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REVIEW

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Lymphopenia an important immunological abnormality in patients with COVID-19: Possible mechanisms

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Abstract

The lymphopenia as a major immunological abnormality occurs in the majority of severe COVID-19 patients, which is strongly associated with mortality rate. A low proportion of lymphocytes may express the main receptor for SARS-CoV-2, called angiotensin-converting enzyme 2 (ACE2). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can also use ACE2-independent pathways to enter lymphocytes. Both SARS-CoV-2- and immune-mediated mechanisms may contribute to the occurrence of lymphopenia through influencing the lymphocyte production, survival or tissue re-distribution. The metabolic and biochemical changes can also affect the production and survival of lymphocytes in COVID-19 patients. Lymphopenia can cause general immunosuppression and promote cytokine storm, both of them play an important role in the viral persistence, viral replication, multi-organ failure and eventually death. Here, a comprehensive view concerning the possible mechanisms that may lead to the lymphocyte reduction in COVID-19 patients is provided, while highlighting the potential intervention approaches to prevent lymphopenia.

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as the cause of COVID-19 has several kinds of structural proteins, including spike (S), nucleocapsid (N), membrane (M) and envelope (E) molecules.[1] Like SARS-CoV, the SARS-CoV-2 needs angiotensin-converting enzyme 2 (ACE2) to enter human cells.[2] The SARS-CoV-2-linked S protein binds to ACE2 with stronger affinity (10- to 20-fold) than that of SARS-CoV,[1] which may be an explanation for the higher transmission speed of SARS-CoV-2. In addition to type 2 alveolar cells, the ACE2 expression has been indicated in various organs such as intestine, heart, liver, bladder, kidney, brain, thyroid and testis.[3,4]

Unpublished data by Zhang et al indicate that a small subset of blood leucocytes may also express ACE2 and can be infected by SARS-CoV-2.[5] Among immune cells, T lymphocytes perform a principal role in viral infections. The $CD4^+$ T lymphocytes provide help for B cells to produce anti-viral antibody, whereas $CD8^+$ T lymphocytes and natural killer (NK) cells kill virus-infected cells to decrease viral load.[6–8] The quantitative and functional disorders of lymphocytes can impair the immune responses against viruses and may lead to the development of immunopathologic responses.[9–11]

Lymphopenia as a major immunological abnormality is observed in up to 96.1% of severe COVID-19 patients, and its degrees correlate with disease outcome.[12] Zheng et al and unpublished data by Zhang et al indicate

Lymphocytopenia was associated with mortality, particularly in patients with low blood proportions of $CD3^+$ T, $CD4^+$ T and $CD8^+$ T cells.[9,13] The proportion of blood lymphocyte has demonstrated the most significant and reliable correlation with disease progression in patients who died due to COVID-19.[14] The percentage of blood lymphocytes can be considered as a valid and accurate indicator for classification of COVID-19 patients in moderate, severe and critical cases.[14] In this review, the possible mechanisms that could contribute to the lymphocyte reduction in COVID-19 patients are explained. Understanding of the mechanisms which are responsible for the reduction of lymphocyte is essential to design effective strategies to control lymphopenia in COVID-19 patients.

2 | ALTERATION IN THE TOTAL AND DIFFERENTIAL BLOOD COUNTS OF LYMPHOCYTES IN COVID-19

Severe COVID-19 patients display a lower blood count of lymphocytes and greater neutrophil/lymphocyte ratio.[12] The blood numbers of T cells, including $CD4^+$ Th- and $CD8^+$ T cells, were reduced in patients with COVID-19, and blood numbers of $CD4^+$ Th cell and $CD8^+$ cells were decreased further in severe patients.[9,12] Moreover, the blood count of naïve Th cells increases, while the count of memory T cells decreases in severe COVID-19 patients.[12]

Table 1 summarizes the total blood number of lymphocytes in COVID-19 patients according to their disease forms. With few exceptions, the absolute counts of blood lymphocytes in severe COVID-19 patients were significantly lower compared with mild/moderate patients. According to the results summarized in Table 2, the lymphopenia frequency was reported in 0.6%-80.4% of patients with mild/moderate COVID-19 and in 32.7%-96.1% of severe COVID-19 patients. In the majority of studies, the lymphopenia frequency was significantly higher in severe COVID-19 patients in comparison with mild/moderate cases.

Table 3 summarizes the absolute blood number of total $CD3^+$ T lymphocytes in COVID-19 patients according to their disease forms. With few exceptions, severe COVID-19 patients exhibit significantly lower blood counts of total $CD3^+$ T lymphocytes than those in mild/moderate patients. Tables 4 and 5 summarize the absolute blood numbers of $CD4^+$ T- and $CD8^+$ T lymphocytes in COVID-19 patients. With very few exceptions, the blood counts of $CD4^+$ T- and $CD8^+$ T lymphocytes in severe COVID-19 patients were also significantly lower in comparison with mild/moderate patients.

The blood number of B lymphocyte maybe also diminished in COVID-19 patients.[66] Concerning the B cells, some studies reported significantly lower blood number of B lymphocytes in severe COVID-19 patients compared to mild/moderate patients, while others did not measure significant differences between different forms of disease regarding the blood number of B cells (Table 6).

Table 7 summarizes the absolute blood number of NK cells in COVID-19 patients. With few exceptions, the blood count of NK cells in severe COVID-19 patients was significantly lower compared with mild/moderate patterns of disease. COVID-19 patients also exhibit the enhanced expression of NKG2A (an inhibitory molecule) on their NK- and $CD8^+$ T cells, indicating functional exhaustion of NK- and $CD8^+$ T cells.[67] In COVID-19 patients, the proportions of the NK- and $CD8^+$ T cells expressing CD107a, IFN-γ and IL-2 are also reduced, confirming the exhaustion of cytotoxic lymphocytes.[9]

Deng et al evaluated dynamic alterations in the blood count of lymphocytes of COVID-19 patients. In recovered patients, the blood numbers of $CD3^+$ T-, $CD4^+$ T-, $CD8^+$ T-, $CD19^+$ B- and $CD56^+$ NK cells were below the normal levels in the first week after the disease onset, reaching to the minimal levels in the second week, then increasing slowly in the third week and returning to normal levels in the fifth week.[68]

3 | POSSIBLE MECHANISMS CAUSE LYMPHOCYTE REDUCTION IN COVID-19

Multiple mechanisms mentioned here may act together and overlap in some cases to cause lymphopenia in COVID patients. However, further in vitro and in vivo research needs to be performed to determine the importance of each part in the occurrence of lymphopenia.

