

## Review

# Peripheral T cell lymphopenia in COVID-19: potential mechanisms and impact

Sifan Zhang<sup>1</sup>, Becca Asquith<sup>1</sup>, Richard Szydlo<sup>2</sup>,  
John S. Tregoning<sup>1,†</sup> and Katrina M. Pollock<sup>1,\*</sup>

<sup>1</sup>Department of Infectious Disease, Imperial College London, London, UK and <sup>2</sup>Centre for Haematology, Department of Immunology and Inflammation, Imperial College London, London, UK

<sup>†</sup>These authors contributed equally to this work.

\*Correspondence: Katrina Pollock, Department of Infectious Disease, Imperial College London, London, UK. Email: [k.pollock@imperial.ac.uk](mailto:k.pollock@imperial.ac.uk)

Received 28 March 2021; Revised 10 June 2021; Accepted 30 June 2021

## Summary

Immunopathogenesis involving T lymphocytes, which play a key role in defence against viral infection, could contribute to the spectrum of COVID-19 disease and provide an avenue for treatment. To address this question, a review of clinical observational studies and autopsy data in English and Chinese languages was conducted with a search of registered clinical trials. Peripheral lymphopenia affecting CD4 and CD8 T cells was a striking feature of severe COVID-19 compared with non-severe disease. Autopsy data demonstrated infiltration of T cells into organs, particularly the lung. Seventy-four clinical trials are on-going that could target T cell-related pathogenesis, particularly IL-6 pathways. SARS-CoV-2 infection interrupts T cell circulation in patients with severe COVID-19. This could be due to redistribution of T cells into infected organs, activation induced exhaustion, apoptosis, or pyroptosis. Measuring T cell dynamics during COVID-19 will inform clinical risk-stratification of hospitalised patients and could identify those who would benefit most from treatments that target T cells.

