PBMCs	Flow cytometry	SARS-CoV-2-specific CD4+ and CD8+ T cells were detected in 10 out of 10 and 8 out of 10 patients, respectively. Low levels of SARS-CoV-2-reactive T cells were detected in 2 out of 10 healthy controls not previously exposed to SARS-CoV-2. The strongest T cell responses were directed to the spike surface glycoprotein and SARS-CoV-2-specific T cells predominantly produced effector and Th1 cytokines.	NR	24
42 patients following recovery (28 with mild disease and 14 with severe disease) and 16 unexposed donors	PBMCs	Flow cytometry and ELISPOT	The breadth and magnitude of T cell responses were significantly higher in severe as compared with mild cases. Peptide-MHC pentamer-positive cells displaying the central and effector memory phenotype. In mild cases, higher proportions of SARS-CoV-2-specific CD8+ T cells were observed.	NR	25
patients who recovered (n = 36) and patients who recovered from SARS (n = 23) 17 years after infection, healthy donors (n = 26)	PBMCs	Flow cytometry and ELISPOT	CD4 and CD8 T cells recognized multiple regions of the N protein. Patients who recovered from SARS possess long-lasting memory T cells that are reactive to the N protein of SARS-CoV 17 years after the outbreak of SARS in 2003; these T cells displayed robust cross-reactivity to the N protein of SARS-CoV-2. SARS-CoV-2-specific T cells were also detected in individuals with no history of SARS	NR	28

(Continues)

TABLE 1 (Continued)

Cohort	Sample	Methods used	T cell immunobiology	Cytokine storm	References
18 healthy adult donors	PBMCs	Flow cytometry and FluoroSPOT	A range of pre-existing memory CD4+ T cells that are cross-reactive with comparable affinity to SARS-CoV-2 and the common cold coronaviruses human coronavirus (HCoV)-OC43, HCoV-229E, HCoV-NL63 and HCoV-HKU1.	NR	29
68 healthy donors and 25 patients	PBMCs	Flow cytometry	Spike-reactive CD4+ T cells were detected not only in 83% of patients with COVID-19 but also in 35% of healthy donors. Spike-reactive CD4+ T cells in healthy donors were primarily active against C-terminal epitopes in the spike protein.	NR	31
125 patients	PBMCs, serum or plasma samples	High-dimensional flow cytometry and Luminesx	Two major immune response components and a third pattern lacking robust adaptive immune responses, thus revealing immunotypes of COVID-19: (a) Immunotype 1 was associated with disease severity and showed robust activated CD4 T cells, a paucity of circulating follicular helper cells, activated CD8 'EMRAs', hyperactivated or exhausted CD8 T cells and PBs. (b) Immunotype 2 was characterized by less CD4 T cell activation, Tbet+ effector CD4 and CD8 T cells and proliferating memory B cells and was not associated with disease severity. (c) Immunotype 3, which negatively correlated with disease severity and lacked obvious activated T and B cell responses	Elevated systemic cytokines and chemokines, including myeloid-recruiting chemokines.	32
7 patients had moderate disease and 28 with severe disease, 7 recovered patients and 12 healthy donors	PBMCs	Flow cytometry	Extensive induction and activation of multiple immune lineages, including T cell activation and Fc and trafficking receptor modulation on innate lymphocytes and granulocytes, that distinguished severe COVID-19 cases from healthy donors or SARS-CoV-2-recovered or moderate severity patients.	NR	35
A patient who died from severe disease	PBMCs, post-mortem biopsies.	Flow cytometry and histological examination	The counts of peripheral CD4 and CD8 T cells were substantially reduced, while their status was hyperactivated, as evidenced by the high proportions of HLA-DR and CD38 double-positive fractions. There was an increased concentration of highly pro-inflammatory CCR6+ Th17 in CD4 T cells. CD8 T cells were found to harbour high concentrations of cytotoxic granules. Interstitial mononuclear inflammatory infiltrates, dominated by lymphocytes, were seen in both lungs.	NR	35

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**TABLE 1** (Continued)

Cohort	Sample	Methods used	T cell immunobiology	Cytokine storm	References
13 patients	Bronchoalveolar lavage fluid immune cells	Single-cell RNA sequencing and cytometric bead array	Moderate cases were characterized by the presence of highly clonally expanded CD8+ T cells.	Pro-inflammatory monocyte-derived macrophages were abundant in the bronchoalveolar lavage fluid from patients with severe COVID-9. Patients with severe/critical infection had much higher levels of inflammatory cytokines, particularly IL-8, IL-6 and IL-1 $\beta$ , in their BALFs	36
2 patients	COVID-19 human lung tissue, human patient sera, healthy human lung tissue	RNA-Seq and Cytokine and Chemokine Protein Analysis	NR	Low levels of type I and III interferons juxtaposed to elevated chemokines and high expression of IL-6.	48
76 patients and 69 healthy individuals	PBMCs	Mass cytometry and CITE-seq single-cell RNA sequencing	There was a notable increase in the frequency of effector CD8 T cells in all infected individuals. The kinetics of the CD8 effector T cell response were prolonged and continued to increase up to day 40 after onset of the symptoms	43 cytokines, including IL-6, MCP-3 and CXCL10, were significantly upregulated. Enhanced plasma levels of inflammatory mediators—including EN-RAGE, TNFSF14 and oncostatin M—which correlated with disease severity and increased bacterial products were detected in plasma.	50
41 patients	Plasma samples	Human Cytokine Standard 27-Plex Assays panel and the Bio-Plex 200 system	NR	ICU patients had higher plasma levels of IL2, IL7, IL10, GSCF, IP10, MCP1, MIP1A and TNF- $\alpha$ .	51
102 mild and 21 severe patients	PBMCs, plasma samples	Flow cytometry, cytokine and chemokine measurements	There were significant differences in CD4+ T, CD8+ T, IL-6 and IL-10 between mild and severe groups. There were significant positive correlations between CD4+ T and CD8+ T, IL-6 and IL-10 in the mild group.	CD4+ T, CD8+ T, IL-6 and IL-10 can be used as indicators of disease evolution.	52