3.1 | SARS-COV-2-induced apoptosis of lymphocytes

Both MERS-CoV and SARS-CoV directly infect human primary T cells and induce massive apoptosis and lymphopenia, while the viral expansion in these cells is abortive.[70–72] The MHV-3, a murine coronavirus, also infects and destroys lymphocytes, thus facilitating viral replication and persistence.[73]

The unpublished data by Chen et al indicate the lack of ACE2 expression by human lymphocytes,[74] whereas Xu et al reported that a small proportion of lymphocytes (<5.0%) originated from oral mucosa can express ACE2.[75] The unpublished data by Biegler et al and Wang et al indicate that SARS-CoV-2 can use other receptors such as CD147 for

TABLE 1 Blood count of total lymphocytes in patients with COVID-19 according to their disease form

Country/ Region	Lymphocyte count in all patients ($\times 10^9$/L)*	Lymphocyte count in mild COVID-19 ($\times 10^9$/L)*	Lymphocyte count in moderate COVID-19 ($\times 10^9$/L)*	Lymphocyte count in severe COVID-19 ($\times 10^9$/L)*	*P* value	Ref.
China/ Wuhan	1.37 (0.32-2.33)	1.487 (0.57-2.33)	—	.9333 (.32-1.76)	.0001	9
China/ Wuhan	2.99 (2.36-4.17)	2.92 (2.53-3.43)	3.04 (2.18-4.86)	—	.56	15
China/ Beijing	—	1.76756 ± 0.588	1.2024 ± 0.4837	.8615 ± .465	.001	16
China	1.03 (0.7-1.45)	—	1.13 (0.79-1.53)	.78 (.52-1.08)	.0001	17
China/ Chongqing	1.1 (0.7-1.5)	1.2 (0.8-1.6)	—	.8 (.6-1.0)	.0001	18
China/ Beijing	1.31 (0.88-1.61)	1.54 (1.17-1.82)	—	.775 (.4925-1.0425)	.0001	19
China/ Wuhan	0.9 (0.7-1.3)	1.1 (0.8-1.4)	—	.6 (.6-.8)	Not mentioned	20
China/ Anhui	—	1.07 ± 0.40†	—	1.20 ± .42†	.309	21
China/ Wuhan	—	1.55 ± 0.75†	—	.68 ± .60†	.01	22
China/ Ningbo	1.35 (0.98-1.66)	1.4 (1.05-1.75)	—	.9 (.7-1.3)	Not mentioned	23
China/ Wuhan	1.0 (0.6-1.4)	1.2 (0.9-1.8)	—	.8 (.5-1.0)	.001	24
China/ Chongqing	—	1.3 (0.7-1.5)	—	.9 (.6-1.1)	.0001	25
China/ Wuhan****	—	1.25 (0.90-1.59)	—	.82 (.59-1.01)	.001	26
China/ Nanchang	—	1.21 (0.99 - 1.6)	—	.45 (.3 - .75)	.001	27
China/ Zhejiang	2.4 ± 0.8†	2.8 ± 1.0†	2.0 ± 0.7†	—	.0083	28
China/ Wuhan	0.9 ± 0.4†	—	1.1 ± 0.3†	.7 ± .3†	.048	29
China/ Wuhan	0.835 (0.608-1.13)	—	0.96 (0.635-1.35)	.91 (.67-1.12)	.012	30
China/ Wuhan	0.8 (0.6-1.2)	—	—	—	Not mentioned	31
China/ Wuhan	0.9 (0.6-1.2)	1.0 (0.7-1.3)		0.8 (0.6-1.1)	.001	12
Singapore	1.2 (0.8-1.6)	1.3 (0.9-1.7)		0.5 (0.48-0.8)	.0002	32
China/ Wuhan	0.8 (0.6-1.1)	0.8 (0.6-1.2)		0.7 (0.5-1.0)	.048	33
China/ Wuhan	1 (0.7-1.3)	1 (0.8-1.4)		0.8 (0.6-1)	Not mentioned	34
China/ Wuhan	0.8 (0.6-1.1)	1.0 (0.7-1.1)		0.4 (0.2-0.8)	.0041	35
China/ Wuhan	0.98 (0.61-1.35)	1.00 (0.68-1.39)		0.53 (0.30-1.15)	.075	36
China/ Wuhan	0.8 (0.6-1.1)	0.9 (0.6-1.2)		0.8 (0.5-0.9)	.03	37
Iran/Shiraz	1.16 ± 0.66†	1.14 ± 0.66†		1.37 ± 0.62†	.386	38
China/ Wuhan	1.15 (0.82-1.46)	1.19 (0.95-1.46)		0.61 (0.37-1.00)	.002	39
China/ Chengdu	1.81 ±1.26†	1.64 ± 1.12†		2.19 ± 1.44†	.05	40
China/ Wuhan	0.8 (0.6-1.1)	—		0.7 (0.4-0.9)	.001	41#
China/ Shenzhen	1.2 (0.9-1.7)	1.3 (1.0-1.8)		0.97 (0.65-1.19)	.001	42
China/ Chongqing	1.1 (0.7-1.6)	1.3 (0.9-1.7)		0.37 (0.3-0.6)	.001	43#
China/ Wuhan	0.9 (0.5-1.2)	1.0 (0.8-1.4)		0.7 (0.4-1.1)	.001	35
Italy	0.94 (0.69-1.28)	0.98 (0.83-0.123)		0.85 (0.62-0.13)	.065	44
China/ Wuhan	0.8 (0.6-1.1)	0.8 (0.6-1.1)		0.7 (0.5-0.8)	.046	45
China/ Wuhan	—	1.08 (0.72-1.45)		0.67 (0.49-0.99)	.004	46
China/ Huizhou	—	1.01 ± 0.45†		1.16 ± 0.55†	.593	47
China/ Wuhan	0.9 (0.6-1.3)	1 (0.8-1.4)		0.6 (0.4-0.9)	.001	48