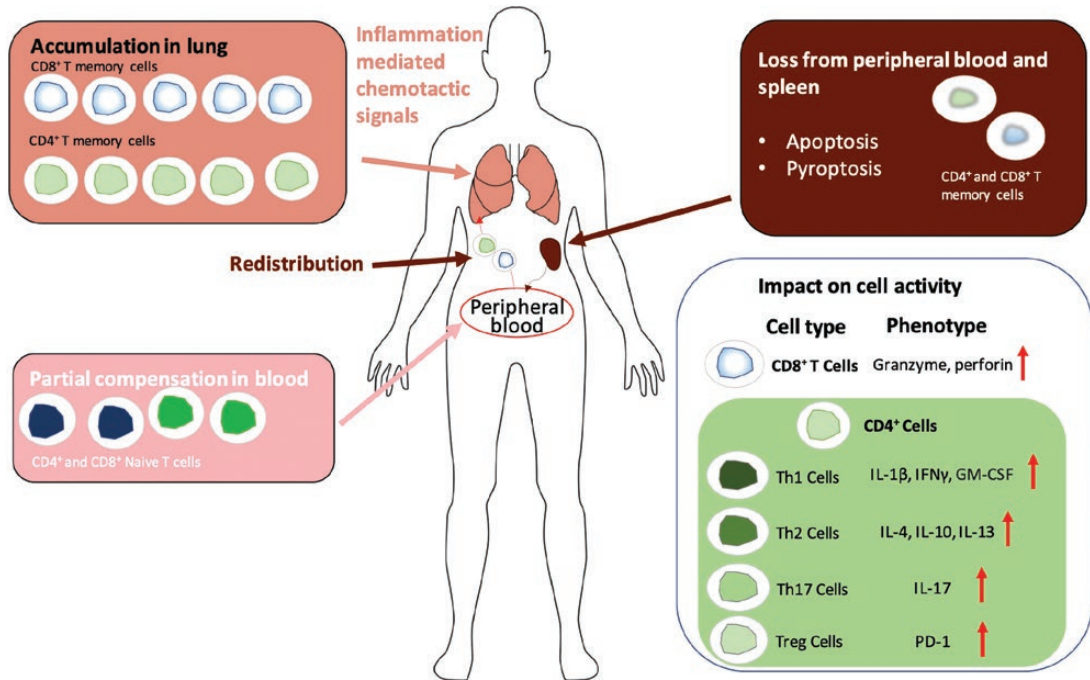
---

Abbreviations: ACE2: Angiotensin-converting enzyme 2; CCR5: C-C chemokine receptor type 5; CD: Cluster of differentiation; COVID-19: Coronavirus disease 2019; H&E: Haematoxylin and eosin; HIV: Human immunodeficiency virus; HLA-DR: Human leukocyte antigen – DR isotype; ICU: Intensive care units; IFN: Interferon; IHC: Immunohistochemistry; IL: Interleukin; mTOR, mechanistic target of rapamycin; NK: Natural killer; P53: Tumour protein P53; PBMC: Peripheral blood mononuclear cell; PCR: Polymerase chain reaction; PD-1: Programmed cell death protein 1; RNA: Ribonucleic acid; SARS-CoV: Severe acute respiratory syndrome coronavirus; Th: T helper; Tim-3: T-cell immunoglobulin mucin 3; Treg: regulatory T cell.

© The Author(s) 2021. Published by Oxford University Press on behalf of the British Society for Immunology.

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted reuse, distribution, and reproduction in any medium, provided the original work is properly cited.

## Graphical Abstract



In this review, we demonstrate that CD4<sup>+</sup> and CD8<sup>+</sup> T cell lymphopenia is a feature of severe COVID-19 compared with moderate disease in hospitalised patients. Pathology data indicate T cell infiltration into infected organs, particularly the lung. Potential mechanisms affecting T cells in severe disease due to SARS-CoV-2 infection include T cell redistribution and sequestration, pyroptosis, and apoptosis.

**Keywords:** CD4 cell, CD8 cell, SARS-CoV-2 virus, COVID-19, T cell biology

## Introduction

SARS-CoV-2 is the causative agent of the COVID-19 pandemic, responsible for a global health crisis unprecedented in recent times. A number of immunological, pathological, and histological studies indicate a role for T cells in the pathogenesis underlying COVID-19 [1–3]. However, the speed and spread of SARS-CoV-2, coupled with challenges in collecting experimental clinical evidence means that characterisation of immunopathogenesis has thus far been limited.

CD4<sup>+</sup> and CD8<sup>+</sup> T cells play key roles in containing and resolving viral infections. Suppression of T cell responses is associated with a failure to achieve sterilising immunity against viral infection, classically demonstrated by HIV infection [4, 5]. Viral pathogenicity can suppress T cell function through a number of mechanisms including direct and indirect cytotoxicity, organ-based sequestration, and suppression of both antigen recognition and the downstream effector mechanisms that contain infection [6–10]. Damage to the T cell compartment

can also have longer term clinical and immunological sequelae, limiting responses to other pathogens even in recovered individuals [11–14].

Evidence from observational studies indicates that immunopathology is an important driver of the clinical features of severe COVID-19 [15, 16]. The mechanisms of this immunopathology in COVID-19 are unclear. An excess inflammatory response has been widely observed and is associated with the later stages of disease and multi-organ failure. Dysregulation of both CD8<sup>+</sup> and CD4<sup>+</sup> T cell circulation and function within specific tissues could contribute to this immune injury.

The quality and quantity of T cell function is important in all stages of SARS-CoV-2 infection, once viral replication is established, including viral containment, the resolution of infection and recovery. Severe COVID-19 therefore mainly represents a failure of normal T cell function to contain and resolve SARS-CoV-2 infection. We systematically reviewed clinical observational data from histopathology and immunological studies of

autopsies and *in vivo* clinical observational cohorts to identify whether the data gathered so far supports this idea.

### Search strategy and selection criteria

Observational studies for this review were identified through a search of PubMed for articles published from 1 December 2019 to 31 December 2020, by use of the terms ‘COVID-19’ and ‘T cells’. Articles published in English and Chinese were included. Observational studies were selected if they reported original T cell counts in patients with severe and non-severe COVID-19. The selection process is shown as a flow chart (Fig. 1).