(Continues)

TABLE 1 (Continued)

Cohort	Sample	Methods used	T cell immunobiology	Cytokine storm	References
113 patients with moderate or severe disease	PBMCs, plasma samples	Flow cytometry and multiple microspheres flow immunofluorescence	Patients with COVID-19 presented with marked reductions in the number and frequency of both CD4+ and CD8+ T cells.	An early elevation in cytokine levels was associated with worse disease outcomes. Following an early increase in cytokines, patients with moderate COVID-19 displayed a progressive reduction in type 1 (antiviral) and type 3 (antifungal) responses. Severe COVID-19 was accompanied by an increase in multiple type 2 (antihelminths) effectors, including IL-5, IL-13, immunoglobulin E and eosinophils.	53
63 patients	PBMCs, serum or plasma samples	Flow cytometry and cytokine analysis	Highly cycling T cells and CD8+ T cells co-expressed exhaustion-associated markers, PD-1 and TIM3. $\alpha\beta$ and $\gamma\delta$ T cells were depleted and the composition of the B cell compartment was altered. T lymphopenia most overtly affected CD8+ cells and $\gamma\delta$ cells	A third set of traits, including a triad of IP-10, interleukin-10 and interleukin-6, anticipate subsequent clinical progression.	54
37 adult patients	PBMCs, serum or plasma samples	Mass Cytometry and plasma protein profiling	The recovery of T cells after the initial lymphopenia occurs over the following 2-3 weeks and is dominated by CD127-expressing effector and central memory CD4+ T cells, as well as CD57-expressing and differentiated memory CD8+ T cells. The CD4+ T cell response was initially dominated by effector and central memory responses, followed by an increase in regulatory Tregs ~ 4 days after admission. The CD8+ T cell responses are dominated by activated cells expressing high CD38 and also a subset of effector cells upregulating the CD147 receptor from ~ 1 week onward	An IFN $\gamma$ -eosinophil axis activated before lung hyperinflammation and changes in cell-cell co-regulation during different stages of the disease.	55
48 patients	PBMCs, plasma samples	Flow cytometry and ELISA	The occurrence of lymphopenia in COVID-19 patients, mainly affected CD3+ T cells.	Higher levels of inflammatory cytokines were observed in COVID-19 patients than in healthy donors. Both IL-6 and IL-8 were negatively correlated with perforin content in both innate (NK) and adaptive (CD3) immune cells.	56

(Continues)



TABLE 1 (Continued)

Cohort	Sample	Methods used	T cell immunobiology	Cytokine storm	References
3 COVID-19 patients and 10 healthy volunteers	Whole blood	Daily transcriptomic profiling	The CD4, CD8A and CD8B mRNA transcript levels were the lowest among all the subjects.	The pro-inflammatory response may be intertwined with T cell activation that could exacerbate disease or prolong the infection. Most inflammatory gene expression peaked after respiratory function nadir, except expression in the IL1 pathway.	70
10 patients and 5 healthy donors	PBMCs	Single-cell RNA sequencing technique	CD4+ T cells and CD8+ T cells decreased significantly and expressed high levels of inflammatory genes in the early recovery stage.	IL-1 $\beta$ and M-CSF may be novel candidate target genes for inflammatory storm and that TNFSF13, IL-18, IL-2 and IL-4 may be beneficial for the recovery of COVID-19 patients.	71
10 patients who died from disease	Post-mortem needle autopsies	Immunohistochemistry	The cell composition of the spleen decreased, white pulp atrophied at different levels, meanwhile lymphoid follicles decreased or absent; the ratio of red pulp to white pulp increased with varying degrees. the T and B lymphocyte components of the spleen in all cases decreased in varying degrees. CD3(+), CD4(+) and CD8(+)/T cells were decreased.	NR	97
13 convalescent patients and 13 healthy individuals	PBMCs, plasma samples	Flow cytometry, magnetic chemiluminescence enzyme antibody immunoassay, and measurement of cytokine and chemokine	More severe individuals showed higher frequency of TEM and TFH-EM cells but a lower frequency of TCM, TFH-CM and TNaive cells, relative to mild and moderate patients. cTFH1 cell associated with SARS-CoV-2 targeting antibodies.	Around 4-fold higher of IL-6 production was observed in COVID-19 convalescent patients. Higher level of IL-1 $\beta$ while comparable IFN- $\gamma$ has been noticed in convalescents. Around 46% of COVID-19 convalescents displayed higher TNF- $\alpha$ and exhibited higher plasma level of CXCL11,	98

Abbreviations: GM-CSF, granulocyte-macrophage colony-stimulating factor; ICU, intensive care unit; NR, not reported; PBMC, peripheral blood mononuclear cell; PD1, programmed cell death protein 1; TFH cell, T follicular helper cell; TH1 cell, T helper 1 cell; TIM3, T cell immunoglobulin and mucin domain-containing protein 3.

Pathological findings of one COVID-19 case with ARDS<sup>35</sup> confirmed that inflammatory lymphocytes infiltrate both lungs, which were high cytotoxic CD8 T cells and hyperactivated Th17. Furthermore, single-cell RNA sequencing uncovered lung bronchoalveolar immune cells in patients with COVID-19.<sup>36</sup> CD8+ T cells in bronchoalveolar lavage fluid (BALFs) from patients with severe/critical infection were less expanded, more proliferative and more phenotypically heterogeneous, whereas a larger proportion of CD8+ T cell effectors with tissue-resident and highly expanded features were present in BALFs from patients with moderate infection.<sup>36</sup> These aberrant T cell responses may enter and reside in the lung in high numbers and damage this organ lethally in severely ill patients with COVID-19.