(Continues)

TABLE 1 (Continued)

Country/ Region	Lymphocyte count in all patients ($\times 10^9$/L)*	Lymphocyte count in mild COVID-19 ($\times 10^9$/L)*	Lymphocyte count in moderate COVID-19 ($\times 10^9$/L)*	Lymphocyte count in severe COVID-19 ($\times 10^9$/L)*	*P* value	Ref.
China/ Wuhan	—	1.21 ± 0.53		0.60 ± 0.31	.001	49#
China/ Beijing	1.0 (0.8-1.4)	1.1 (0.9-1.4)		0.9 (0.7-1.1)	.038	50#
China/ Shanghai	1.15 (0.78-1.15)	1.23 (0.86-1.565)		0.76 (0.53-0.94)	.001	51#
China/ Beijing	—	1.53 (1.28-2.02)		0.81 (0.50-1.11)	.001	52
Spain/ Ciudad Real	—	0.97 ± 0.53†		0.73 ± 0.47†	Not mentioned	53
China/ Wuhan	—	1.36 (0.95 - 1.61)		1.10 (0.65 −1.46)	.007	54
China/ Wuhan	0.73 (0.56-1.07)	—		—	Not mentioned	55
China/ Wuhan	0.9 ±0.5†	—		—	Not mentioned	56
USA/ Washington state	0.72 (0.52-1.375)	—		—	not mentioned	57
Netherlands/Dordrecht	1.0 (0.9-1.1)	1.1 (0.9-1.2)		0.9 (0.8-1.1)	.17	58
China/ Wuhan	0.90 (0.59-1.29)	0.97 (0.68-1.37)**		0.57 (0.39-0.84)***	.001	59
China/ Wuhan	1.0 (0.6-1.3)	1.1 (0.8-1.5)**		0.6 (0.5-0.8)***	.0001	60
China/ Shanghai	1.0 (0.6-1.4)	1.2 (0.7-1.6)**		0.7 (0.3-0.7)***	.001	61

*Normal range of total lymphocyte count was considered as: 1.1-3.2 × 10^9/L.

**The results from patients with survival outcome.

***The results from patients with dead outcome.

****Total lymphocyte count of critically patients was 0.52 (0.37- 0.88) × 10^9/L.

†Total lymphocyte count expressed as Mean ± Standard deviation.

#Unpublished data.

entrance into T cells.[76,77] Accordingly, lymphocytes can be infected by SARS-CoV-2 via ACE2-dependent and ACE2-independent routes.

Higher expression of p53, a key pro-apoptosis gene, was measured in PBMCs collected from COVID-19 patients, suggesting that lymphopenia may be partly due to apoptosis.[78] Future in vitro experiments will shed light on the possibility of the direct SARS-CoV-2-induced apoptosis in lymphocytes.

3.2 | SARS-COV-2-induced pyroptosis of lymphocytes

The activation of caspase-1 as an effector element of inflammasome promotes IL-1β production and induces pyroptosis.[79] It was reported that SARS-CoV-related Viroporin 3a activates the NLRP3 inflammasome and induces the secretion of IL-1β, which indicate that the SARS-CoV infection can cause cell pyroptosis.[80] The Viroporin 3a has also been identified on the genome of SARS-CoV-2, which represents that SARS-CoV-2 may cause NLRP3 inflammasome activation.[81] SARS-CoV-2 can induce pyroptosis, particularly in lymphocytes, via the induction of NLRP3 inflammasome.[82] Elevated serum levels IL-1β in COVID-19 patients also indicate the occurrence of pyroptosis, because IL-1β release is a downstream process of cell pyroptosis.[35,82]

3.3 | SARS-COV-2-mediated bone marrow impairment

High expression of CXCL10 (IP-10) and CCL2 (MCP-1) was observed in patients with SARS-CoV infection.[83,84] CXCL10 and CCL2 can suppress the development of haematopoietic precursor cells[85,86] which may contribute to the SARS-associated lymphopenia.[83] Similarly, elevated levels of CXCL10 and CCL2 have also been measured in COVID-19 patients, in particular in severe cases requiring ICU facilities,[35,87] that may provide justification for lymphopenia in SARS-CoV-2-infected patients. If the role of chemokines in lymphopenia is proved, then the targeting of chemokines or their receptors using blocking monoclonal antibodies, small molecule antagonists and small interfering RNA (siRNA) can prevent lymphopenia.[88]

Elevated quantities of IL-6, a powerful proinflammatory cytokine, were measured in COVID-19 patients, and there was

TABLE 2 The frequency of blood lymphopenia in patients with COVID-19 according to their disease form