Autopsy studies for this review were identified through a search of PubMed for articles published from 1 December 2019 to 31 December 2020, by use of the terms ‘COVID-19’ and ‘Autopsy’. Articles published in English and Chinese were included. The inclusion criteria for post-mortem studies were measurement of T lymphocytes in patients who died of COVID-19 by haematoxylin and eosin (H&E) or immunohistochemistry (IHC) staining. The selection process is shown as a flow chart (Fig. 1).

Clinical trials for this review were identified through a search of ClinicalTrials.gov database for trials started from 1 December 2019 to 31 December 2020, by use of the terms ‘COVID-19’ and ‘CD147/IL-6/CCR5/PD-1/mTOR’. Phase 1 clinical trials were excluded; phase 2, 3, and 4 clinical trials were included.

### Clinical classification of COVID-19 and data extraction

Clinical descriptions in the eligible publications, which were from China, the Republic of Korea, Italy, France, Poland, Turkey, and Spain, followed broadly similar guidelines to classify patients with COVID-19 by disease severity. Four categories of COVID-19 disease were described, all of which had confirmed COVID-19 by polymerase chain reaction (PCR) testing or suspected COVID-19 based on clinical diagnostic criteria such as the Chinese Clinical Guidance of COVID-19 Pneumonia Diagnosis and Treatment [17] (Supplementary Table 1). Cases were asymptomatic, mild-moderate, severe, or critical. Mild-moderate cases had fever and respiratory symptoms such as dry cough, nasal obstruction, sore throat; severe cases were defined as those with pneumonia causing respiratory compromise and an oxygen saturation  $\leq 93\%$  when breathing room air at rest, and critical illness was defined as cases of COVID-19 where invasive ventilation was required. A summary of clinical features measured in the included publications is shown in the Supplementary Table 1. The reported CD3<sup>+</sup> cell count ( $\times 10^6$  cells/L), CD4<sup>+</sup> cell count ( $\times 10^6$  cells/L), CD8<sup>+</sup> cell count ( $\times 10^6$  cells/L), and CD4:CD8 ratio were extracted from the selected publications. Cases that were admitted to intensive care unit (ICU), did not survive or were designated as critical or severe in the original publication were allocated to the severe group, cases that did not meet these criteria were

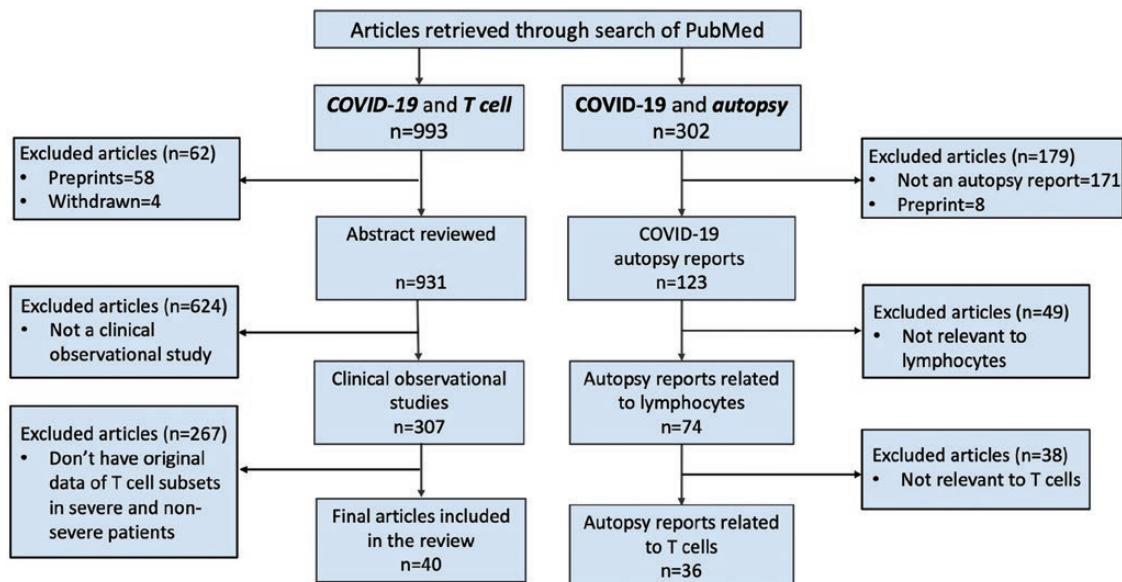


Figure 1. Flow chart of the study selection process.