Consistent with SARS or MERS, it is striking that children always develop mild clinical disease, the elderly cases experience much worse outcomes following infection with COVID-19,<sup>10</sup> suggesting that mature extravagant immune responses to the novel coronavirus infection play a crucial role in triggering ARDS and organ failures. The T cell compartment undergoes senescence in the older population, which results in higher risk and severity of infections and inhibits immunogenicity and vaccine efficacy in this population. Moreover, males may be more susceptible to COVID-19 than females.<sup>37-39</sup> Females experience a lower risk of infections and chronic inflammatory disease but are generally more vulnerable to autoimmunity.<sup>40</sup> As the ACE2 gene localizes on the X-chromosome, ACE2 levels in the blood are higher in males than in females as well as in patients with diabetes or cardiovascular diseases.<sup>41</sup> Therefore, male patients may be more likely to die from COVID-19 because of the high expression of ACE2, though further research on the mechanism is needed. Immunological ageing may, therefore, be accounted for as injury from immune responses to novel virus infection in elderly life. Thus, constant immunosurveillance against COVID-19 seems to be more demanding for elderly males.

### 3 | CYTOKINE STORM AND IMMUNOMODULATORY THERAPY

Cytokine storms (CS) are underlying a range of infectious and non-infectious diseases. The first use of 'cytokine storm' appears to be on graft-versus-host disease published in 1993<sup>42</sup> and later in virus infectious diseases including cytomegalovirus,<sup>43</sup> EBV-associated hemophagocytic lymphohistiocytosis<sup>44</sup> and SARS-CoV.<sup>45</sup> CS is thought to be an overwhelming immune reaction mediated by immune toxicity. The clinical symptoms and signs of CS affect multiple organ systems, among which acute lung injury is a typical product of damages in the lung alveoli and can progress into respiratory failure.<sup>46</sup> SARS is an instance of cytokine storms

that give rise to a robust pro-inflammatory reaction in the lungs characterized by pulmonary fibrosis, inflammation and hypercytokinemia.<sup>47</sup>

Similarly, cytokine storm is a critical profile of patients with COVID-19 (Table 1) defined by low levels of type I and III interferons juxtaposed to elevated chemokines and high expression of IL-6.<sup>48-50</sup> Higher plasma concentrations of IL-2, IL2R, IL-6, IL-7, IL-10, G-CSF, IP10, MCP1, MCP-3, IL-1ra, MIP1A, IFN- $\gamma$  and TNF- $\alpha$  were observed in ICU patients than non-ICU patients with COVID-19,<sup>10,17,51,52</sup> indicating that cytokine storm was related to disease severity and fatal outcome.<sup>53</sup> A triad of IP-10, interleukin-10 and interleukin-6, anticipate subsequent clinical progression of COVID-19.<sup>54</sup> Lung macrophages in severe patients with COVID-19 may contribute to local inflammation by recruiting inflammatory monocytic cells and neutrophils.<sup>36</sup> Levels of cytokine in severe patients with COVID-19 surviving the disease gradually restored to levels comparable to the mild cases.<sup>13,17</sup> It is noted that C-reactive protein, ferritin and neutrophil counts were considerably higher in severe patients than moderate patients, while eosinopenia appeared in the majority of COVID-19 patients.<sup>10,15,38,55</sup> Furthermore, the dynamic changes of T cell counts are reversely correlated with the dynamic changes of most cytokine levels in the peripheral blood in severe COVID-19 patients.<sup>17,56</sup>

Because the severity of COVID-19 is associated with a cytokine storm, it would be reasonable to control this storm to mitigate the self-imposed damages launched by the host anti-infection responses. The treatment of CS adheres to a grading and risk-adapted strategy.<sup>57,58</sup> Due to the role of IL-6 in disease pathology, the selective blockade of IL-6 signaling by the IL-6 receptor antagonist or anti-IL-6 antibody has been the backbone of CS remedy, resulting in rapid relief of CS symptoms within a few hours. Interestingly, it appears that IL-6 blockade does not suppress CAR-T cell function in humans and mice and does not impact prognosis,<sup>59-62</sup> which may be helpful for not hurting potential antiviral immunity in patients with COVID-19. Several reports worldwide emphasized elevated plasma concentrations of IL-6 and provided a rationale for the introduction of anti-IL-6 therapies in randomized clinical trials.<sup>63-69</sup> Moreover, IL-1 pathways may be another novel targets for inflammatory storm.<sup>70,71</sup>

It has not been definitively identified the reason that intravenous immunoglobulin (IVIG) restrains harmful inflammation. IVIG conducts several immunomodulatory roles through blocking Fc receptors, which are relevant to the tolerance of the self and the inflammation severity.<sup>72</sup> This tactics have been used to abate viral-triggered CS and were verified to have improved the outcome of the infection, including SARS and the 2009 H1N1 pandemic influenza.<sup>73,74</sup> Administration of hyperimmune IV immunoglobulin within five days of symptom onset was associated with a decreased viral load and lower mortality in patients with severe A

(H1N1) infection.<sup>73</sup> These reports implied that passive IVIG is a potential programme for treating severe COVID-19.

Corticosteroids are pretty efficient in the therapy of CS and inhibit the inflammatory response, but they also impair T cell function and may hamper the persistence and activity of antiviral T cells. The evidence in support of the administering corticosteroids in COVID-19 is inconclusive,<sup>75-77</sup> but experiences from China recommend corticosteroids treatment to be an adjuvant therapy for critically ill patients with COVID-19 at a low-to-moderate dose and short term (methylprednisolone 0.5-1/mg/kg/day, 3-5 days or shorter than 10 days).<sup>78-81</sup> Furthermore, pathological pulmonary oedema and hyaline membrane formation indicate corticosteroids should be used timely and appropriately for severe patients with COVID-19 to prevent the occurrence of ARDS.<sup>35</sup> The RECOVERY Collaborative Group reported that the use of dexamethasone (oral or intravenous dexamethasone at a dose of 6 mg once daily for up to 10 days, or until hospital discharge if sooner) resulted in lower 28-day mortality among patients receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support.<sup>82</sup> Bruno M. Tomazini et al supported that dexamethasone (dexamethasone 20 mg intravenously once daily for 5 days, followed by 10 mg intravenously once daily for additional 5 days or until ICU discharge) plus standard care resulted in longer days alive and free of mechanical ventilation over 28 days for COVID-19 patients with moderate to severe ARDS.<sup>83</sup> It suggests that corticosteroids should be applied to patients with severe cases of COVID-19, especially for those requiring respiratory support.