Country/Region	All patients	Mild COVID-19	Moderate COVID-19	Severe COVID-19	Lymphopenia cutoff	*P* value	Ref.
China	47.3%	—	38.6%		72.2%	.0001	17
China/ Chongqing	—	38.0%	—	80.0%	$<1.1 \times 10^9$/L	.2938	18
China/ Wuhan	—	44.4%	—	84.6%	$<1 \times 10^9$/L	Not mentioned	20
China/ Chongqing	—	40.0%	—	86.0%	$<1.1 \times 10^9$/L	.3104	25
China/ Zhejiang	31.0%	11.7%	47.0%	—	—	.0083	28
China/ Wuhan	42.9%	—	10.0%	72.2%	$<0.8 \times 10^9$/L	.008	29
China/ Wuhan	72.73%	—	63.27%	73.77%	$<1.1 \times 10^9$/L	.13	30
China/ Wuhan	75.4%	70.7%		82.1%	$<1.1 \times 10^9$/L	.160	33
China/ Wuhan	—	80.4%		96.1%	$<1.5 \times 10^9$/L	Not mentioned	34
China/ Wuhan	—	54.0%		85.0%	$<1 \times 10^9$/L	.045	35
Iran/ shiraz	12.6%	9.8%		36.4%	$<1.5 \times 10^9$/L	.030	38
China/ Shanghai	8.9%	0.6%		84.2%	Not mentioned	Not mentioned	51[#]
China/ Shenzhen	38.9%	31.9%		67.2%	Not mentioned	<.001	42
China/ Wuhan	42%	32%		79%	$<1.1 \times 10^9$/L	.002	39
China/ Wuhan	56.2%	56.6%		54.5%	$0.5\text{-}1.1 \times 10^9$/L*	.788	41
	17.6%	12.7%		32.7%	$<0.5 \times 10^9$/L**	.001	
Singapore	—	28.6%		33.3%	$0.5\text{-}1.1 \times 10^9$/L*	.0001	32
	—	1.8%		44.4%	$<0.5 \times 10^9$/L**	.0001	
Netherlands/ Dordrecht	—	82.0%		85.0%	$<1.5 \times 10^9$/L	.65	58
	—	55.0%		67.0%	$<1 \times 10^9$/L	.19	
Spain/Ciudad Real	—	54.9		81.5	$<1 \times 10^9$/L	.01	53
China/ Wuhan	—	72.2		90.5	$<1.1 \times 10^9$/L	.089	45
China/ Ningbo	30.77%	—		—	$<1 \times 10^9$/L	Not mentioned	23
China/ Wuhan	70.3%	—		—	$<1.1 \times 10^9$/L	.03	62
China/ Chongqing	51.0%	—		—	Not mentioned	<.001	43
China/ Wuhan	72.0%	—		—	$<1.1 \times 10^9$/L	Not mentioned	31
USA/ Washington state	75.0%	—		—	$<1.5 \times 10^9$/L	Not mentioned	57
China/Wuhan	35.0%	—		—	Not mentioned	Not mentioned	56
China/Anhui	85.0%	—		—	Not mentioned	Not mentioned	63
China/ Wuhan	40%	26%***		76%****	$<0.8 \times 10^9$/L	<.0001	60

*Patients with moderate lymphopenia

**Patients with severe lymphopenia

***The results from patients with survival outcome.

****The results from patients with dead outcome.

[#]Unpublished data.

a powerful association between IL-6 quantities and disease severity.[89,90] Using various mouse models, it has been indicated that IL-6 suppresses lymphopoiesis via direct effects on haematopoietic stem/progenitor cells.[91,92] There was an inverse association between serum IL-6 concentrations and absolute blood count of lymphocytes in COVID-19 patients.[93] The absolute blood number of lymphocytes increased within the 24 hours following treatment with Tocilizumab, a monoclonal antibody against IL-6R.[93] The results from another clinical trial indicate that the Tocilizumab administration to COVID-19 patients improves the blood number of lymphocytes and the levels of C-reactive protein.[94] Accordingly, the blocking of IL-6 may have the capacity to attenuate the lymphocyte reduction in COVID-19 patients.

It should be also mentioned that the normal human bone marrow tissue expresses very small levels of ACE2.[3] There is evidence that the receptor of SARS-CoV-2, ACE2, is expressed on the membrane of haematopoietic stem cells

TABLE 3 The blood count of total $CD3^+$ T lymphocytes in patients with COVID-19 according to their disease form

Country/Region	$CD3^+$ T cell count in all patients (Cell/μL)	$CD3^+$ T cell count in mild COVID-19 (Cell/μL)	$CD3^+$ T cell count in moderate COVID-19 (Cell/μL)	$CD3^+$ T cell count in severe COVID-19 (Cell/μL)	*P* value	Ref.
China/ Wuhan	2419 (1869-3059)	2249 (1777-2711)	2525 (1887-3614)	—	.10	15
China/ Beijing	—	1210.75 ± 408.81†	808.97 ± 371.22†	522.57 ± 318.73†	.000	16
China/ Wuhan*	—	894.50 (662.75- 1192.00)	—	593.00 (412.00 - 725.00)	.001	26
China/ Wuhan	700 (400-1000)	900 (600-1300)	—	500 (300-700)	.001	24
China/ Wuhan	437.5 (308.75-648.25)	—	509 (336.5-873.5)	517 (376-651.5)	.001	30
China	712 (482-1.036)	—	764 (513-1.069)	538 (277-860)	.0001	17
China/ Wuhan	541.5 ± 292.7†	663.8 ± 291.3†		461.6 ± 264.7†	.027	12
China/ Wuhan	—	633 (467-846)		446.50 (231.00- 633.75)	.07	46
China/ Beijing	—	991 (740-1154)		378 (258-576)	.001	52
China/ Nanchang	—	641.5 (410.75-980)		209 (131-285)	.0001	64
China/ Wuhan	—	914.0 (468.0-1214.0)		343.5 (237.0-730.3)	.004	55
Spain/Ciudad Real	—	701.0 ± 408.5†		528.3 ± 350.9†	.018	53
China/ Wuhan	—	76.46 (65.74- 81.69)		75.94 (65.40- 83.51)	.4308	54
China/ Shanghai	556.9 (206.3-880.3)	1073.3 (842.0-1499.3)**		322.2 (125.0-471.3)***	.001	62

*The count of $CD3^+$ T lymphocytes in critical COVID-19 patient was 287.50 (240.50-528.50)/μL.

**The results from patients with survival outcome.

***The results from patients with dead outcome.

†The count of $CD3^+$ T lymphocytes expressed as Mean ± Standard deviation.

(HSCs).[95–97] It has been postulated that SARS-CoV-2 may directly infect the pool of HSCs and cause pyroptosis in these cells.[97] Therefore, the possible infection of bone marrow precursor cells by SARS-CoV-2 can contribute to the reduction of lymphocyte production.