In refractory cases, ibrutinib, JAK inhibitors or TNF- $\alpha$  blocker, T cell depleting alemtuzumab (anti-CD52 monoclonal antibody) and ATG, and N-acetylcysteine (NAC) or vitamin C or convalescent plasma or hemofiltration might be beneficial,<sup>84-93</sup> although reports are limited. Interleukin-17 blockade might help those COVID-19 patients who have a high plasma concentration of interleukin-17.<sup>35</sup> Mesenchymal stem cells (MSCs) are believed to have a comprehensive, powerful immunomodulatory function. It seems that the intravenous infusion of MSCs was safely effective for treating patients with severe COVID-19 pneumonia.<sup>94,95</sup>

## 4 | IMPROVING IMMUNE RECONSTITUTION

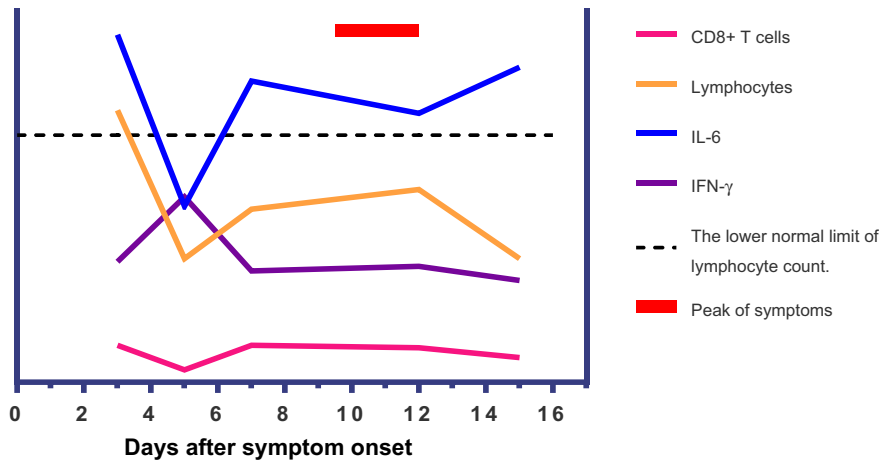
The hallmark of COVID-19 is the continued T cell depletion, resulting in gradual immunodeficiency, secondary infection and even death. Hypoplastic bone marrow and decreased numbers of lymphocyte, cell degeneration and necrosis in the spleen were found pathologically in three COVID-19 cases.<sup>96,97</sup> Hyperactivation of T cells or high

levels of expression of pro-apoptotic molecules, such as FAS or TRAIL, could also contribute to T cell depletion.<sup>32</sup> T cell counts in surviving patients with severe COVID-19 gradually recovered to levels comparable to the mild cases.<sup>13,16,17</sup> Fang Gong et al comprehensively analysed circulating CD4+ T cells of 13 COVID-19 convalescent patients.<sup>98</sup> They found that more severe individuals showed higher frequency of TEM and TFH-EM cells but a lower frequency of TCM, TFH-CM and TNaive cells, relative to mild and moderate patients. Immune reconstitution (IR), marked by an increase in T cell number, is the most crucial process that takes place in COVID-19 patients after treatment. Enhancing immune reconstitution, in particular COVID-19-specific T cells, therefore, is an area of urgent research.

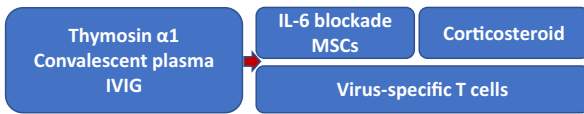
T cell reconstitution usually depends on homeostatic peripheral expansion and thymopoiesis. Cytokine-based approaches to improve IR through peripheral expansion are mostly investigated in the field of hematopoietic stem cell transplantation (HSCT), including IL-2, IL-7 and IL-21, and so on. These cytokines could function in T cell differentiation into effector cells and T, B and NK cell proliferation. However, early T cell immunity through peripheral expansion is almost unavailable on account of a substantially limited T cell receptor (TCR) diversity for this novel coronavirus, as thymopoiesis could mainly supply new TCR clones in naive T cells.

Thymosin  $\alpha$  1 (T $\alpha$ 1) has been explored to enhance T cell IR in the HSCT setting, as the thymus naturally promotes T cell development through secreting the hormone. Subcutaneous administrations of T $\alpha$ 1 after allo-HSCT led to faster CD4+ T cell recovery and pathogen-specific T cells to emerge at 1 month after transplantation, which was earlier and in higher numbers as compared to controls.<sup>99</sup> T $\alpha$ 1 (Thymalfasin/Zadaxin) is an orphan drug approved by the FDA for the therapy of chronic hepatitis B without adverse effects.<sup>100</sup> Adoptive transfer of antigen-specific T cells seems promising to improve immune reconstitution, which has been extensively used to treat patients with refractory CMV or EBV infection.<sup>101,102</sup> We have developed effective methods to expand tumour-infiltrating lymphocytes and virus-specific T cells.<sup>103,104</sup> Infusion of COVID-19-specific T cells could be a life-saving strategy for severe COVID-19-infected patients, considering COVID-19-specific T cells have been identified.<sup>21-25,31</sup>

As Tim3 and PD-1 highly expressed on both CD4+ and CD8+ T cells from severe COVID-19 patients,<sup>13,15,32-34</sup> whether the reversing T cell exhaustion with immune checkpoint inhibitors (ICI) is beneficial remains unanswered at the moment. It assumes that ICI could theoretically restore exhausted T cells in the early stage of virus infections including COVID-19 infection.<sup>20,105,106</sup> Preliminary data from cancer patients with COVID-19 infection suggest PD-1 blockade exposure seemed to be not associated with increased risk



**FIGURE 1** T cell immune reconstitution and kinetics of cytokines in one patient who progresses to severe COVID-19 during a typical course, and proposed ways to control these aberrant immune responses



of severity of COVID-19.<sup>107</sup> However, further studies are warranted to carefully address ICI-related side effects as hyperactivated lymphocytes and cytokine storm are might be augmented and worsen COVID-19 outcomes.