3.4 | SARS-COV-2-mediated thymus suppression

Several thymic alterations, such as thymus atrophy, decreased weight and cellularity of the thymus, and depletion of $CD4^+CD8^+$ thymocytes were indicated in mouse models of coronavirus infection.[98,99] Thymus suppression-associated lymphopenia has also been proposed in SARS-CoV infection.[100]

Although the ratio of naïve Th cells to memory T cells is increased in severe COVID-19 patients, the direct infection of primary lymphoid organs, especially thymus (as the site of T cell maturation), cannot be ignored in COVID-19 patients.[12] In certain lymphoid organs, such as the spleen, lymphocyte loss, cell degeneration and necrosis were observed during SARS-CoV-2 infection.[69] However, the occurrence of thymus suppression in COVID-19 needs to be evaluated in future research. As noted above, the serum quantities of IL-6 were increased in COVID-19 patients.[89,90] Using an animal model, the inhibitory effects of IL-6 on the $CD4^+$ $CD8^+$ thymocytes (double-positive thymocytes) were indicated.[101] There was an inverse association between serum IL-6 quantities and the double-positive thymocytes and the blood number of lymphocytes in elderly people.[102] Therefore, it seems that IL-6 may partly play a role in lymphopenia observed in COVID-19 patients.

3.5 | Cytokine storm-induced apoptosis of lymphocytes

Cytokine storm resulting from the secretion of the excessive quantities of proinflammatory cytokines and chemokines, which carry out a crucial role in the appearance of some SARS-CoV-2-related complications, in particular acute respiratory distress syndrome (ARDS).[103] In addition to IL-6, TNF-α is another key cytokine of the cytokine storm associated with COVID-19 severity.[104] A negative correlation has been indicated between serum TNF-α quantities

TABLE 4 The blood count of $CD4^+$ T lymphocytes in patients with COVID-19 according to their disease form

Country/Region	$CD4^+$ T cell count in all patients (Cell/μL)	$CD4^+$ T cell count in mild COVID-19 (Cell/μL)	$CD4^+$ T cell count in moderate COVID-19 (Cell/μL)	$CD4^+$ T cell count in severe COVID-19 (Cell/μL)	*P* value	Ref.
China/ Wuhan	491.39 (108.47-1040)	509.8 (108.47-1040)	—	413.3 (140-885.63)	.3145	9
China/ Wuhan	1144 (848-1727)	1117 (834-1492)	1237 (892-1900)	—	.14	15
China/ Wuhan	276 (178-402.25)	—	290 (172.5-506)	292 (237.5-399.5)	.005	30
China	418 (273-636)	—	449 (312-659)	327 (160-587)	.0001	17
China/ Beijing	—	689.38 ± 251.29†	436.8 ± 225.08†	257.86 ± 129.48†	.000	16
China/ Chongqing	—	451.3 ± 23.0†	—	263.2 ± 28.83†	.0005	25
China/Wuhan*	—	573.50 (426.75-771.00)	—	299 (249- 460]	.001	26
China/ Nanchang	—	462 (239-636)	—	125 (60-107)	.001	27
Wuhan/ china	400 (200-600)	500 (300-800)	—	200 (100-400)	.001	24
China/ Wuhan	—	371 (283-572)		234.0 (136.75-398.0)	.25	46
China/ Beijing	—	544 (364-667)		199 (128-325)	<.001	52
China/ Wuhan	—	591.0 (266.0-718.5)		217.5 (112.8-324.5)	.006	55
Spain/Ciudad Real	—	395.9 ± 241.0†		340.30 ± 251.9†	Not mentioned	53
China/ Chengdu	471.65 ± 355.85†	553.25 ± 377.81†		273.92 ± 185.21†	.001	40
Italy	393 (209.5-650.5)	461 (275-654)		348 (206-616)	.0062	44
China/ Wuhan	114.3 (62.9-195.3)	128.3 (73.5-201.7)		68.0 (55.1-148.8)	.066	45
Netherlands/Dordrecht	581 (486-696)	532 (442-640)		666 (481-912)	.54	58
China/ Nanchang	—	387.5 (251-542.75)		125 (88-178)	.0001	64
China/ Wuhan	—	46.31 (38.92, 51.53)		43.68 (35.38, 55.33)	.7632	54
China/ Wuhan	1469 ± 872	—		—	.271	65
China/ Wuhan	314 (190-484)	349 (217-516)**		191 (107-282)***	<.001	59
China/ Shanghai	369.8 (107.3-587.0)	707.5 (505.0-924.5)**		216.4 (85.3-239.3)***	<.001	61

*The count of $CD4^+$ T lymphocytes in critical COVID-19 patient was 287.50 (240.50- 528.50)/μL.

**The results from patients with survival outcome.

***The results from patients with dead outcome.

†The count of $CD4^+$ T lymphocytes expressed as Mean ± Standard deviation.

TABLE 5 The blood count of $CD8^+$ T lymphocytes in patients with COVID-19 according to their disease form

Country/Region	$CD8^+$ T cell count in all patients (Cell/μL)	$CD8^+$ T cell count in mild COVID-19 (Cell/μL)	$CD8^+$ T cell count in moderate COVID-19 (Cell/μL)	$CD8^+$ T cell count in severe COVID-19 (Cell/μL)	*P* value	Ref.
China/ Wuhan	973 (707-1249)	963 (674-1181)	1014 (710-1281)	—	.30	15
China/ Chongqing	—	288.6 ± 14.23†	—	179 ± 23.87†	.0013	25
China/ Beijing	—	462.88 ± 154.43†	355.33 ± 166.86†	205.14 ± 153.09†	.004	16
China/ Wuhan	146.5 (89.75-257.25)	—	161 (101-302.5)	200 (93-261)	.001	30
China	247 (155-388)	—	266 (165-414)	179 (106-286)	.0001	17
China/ Nanchang	—	267 (210-405)	—	65 (33-112)	.001	27
Wuhan/ china	200 (100-400)	300 (200-500)	—	200 (100-300)	.001	24
China/ Wuhan*	—	323.5 (232.75-448.75)	—	188.0 (134.0 −274.0)	.001	26
China/ Wuhan	—	241.0 (159.00-323.0)		157.5 (76.0- 289.5)	.05	46
China/ Beijing	—	417 (309-539)		134 (91-237)	.001	52
China/ Wuhan	—	288.0 (165.0-414.5)		122.5(76.0-256.8)	.011	55
Spain/ Ciudad Real	—	287.6 ± 223.8†		172.4 ± 123.9†	.001	53
China/ Wuhan	—	20.53 (15.78-25.37)		24.19 (18.40-33.15)	.03	54
China/ Chengdu	306.24 ± 238.28†	349.13 ± 256.50†		202.31 ± 144.31	.05	40
Italy	162 (90.5-249)	184 (132-334)		100 (83-198)	.006	44
China/ Wuhan	75.5 (45.5-125.0)	104.5 (58.5-142.7)		47.9 (25.4-73.8)	.001	45
Netherlands/ Dordrecht	81 (64-101)	96 (68-128)		67 (47-93)	.06	58
China/ Nanchang	—	211.5 (115-356.25)		52 (37-98)	.0001	64
China/ Wuhan	179 (85-286)	204 (97-298)**		73 (42-160)***	.001	59
China/ Shanghai	168.5 (53.3-265.0)	327.6 (256.3-365.8)**		96.2 (32.5-131.5)***	.001	61

*The count of $CD8^+$ T lymphocytes in critical COVID-19 patient was 92.50 (70.75 - 141.50)/μL.

**The results from patients with survival outcome.

***The results from patients with dead outcome.

†The count of $CD8^+$ T lymphocytes expressed as Mean ± Standard deviation.

and the blood number of lymphocytes in COVID-19 patients.[105] The results from an in vitro experiment indicate that TNF-α can induce apoptosis in human T lymphocytes mainly through binding to TNF-RI.[106] Furthermore, TNF-α-induced T cell apoptosis can directly diminish the T cell count in the SARS-CoV infection.[107] It has been proposed that the TNF-α produced by infected macrophages causes apoptosis in T lymphocytes of COVID-19 patients.[108] Moreover, the serum levels of soluble IL-2R were positively related to the levels of IL-6, TNF-α, IL-8 and IL-10 and inversely associated with blood count of lymphocyte in COVID-19 patients.[109] The ratio of IL-2R to lymphocytes was markedly higher in critical and severe COVID-19 patients in comparison with mild patients.[109] Perhaps, the raised levels of soluble IL-2R in COVID-19 limit the accessibility of lymphocytes to their survival and growth factors.

3.6 | Tissue re-distribution of lymphocytes

The reduction of the blood T lymphocytes, including both $CD4^+$ T and $CD8^+$ T subsets were reported in acute SARS-CoV infection.[110,111] Based on the rapid clinically restoration of blood lymphocytes in recovering SARS patients, lymphocyte sequestration in target organs such as the lungs and gastrointestinal tract has been hypothetically suggested as a reason for the reduction of blood lymphocytes.[111] It has been assumed that the rapid increase in blood count of lymphocytes during recovery is not due to newly produced lymphocytes by the thymus, but is likely due to lymphocyte recirculation between organs and peripheral blood.[111,112]

In COVID-19, various kinds of leucocytes, such as monocytes, lymphocytes, eosinophils and neutrophils, infiltrate the alveoli at various degrees.[69] Most of the infiltrated lymphocytes are $CD4^+$ T cells.[69] As a consequence, the sequestration

TABLE 6 The blood count of B lymphocytes in patients with COVID-19 according to their disease form

Country/Region	B cell count in all patients (Cell/μL)	B cell count in mild COVID-19 (Cell/μL)	B cell count in moderate COVID-19 (Cell/μL)	B cell count in severe COVID-19 (Cell/μL)	*P* value	Ref.
China/ Wuhan	157.451 (39-356)	158.4 (66-356)	—	114.6 (39-270.71)	.1119	9
China/ Beijing	—	330.71 ± 177.65[†]	148.92 ± 89.33[†]	128.83 ± 42.44[†]	.001	16
China/ Wuhan	635 (401-1021)	564 (420-710)	764 (389-1201)	—	.13	15
China/ Wuhan	119.5 (77.75-178.75)	—	114 (62.5-197)	131 (95.5-194.5)	not significant	30
China/ Chongqing	—	166 ± 11.98[†]	—	125.3 ± 13.49[†]	.137	69
China/ Wuhan[*]	—	213.5 (152.25-314.25)	—	97.0 (74.00 - 162.0)	.001	26
Wuhan/ china	100 (100-200)	100 (100-200)	—	100 (50-100)	.082	24
China/ Wuhan	20.5 ± 10.9[†]	196.1 ± 144.9[†]		169.0 ± 140.9[†]	.559	12
Netherlands/ Dordrecht	143 (119-174)	121 (93-156)		170 (129-217)	.85	58
China/ Beijing	—	163 (126-224)		92 (56-135)	.001	52
China/ Wuhan	—	174.0 (69.5-306.5)		105.0 (55.8-235.5)	.360	55
China/ Nanchang	—	133 (76-182)		83 (57-123)	.029	64
China/ Shanghai	115.4 (41.5-150.3)	114.1 (49.8-167.5)[**]		116.0 (36.8-146.8)[***]	.958	61

*The count of B lymphocytes in critical COVID-19 patient was 73.00 (36.50 - 101.75) cell/μL.

**The results from patients with survival outcome.

***The results from patients with dead outcome.

[†]The count of B lymphocytes expressed as Mean ± Standard deviation.

of lymphocytes in the lungs and perhaps other infected organs may be responsible for a part of the lymphopenia in COVID-19 patients.