## 5 | SUMMARY AND OUTLOOK

Cure of COVID is often hampered by T cell deficiency and cytokine storm. Levels of T cell subsets and cytokine storm could predict the transition from mild to severe. It indicates that during COVID-19 infection, some aspects of the immune response require strengthening at moments and require inhibiting at other moments. The immune system early in the infection, when the virus is replicating quickly and climbing its peak, could be substantially distinct from when the pathogen achieves a balance or is clearing up due to antiviral drugs or host immune response. Variations in individuals' reactions to infection and medications are likely to be complicated and influenced by host and pathogen genetic makeup as well as by individual immune memory.

Fortunately, we now have a clearer picture of this changing immune response of COVID-19, as well as its connection with age and gender. Taking into account the acme course (9.5-12 days from onset),<sup>9,108,109</sup> kinetic changes of lymphocytes and cytokines of this disease, several rational therapies identified so far to direct at the specific stage of the immune cascade and implement those at the right moment should be considered (Figure 1). It suggests that Thymosin  $\alpha$ 1 and adoptive COVID-19-specific T cells could improve IR while convalescent plasma or IVIG, IL-6 blockade, MSCs and corticosteroids could suppress CS. Timing the therapeutic window of checkpoint inhibitors warrants meticulous assessment,

regarding the exhausted T cells at an early stage of the disease. More in-depth clinical studies in this field worldwide are urgently warranted, both in terms of reconstitution of T cell immunobiology and abating cytokine storm, which would pave the way for therapy of COVID-19 in the future.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## ORCID

Xiao-Hua Luo  <https://orcid.org/0000-0002-0657-7738>

## REFERENCES

- Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med.* 2020;382(8):727-733.
- Holshue ML, DeBolt C, Lindquist S, et al. First case of 2019 novel coronavirus in the United States. *N Engl J Med.* 2020;382(10):929-936.
- WHO. Novel coronavirus (2019-nCoV) situation report - Oct 14, 2020. <https://covid19.who.int/table> (accessed Oct 14, 2020)
- Li X, Song Y, Wong G, Cui J. Bat origin of a new human coronavirus: there and back again. *Science China Life Sciences.* 2020;63(3):461-462.
- Lam TT-Y, Jia N, Zhang Y-W, et al. Identifying SARS-CoV-2-related coronaviruses in Malayan pangolins. *Nature.* 2020;583(7815):282-285.
- Chandrashekar A, Liu J, Martinot AJ, et al. SARS-CoV-2 infection protects against rechallenge in rhesus macaques. *Science* 2020;369:812-817.
- He ZP, Zhao CH, Dong QM, et al. Effects of severe acute respiratory syndrome (SARS) coronavirus infection on peripheral blood lymphocytes and their subsets. *Int J Infect Dis.* 2005;9:323-330.
- Arabi YM, Arifi AA, Balkhy HH, et al. Clinical course and outcomes of critically ill patients with middle east respiratory