3.7 | Activation-induced cell death (AICD) of lymphocytes

AICD leads to T cell contraction by enhancing apoptosis in previously stimulated T lymphocytes when they are re-activated via T cell receptor (TCR).[113] Repeated TCR engagement renders T lymphocytes susceptible to AICD, which is mediated through the interaction of Fas expressed on stimulated T cells with FasL.[113] During HIV infection, the overproduction of Th2 cell-related cytokines (such as IL-4 and IL-10) increases the susceptibility of T lymphocytes to AICD, whereas Th1 cell-linked cytokines (such as IL-12 and IFN-γ) can be protective.[114] The results from an in vitro experiment have indicated the TNF-α-mediated AICD in $CD8^+$ T lymphocytes following stimulation with a mixture of viral peptides.[115]

The extended antigenic stimulation of T cells with viral antigens may cause AICD, which is mediated by interaction of Fas and FasL.[116] AICD reduces the clonal expansion, diminishes the immune responses, decreases the effective clonal proliferation and impairs the development of immunological memory.[113] Indeed, a lower proportion of memory T cells and a greater ratio of naïve T cells to memory T cells were measured in severe forms of COVID-19.[12] An inverse relation has also been observed between the Fas expression and the blood count of $CD4^+$ T lymphocytes.[117] Higher expression of Fas in $CD4^+$ T and $CD8^+$ T lymphocytes was related to lower frequency of naive T cells.[117] It was suggested the raised Fas expression can render T cells to apoptosis during COVID-19.[117] The unpublished data by Chen et al using immunohistochemistry examinations indicated that the Fas expression is markedly increased in SARS-CoV-2-infected spleens and lymph nodes, whereas Fas expression is not detected in normal biopsies.[74] These observations suggest that a portion of lymphopenia may be due to AICD. AICD is efficiently blocked by suppressing the Fas-FasL interaction.[113]

3.8 | Autophagy-mediated death of lymphocytes

Autophagy has been considered as a powerful anti-viral tool of host cells.[118] During autophagy, the viruses are trapped in vesicles called autophagosomes, and these viral cargos are then rendered to the lysosomes for degradation.[118] Several types of viruses, such as coronaviruses (including SARS-CoV and MHV-3), can trigger autophagy.[118–120] However, some viruses, especially RNA viruses, have been equipped with

TABLE 7 The count of blood natural killer (NK) cells in patients with COVID-19 according to their disease form

Country/ Region	NK cell count in all patients (Cell/ μL)	NK cell count in mild COVID-19 (Cell/μL)	NK cell count in moderate COVID-19 (Cell/μL)	NK cell count in severe COVID-19 (Cell/μL)	*P* value	Ref.
China/ Wuhan	374 (212-509)	316 (160-477)	390 (270-543)		.048	9
China/ Beijing		288 ± 175.93†	203.63 ± 209.433†	185.00 ± 8.11†	.310	16
China/ Wuhan	109 (64.75-170)		118 (76.5-184)	99 (54.5-160)	Not significant	30
China/ Chongqing		147 ± 10.36†		119.6 ± 16.5†	.258	25
China/ Wuhan*		107.50 (82.75-149.75)		93.0 (6.0- 161.0)	.001	26
Wuhan/ china	100 (100-200)	200 (100-300)		100 (100-200)	.074	24
China/ Wuhan	131.7 ± 83.1†	160.2 ± 90.8†		113.0 ± 71.8†	.072	12
Netherlands/ Dordrecht	164 (132-198)	192 (148-250)		132 (100-180)	.04	58
China/ Beijing		186 (122-302)		122 (51-162)	.005	52
China/ Wuhan		149.0 (58.5-240.5)		123.5 (44.5-177.8)	.352	55
China/ Nanchang		107 (73-175)		77 (41-102)	.0105	64
China/ Shanghai	104.1 (26.5-121.0)	223.3 (99.8-293.5)**		49.9 (15.0-69.8)***	.001	61

*The count of NK cells in critical COVID-19 patient was 55.50 (32.00 - 91.25) cell/μL.

**The results from patients with survival outcome.

***The results from patients with dead outcome.

†The count of B lymphocytes expressed as Mean ± Standard deviation.

effective mechanisms to manipulate autophagy and evade the immune system.[118] The pathogenic strain of the avian influenza H5N1 virus induces autophagy via inhibiting mTOR.[121] This virus reduces the phosphorylation of tuberin (TSC2), an inhibitor located upstream of mTOR, and the autophagy-linked death may justify the high mortality rate attributed to this virus.[118,121] Sharp lymphopenia also occurs in Ebola virus infection, which is highly strongly associated with mortality. The abortive infection of T cells with Ebola virus leads to the endoplasmic reticulum-stress stimulated autophagy and ultimately to cell death.[122] Similar autophagy-related cell death mentioned for avian influenza H5N1 virus and Ebola virus may occur in SARS-CoV-2-infected lymphocytes. Indeed, the upregulation of several autophagy-associated genes has been found in PBMCs collected from COVID-19 patients.[78]

3.9 | CD8$^+$ cytotoxic T lymphocyte (CTL)-dependent killing of SARS-CoV-2-infected lymphocytes

The CD8$^+$ CTL-dependent killing of T lymphocytes has been indicated in several viral infections, such as HIV and influenza viruses.[7,123] Several epitopes that are recognized by specific CD8$^+$ CTLs were identified within a non-structural protein of SARS-CoV.[124] As described above, SARS-CoV-2 can infect lymphocytes through ACE2-related and ACE2-unrelated manner. Thus, during severe blood viremia of COVID-19 infection, a proportion of blood lymphocytes may be infected with SARS-CoV-2. The coronavirus-infected lymphocytes are then can be eliminated by virus-specific CD8$^+$ CTLs. CTLs eliminate the virus-infected lymphocytes through FasL-Fas interaction, TRAIL-TRAILR interaction, releasing of perforin and granzymes.[7]

3.10 | Antibody-dependent killing of SARS-CoV-2-infected lymphocytes

Specific antibodies against surface antigens of a free virus can prevent viral attachment to its target cell.[125] However, the anti-viral antibodies can also bind to virus-infected cells by recognizing virus-specific antigens on the membrane of infected cells.[126] During HIV infection, the antibody-coated infected cells can be killed by various mechanisms, including ADCC, complement activation and phagocytosis.[127] It should be noted that complement-mediated lysis occurs both by the antibody-dependent classical and/or by the antibody-independent alternative pathways.[127]

It appears that anti-SARS-CoV-2 antibodies can contribute to lymphopenia, if a large blood number of lymphocytes become infected. Indeed, a positive association has been found between the serum quantities of anti-SARS-CoV-2

antibodies and COVID-19 severity.[128] Patients with severe COVID-19 exhibit higher titre of specific anti-virus IgG and IgM, and more profound lymphopenia compared with moderate and mild cases.[14,128] These findings suggest that some anti-SARS-CoV-2 antibodies may contribute in lymphopenia in severe COVID-19 patients. The evaluation of the association of the levels of anti-SARS-CoV-2 antibodies with lymphopenia degree needs to be cleared in future studies. If the contribution of the anti-virus antibodies to the lymphocyte reduction is proved, plasmapheresis can be implemented as an alternative approach for the treatment of severe COVID-19 causes.