- syndrome Coronavirus infection. *Ann Intern Med.* 2014;160(6):389-397.
9. Wang D, Hu B, Hu C, et al. *Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan.* 11th ed. *Jama: China;* 2020;323:1061.
  10. Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with Coronavirus 2019 (COVID-19) in Wuhan, China. *Clin Infect Dis.* 2020;71(15):762-768.
  11. Chen G, Wu D, Guo W, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Investig.* 2020;130(5):2620-2629.
  12. Wang F, Nie J, Wang H, et al. Characteristics of peripheral lymphocyte subset alteration in COVID-19 pneumonia. *J Infect Dis.* 2020;221:1762-1769.
  13. Diao B, Wang C, Tan Y, et al. Reduction and functional exhaustion of T cells in patients with coronavirus disease 2019 (COVID-19). *Front Immunol.* 2020;11. <http://dx.doi.org/10.3389/fimmu.2020.00827>
  14. Wang F, Hou H, Luo Y, et al. The laboratory tests and host immunity of COVID-19 patients with different severity of illness. *JCI Insight.* 2020;5(10):e137799.
  15. Zhou Y, Fu B, Zheng X, et al. Pathogenic T cells and inflammatory monocytes incite inflammatory storm in severe COVID-19 patients. *Natl Sci Rev.* 2020;7(6):998-1002.
  16. Zheng M, Gao Y, Wang G, et al. Functional exhaustion of antiviral lymphocytes in COVID-19 patients. *Cell Mol Immunol.* 2020;17(5):533-535.
  17. Liu J, Li S, Liu J, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. *EBioMedicine.* 2020;55. <http://dx.doi.org/10.1016/j.ebiom.2020.102763>
  18. Jiang M, Guo Y, Luo Q, et al. T-Cell subset counts in peripheral blood can be used as discriminatory biomarkers for diagnosis and severity prediction of Coronavirus Disease 2019. *J Infect Dis.* 2020;222(2):198-202.
  19. Du R-H, Liang L-R, Yang C-Q, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. *Eur Respir J.* 2020;55(5). <http://dx.doi.org/10.1183/13993003.00524-2020>
  20. Thevarajan I, Nguyen THO, Koutsakos M, et al. Breadth of concomitant immune responses prior to patient recovery: a case report of non-severe COVID-19. *Nat Med.* 2020;26(4):453-455.
  21. Ni L, Ye F, Cheng M-L, et al. Detection of SARS-CoV-2-Specific Humoral and Cellular Immunity in COVID-19 Convalescent Individuals. *Immunity.* 2020;52(6):971-977.e3.
  22. Sekine T, Perez-Potti A, Rivera-Ballesteros O, et al. Robust T cell immunity in convalescent individuals with asymptomatic or mild COVID-19. *Cell.* 2020;183(1):158-168.e14.
  23. Grifoni A, Weiskopf D, Ramirez SI, et al. Targets of T cell responses to SARS-CoV-2 Coronavirus in humans with COVID-19 disease and unexposed individuals. *Cell.* 2020;181(7):1489-1501.e15.
  24. Weiskopf D, Schmitz KS, Raadsen MP, et al. Phenotype and kinetics of SARS-CoV-2-specific T cells in COVID-19 patients with acute respiratory distress syndrome. *Science Immunology.* 2020;5(48):eabd2071. <http://dx.doi.org/10.1126/sciimmunol.abd2071>
  25. Peng Y, Mentzer AJ, Liu G, et al. Broad and strong memory CD4+ and CD8+ T cells induced by SARS-CoV-2 in UK convalescent individuals following COVID-19. *Nat Immunol.* 2020;21(11):1336-1345.
  26. Zhu F-C, Guan X-H, Li Y-H, et al. Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebo-controlled, phase 2 trial. *The Lancet.* 2020;396:479-488.
  27. Folegatti PM, Ewer KJ, Aley PK, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. *The Lancet.* 2020;396:467-478.
  28. Le Bert N, Tan AT, Kunasegaran K, et al. SARS-CoV-2-specific T cell immunity in cases of COVID-19 and SARS, and uninfected controls. *Nature.* 2020;584:457-462.
  29. Mateus J, Grifoni A, Tarke A, et al. Selective and cross-reactive SARS-CoV-2 T cell epitopes in unexposed humans. *Science.* 2020;370(6512):89-94.
  30. Sette A, Crotty S. Pre-existing immunity to SARS-CoV-2: the knowns and unknowns. *Nat Rev Immunol.* 2020;20:457-458.
  31. Braun J, Loyal L, Frentsch M, et al. SARS-CoV-2-reactive T cells in healthy donors and patients with COVID-19. *Nature.* 2020. <http://dx.doi.org/10.1038/s41586-020-2598-9>
  32. Mathew D, Giles JR, Baxter AE, et al. Deep immune profiling of COVID-19 patients reveals distinct immunotypes with therapeutic implications. *Science.* 2020;369(6508):eabc8511. <http://dx.doi.org/10.1126/science.abc8511>
  33. Kuri-Cervantes L, Pampena MB, Meng W, et al. Comprehensive mapping of immune perturbations associated with severe COVID-19. *Science Immunology.* 2020;5(49):eabd7114. <http://dx.doi.org/10.1126/sciimmunol.abd7114>
  34. Zheng H-Y, Zhang M, Yang C-X, et al. Elevated exhaustion levels and reduced functional diversity of T cells in peripheral blood may predict severe progression in COVID-19 patients. *Cell Mol Immunol.* 2020;17(5):541-543.
  35. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med.* 2020;8(4):420-422.
  36. Liao M, Liu Y, Yuan J, et al. Single-cell landscape of bronchoalveolar immune cells in patients with COVID-19. *Nat Med.* 2020;26(6):842-844.
  37. Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel Coronavirus–Infected pneumonia. *N Engl J Med.* 2020;382(13):1199-1207.
  38. Zhang J-J, Dong X, Cao Y-Y, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy.* 2020;75(7):1730-1741.
  39. Bunders MJ, Altfeld M. Implications of Sex Differences in Immunity for SARS-CoV-2 Pathogenesis and Design of Therapeutic Interventions. *Immunity.* 2020;53:487-495.
  40. Bupp MRG. Sex, the aging immune system, and chronic disease. *Cell Immunol.* 2015;294:102-110.
  41. Patel SK, Velkoska E, Burrell LM. Emerging markers in cardiovascular disease: Where does angiotensin-converting enzyme 2 fit in? *Clin Exp Pharmacol Physiol.* 2013;40:551-559.
  42. Ferrara JM, Abhyankar S, Gilliland D. Cytokine storm of graft-versus-host disease: a critical effector role for interleukin-1. Presented at Transplantation proceedings, 1993.
  43. Barry S, Johnson M, Janossy G. Cytopathology or immunopathology? The puzzle of cytomegalovirus pneumonitis revisited. *Bone Marrow Transplant.* 2000;26:591-597.
  44. Imashuku S. Clinical features and treatment strategies of Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis. *Crit Rev Oncol Hematol.* 2002;44:259-272.

45. Huang KJ, Su JJ, Theron M, et al. An interferon- $\gamma$ -related cytokine storm in SARS patients. *J Med Virol.* 2005;75:185-194.
46. Rubenfeld GD, Caldwell E, Peabody E, et al. Incidence and outcomes of acute lung injury. *N Engl J Med.* 2005;353:1685-1693.
47. Cameron MJ, Ran L, Xu L, et al. Interferon-mediated immunopathological events are associated with atypical innate and adaptive immune responses in patients with severe acute respiratory syndrome. *J Virol.* 2007;81:8692-8706.
48. Blanco-Melo D, Nilsson-Payant BE, Liu W-C, et al. Imbalanced host response to SARS-CoV-2 drives development of COVID-19. *Cell.* 2020;181(5):1036-1045.e9. <http://dx.doi.org/10.1016/j.cell.2020.04.026>
49. Moore JB, June CH. Cytokine release syndrome in severe COVID-19. *Science.* 2020;368(6490):473-474.
50. Arunachalam PS, Wimmers F, Mok CKP, et al. Systems biological assessment of immunity to mild versus severe COVID-19 infection in humans. *Science.* 2020;369(6508):1210-1220.
51. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020;395(10223):497-506.
52. Wan S, Yi Q, Fan S, et al. Relationships among lymphocyte subsets, cytokines, and the pulmonary inflammation index in coronavirus (COVID-19) infected patients. *Br J of Haematol.* 2020;189(3):428-437.
53. Lucas C, Wong P, Klein J, et al. Longitudinal analyses reveal immunological misfiring in severe COVID-19. *Nature.* 2020;584:463-469.
54. Laing AG, Lorenc A, del Molino del Barrio I, et al. A dynamic COVID-19 immune signature includes associations with poor prognosis. *Nat Med.* 2020;26(10):1623-1635.
55. Rodriguez L, Pekkarinen PT, Lakshminanth T, et al. Systems-level immunomonitoring from acute to recovery phase of severe COVID-19. *Cell Reports Medicine.* 2020;1(5):100078. <http://dx.doi.org/10.1016/j.xcrm.2020.100078>
56. Bordoni V, Sacchi A, Cimini E, et al. An inflammatory profile correlates with decreased frequency of cytotoxic cells in Coronavirus disease 2019. *Clin Infect Dis.* 2020. <http://dx.doi.org/10.1093/cid/ciaa577>
57. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood, The Journal of the American Society of Hematology.* 2014;124:188-195.
58. Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. *Biol Blood Marrow Transplant.* 2019;25:625-638.
59. Norelli M, Camisa B, Barbiera G, et al. Monocyte-derived IL-1 and IL-6 are differentially required for cytokine-release syndrome and neurotoxicity due to CAR T cells. *Nat Med.* 2018;24:739-748.
60. Barrett DM, Singh N, Hofmann TJ, Gershenson Z, Grupp SA. Interleukin 6 is not made by chimeric antigen receptor T cells and does not impact their function. *Blood.* 2016;128(22):654-654.
61. Lee DW, Kochenderfer JN, Stetler-Stevenson M, et al. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. *The Lancet.* 2015;385:517-528.
62. Schuster SJ, Svoboda J, Chong EA, et al. Chimeric antigen receptor T cells in refractory B-cell lymphomas. *N Engl J Med.* 2017;377:2545-2554.
63. Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: A single center experience. *J Med Virol.* 2020;92(7):814-818.
64. Zhang C, Wu Z, Li J-W, Zhao H, Wang G-Q. Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. *Int J Antimicrob Agents.* 2020;55(5). <http://dx.doi.org/10.1016/j.ijant.2020.105954>
65. Sciascia S, Aprà F, Baffa A, et al. Pilot prospective open, single-arm multicentre study on off-label use of tocilizumab in severe patients with COVID-19. *Clin Exp Rheumatol.* 2020;38(3):529-532.
66. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci.* 2020;117(20):10970-10975.
67. Alattar R, Ibrahim TBH, Shaar SH, et al. Tocilizumab for the treatment of severe coronavirus disease 2019. *J Med Virol.* 2020;92(10):2042-2049.
68. Price CC, Altice FL, Shyr Y, et al. Tocilizumab treatment for cytokine release syndrome in hospitalized patients with coronavirus disease 2019: survival and clinical outcomes. *Chest.* 2020;158:1397-1408.
69. Radbel J, Narayanan N, Bhatt PJ. Use of tocilizumab for COVID-19-induced cytokine release syndrome: A cautionary case report. *Chest.* 2020;158:e15-e19.
70. Ong EZ, Chan YFZ, Leong WY, et al. A dynamic immune response shapes COVID-19 progression. *Cell Host & Microbe.* 2020;27(6):879-882.e2.
71. Wen W, Su W, Tang H, et al. Immune cell profiling of COVID-19 patients in the recovery stage by single-cell sequencing. *Cell Discovery.* 2020;6(1). <http://dx.doi.org/10.1038/s41421-020-0168-9>
72. Bayry J, Thirion M, Misra N, et al. Mechanisms of action of intravenous immunoglobulin in autoimmune and inflammatory diseases. *Neurological Sciences.* 2003;24:s217-s221.
73. Hung IF, To KK, Lee C-K, et al. Hyperimmune IV immunoglobulin treatment: a multicenter double-blind randomized controlled trial for patients with severe 2009 influenza A (H1N1) infection. *Chest.* 2013;144:464-473.
74. Chong PY, Chui P, Ling AE, et al. Analysis of deaths during the severe acute respiratory syndrome (SARS) epidemic in Singapore: challenges in determining a SARS diagnosis. *Arch Pathol Lab Med.* 2004;128:195-204.
75. Villar J, Ferrando C, Martínez D, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. *Lancet Respir Med.* 2020;8(3):267-276.
76. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet.* 2020;395(10223):473-475.
77. Ma Y, Zeng H, Zhan Z, et al. Corticosteroid use in the treatment of COVID-19: A multicenter retrospective study in Hunan, China. *Frontiers in Pharmacology.* 2020;11. <http://dx.doi.org/10.3389/fphar.2020.01198>
78. National Health Commission of the People's Republic of China. The 7th trial version of Diagnosis and Treatment Scheme for Pneumonitis with 2019-nCoV Infection (In Chinese). <http://www.nhc.gov.cn/yzygj/s7653p/202003/46c9294a7dfe4cef80dc7f5912eb1989.shtml>
79. Zhao J, Hu Y, Du R, et al. Expert consensus on the use of corticosteroid in patients with 2019-nCoV pneumonia. *Zhonghua jie he*