3.11 | Autoantibody-dependent killing of lymphocytes

It has been found that murine coronavirus infection activates autoreactive T lymphocytes, induces polyclonal activation of B lymphocytes and elicits autoantibody production.[129,130] Similar events may also occur during SARS-CoV-2 infection. Generation of the cross-reactive antibodies is also demonstrated during infection with SARS-CoV infection.[131] Similarly, the antibodies produced during SARS-CoV-2 infection may bind to markers on lymphocytes through molecular mimicry, resulting in lymphocyte destruction. Furthermore, the blood number of regulatory T (Treg) cells was reduced in COVID-19 patients.[12] Unpublished data by Kalfaoglu et al also indicate that the differentiation of regulatory T (Treg) cells was impaired in severe COVID-19 patients and that could promote autoantibody production.[132] Indeed, the presence of various autoantibodies has been indicated in severe COVID-19 patients without history autoimmune disease.[133] The possible production of autoantibody against lymphocytes in COVID-19 patients needs to be clarified in future studies.

3.12 | Dendritic cell (DC)-dependent killing of lymphocytes

Using a mouse model of H5N1 virus infection, it has been found that the activated T lymphocytes become susceptible to FasL-mediated apoptosis since they express Fas molecule.[123] During H5N1 virus infection in mice, the residential DCs in the lymph node express FasL leading to T cell apoptosis through FasL-Fas interaction.[123] Furthermore, an inhibitory molecule named programmed cell death protein 1 (PD-1) is also upregulated by activated T cells, resulting in exhaustion after ligation with PD-L1 expressed by DCs.[134] Upregulation of the PD-L1 by DCs has been found in many viral infections such as HIV, influenza and Ebola viruses.[135] The blockade of the PD-1/PDL-1 interaction can improve the anti-viral immune response.[135]

As mentioned above, raised Fas expression was observed in blood $CD4^+$ T and $CD8^+$ T lymphocytes of COVID-19 patients.[117] Unpublished data by Diao et al indicate the elevated expression of the PD-1 was also indicated by T lymphocyte from COVID-19 patients, which may cause T cell exhaustion and/or

FIGURE 1 The possible mechanisms that may lead to the lymphopenia in COVID-19 patients. The yellow and green coloured pathways indicated the viral-mediated and immune-mediated pathways of lymphocyte reduction, respectively. The purple coloured pathway indicates the tissue re-distribution of lymphocytes, and pink coloured pathway indicates the effects of metabolic and biochemical on lymphocyte production and survival

apoptosis.[136] Higher PD-1 expression was also detected in both $CD4^+$ T and $CD8^+$ T cell subsets from COVID-19 patients.[117]

3.13 | Metabolic and biochemical changes affect lymphocyte production and survival

In addition to lungs, other organs, especially liver and kidneys, can be damaged in patients with COVID-19.[3,4] The organ failure changes the normal physiological condition to a pathophysiological situation that can influence the production, survival and function of lymphocytes. Unpublished data by Fei et al indicate that the COVID-19 patients with diminished blood number of lymphocytes exhibit the greater levels of bilirubin and direct bilirubin (two liver damage-related markers), and higher levels of creatinine and urea nitrogen (two renal function-related markers) in comparison with patients with normal blood count of lymphocytes.[137] Abnormal lung function-related indices were also associated with lower blood count of lymphocytes in COVID-19 patients.[137] The severe COVID-19 patients also exhibit elevated blood lactic acid levels, which can repress the lymphocyte expansion.[138]

4 | CONCLUSION

Various mechanisms may participate in the occurrence of lymphopenia through influencing the lymphocyte production or lymphocyte survival (Figure 1). The lymphopenia may have serious consequences in severe COVID-19 patients. As coronavirus-specific T cell-mediated immune responses play a key role in the viral elimination, thus the lymphopenia can support viral persistence, replication and tissue damage.[139] Lower numbers of lymphocytes, cell degeneration, necrosis and atrophy have been found in several lymphoid organs of patients with SARS and COVID-19.[69,71] Collectively, the destruction of the large number of lymphocytes and structural abnormalities in lymphoid organs can cause general immunosuppression in COVID-19 patients.

In accordance with SARS and MERS, the lymphopenia and cytokine storm perform a key role in the COVID-19 pathogenesis.[103] Since lymphopenia is usually seen in severe COVID-19 patients, the cytokine storm may be mediated by leucocytes other than T lymphocytes.[37,103] In lymphopenia status, the blood number of Treg cells (as the main modulators of immune responses) is also reduced, reinforcing excessive inflammatory responses and cytokine storm.[12] Collectively, lymphopenia leads to delayed viral elimination, diversion of the adaptive immune responses towards innate-mediated inflammatory responses, hyperactivation of macrophages and neutrophils, uncontrolled cytokine production and cytokine storm, which ultimately lead to multi-organ failure and death. Recently, IL-7 administration to COVID-19 patients has been reported to restore blood lymphocyte counts.[140] The targeting of molecules contributed to the lymphopenia presumably using blocking monoclonal antibodies, small molecule antagonist, siRNA may prevent lymphocyte reduction. Furthermore, eliminating the mediators contributed in the lymphopenia using plasmapheresis may be considered as an alternative approach to the treatment programme of severe COVID-19 causes.

CONFLICT OF INTEREST

The authors have no any conflict of interest.

AUTHOR CONTRIBUTIONS

AJ conceptualized, revised and edited the manuscript. AJ, PN, PM, SJ and MN contributed in the wrote the manuscript.

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