- he hu xi za zhi= Zhonghua jiehe he huxi zazhi= Chinese journal of tuberculosis and respiratory diseases. 2020;43:E007.
80. Shang L, Zhao J, Hu Y, Du R, Cao B. On the use of corticosteroids for 2019-nCoV pneumonia. *Lancet*. 2020;395:683-684.
  81. Zhou W, Liu Y, Tian D, et al. Potential benefits of precise corticosteroids therapy for severe 2019-nCoV pneumonia. *Signal Transduct Target Ther*. 2020;5(1). <http://dx.doi.org/10.1038/s41392-020-0127-9>
  82. . Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report. *N Engl J Med*. 2020. <http://dx.doi.org/10.1056/nejmoa2021436>
  83. Tomazini BM, Maia IS, Cavalcanti AB, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: The CoDEX randomized clinical trial. *JAMA*. 2020;324:1307-1316.
  84. Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential therapy for COVID-19. *Lancet Infect Dis*. 2020;20:398-400.
  85. Geiler J, Michaelis M, Naczek P, et al. N-acetyl-L-cysteine (NAC) inhibits virus replication and expression of pro-inflammatory molecules in A549 cells infected with highly pathogenic H5N1 influenza A virus. *Biochem Pharmacol*. 2010;79:413-420.
  86. Ely JT. Ascorbic acid role in containment of the world avian flu pandemic. *Exp Biol Med*. 2007;232:847-851.
  87. Behrens EM, Kreiger PA, Cherian S, Cron RQ. Interleukin 1 receptor antagonist to treat cytophagic histiocytic panniculitis with secondary hemophagocytic lymphohistiocytosis. *J Rheumatol*. 2006;33:2081-2084.
  88. Matsumoto Y, Naniwa D, Banno S, Sugiura Y. The efficacy of therapeutic plasmapheresis for the treatment of fatal hemophagocytic syndrome: Two case reports. *Ther Apher*. 1998;2:300-304.
  89. Nakakura H, Ashida A, Matsumura H, et al. A case report of successful treatment with plasma exchange for hemophagocytic syndrome associated with severe systemic juvenile idiopathic arthritis in an infant girl. *Ther Apher Dial*. 2009;13:71-76.
  90. Padmanabhan A, Connelly-Smith L, Aqui N, et al. Guidelines on the use of therapeutic apheresis in clinical practice—evidence-based approach from the writing committee of the American society for apheresis: The eighth special issue. *J Clin Apheresis*. 2018;34:171-354.
  91. Marsh RA, Vaughn G, Kim M-O, et al. Reduced-intensity conditioning significantly improves survival of patients with hemophagocytic lymphohistiocytosis undergoing allogeneic hematopoietic cell transplantation. *Blood, J Am Soc Hematol*. 2010;116:5824-5831.
  92. Zhang B, Liu S, Tan T, et al. Treatment with convalescent plasma for critically ill patients with severe acute respiratory syndrome Coronavirus 2 infection. *Chest*. 2020;158(1):e9-e13.
  93. Shen C, Wang Z, Zhao F, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. *JAMA*. 2020;323:1582-1589.
  94. Leng Z, Zhu R, Hou W, et al. Transplantation of ACE2- mesenchymal stem cells improves the outcome of patients with COVID-19 pneumonia. *Aging and Disease*. 2020;11(2):216-228.
  95. Guo Z, Chen Y, Luo X, He X, Zhang Y, Wang J. Administration of umbilical cord mesenchymal stem cells in patients with severe COVID-19 pneumonia. *Crit Care*. 2020;24(1). <http://dx.doi.org/10.1186/s13054-020-03142-8>
  96. Yao X, Li T, He Z, et al. A pathological report of three COVID-19 cases by minimally invasive autopsies. *Zhonghua bing li xue za zhi= Chinese journal of pathology*. 2020;49:E009.
  97. Xu X, Chang X, Pan H, et al. Pathological changes of the spleen in ten patients with new coronavirus infection by minimally invasive autopsies. *Zhonghua Bing li xue za zhi= Chinese Journal of Pathology*. 2020;49:E014-E.
  98. Gong F, Dai Y, Zheng T, et al. Peripheral CD4+ T cell subsets and antibody response in COVID-19 convalescent individuals. *J Clin Investig*. 2020. <http://dx.doi.org/10.1172/jci141054>
  99. Perruccio K, Bonifazi P, Topini F, et al. Thymosin  $\alpha$ 1 to harness immunity to pathogens after haploidentical hematopoietic transplantation. *Ann N Y Acad Sci*. 2010;1194:153-161.
  100. Tuthill C, King R. Thymosin alpha 1—A peptide immune modulator with a broad range of clinical applications. *Clin Exp Pharmacol*. 2013;3:133.
  101. Luo X-H, Chang Y-J, Huang X-J. Improving cytomegalovirus-specific T cell reconstitution after haploidentical stem cell transplantation. *J Immunol Res*. 2014;2014:1-12. <http://dx.doi.org/10.1155/2014/631951>
  102. Zhao X-Y, Pei X-Y, Chang Y-J, et al. First-line therapy with donor-derived human cytomegalovirus (HCMV)-specific T cells reduces persistent HCMV infection by promoting antiviral immunity after allogeneic stem cell transplantation. *Clin Infect Dis*. 2020;70(7):1429-1437.
  103. Liu Z, Meng Q, Bartek J Jr, et al. Tumor-infiltrating lymphocytes (TILs) from patients with glioma. *Oncoimmunology*. 2017;6:e1252894.
  104. Meng Q, Liu Z, Rangelova E, et al. Expansion of tumor-reactive T cells from patients with pancreatic cancer. *J Immunother*. 2016;39:81-89.
  105. Barber DL, Wherry EJ, Masopust D, et al. Restoring function in exhausted CD8 T cells during chronic viral infection. *Nature*. 2006;439:682-687.
  106. Koralnik IJ. Can immune checkpoint inhibitors keep JC virus in check?. *N Eng J Med*. 2019;380(17):1667-1668.
  107. Luo J, Rizvi H, Egger JV, Preeshagul IR, Wolchok JD, Hellmann MD. Impact of PD-1 blockade on severity of COVID-19 in patients with lung cancers. *Cancer Discov*. 2020;10(8):1121-1128.
  108. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020;8(5):475-481.
  109. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062.

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