allocated as non-severe. Infection with SARS-CoV-2 was confirmed in the autopsy cases by PCR, spike protein under transmission electron microscopy, IHC, or RNA hybrid assay.

### Peripheral T cell lymphopenia in severe COVID-19

Data on peripheral blood white cell counts and immune cell subsets have been widely collected during hospital admission for COVID-19. Forty studies have overwhelmingly reported that peripheral T cell lymphopenia was worse in patients with severe COVID-19 compared with those with mild disease (Table 1). Although a wide range of T cell counts were reported with differences evident in standardised reported values for each study, the direction of change between severe and non-severe COVID-19 in these studies was consistent (Table 1). For all studies reporting CD3, CD4, and CD8 counts, the standardised mean difference in severe versus non-severe COVID-19 was significantly lower in severe disease ( $P < 0.00001$  for all three; Fig. 2). For studies which only presented the median and interquartile range (27/40), mean and standard deviations (SD) were estimated using mathematical methods [18].

Where reported (in 30/40 studies), data on the CD4:CD8 ratio were more variable compared with findings for the lymphocyte subsets (Table 1). Overall, the CD4:CD8 ratio was not significantly different in those patients with non-severe disease compared with patients with severe disease ( $P = 0.08$ ), and the direction of change varied across the studies (Table 1, Fig. 2). Normal CD4:CD8 ratio is variously described as  $\geq 1$  or  $\geq 1.2$  and decreases with age [59]. Only one study reported a CD4:CD8 ratio  $<1.2$ , in either severe or non-severe COVID-19, the CD4:CD8 ratio therefore remained within normal range in both non-severe and severe COVID-19. Taken together, and compared with non-severe COVID-19, there is mounting evidence that severe COVID-19 disease is associated with a reduced frequency of CD3<sup>+</sup> T cells affecting both CD4<sup>+</sup> and CD8<sup>+</sup> T cells in the peripheral circulation.

Given that lymphopaenia is known to be a feature of viral infection, rather than unique to severe COVID-19 we searched for observational studies that had measured CD4 and CD8 counts in other respiratory viral infections. Only two studies that reported comparative lymphocyte levels comparing between severe and non-severe infections were found, one in influenza [60] and one for SARS-CoV-1 [61]. Both indicated acute lymphopenia in severe disease (Supplementary Table 2). One study has compared lymphocyte levels between

patients with SARS-CoV-2 and influenza, and the counts were similar [62]. This suggests that lymphopenia may be a common feature of severe respiratory viral infections and not unique to SARS-CoV-2 and therefore strategies that target it may be more broadly beneficial.

### Clinical, virological, and immunological significance of T cell lymphopenia in COVID-19

Lymphopenia could be a risk factor for severity, mortality, and poor prognosis in COVID-19, with T cells the most affected compared with B cells and natural killer (NK) cells [63, 64]. T cell counts negatively correlated with survival and CD4<sup>+</sup> and CD8<sup>+</sup> T lymphocytes decreased significantly in patients with severe disease [40]. In the early stage of the COVID-19 outbreak, a hospital in Wuhan studied lymphocyte subsets in 27 patients; lymphopenia was common (70.4%, 19/27) in severe cases, and T lymphocytes decreased more than B lymphocytes. Interestingly, CD4<sup>+</sup> and CD8<sup>+</sup> T cells but not B lymphocytes or NK cells, were significantly elevated after treatment of symptomatic disease suggesting that clinical and immunological recovery may be correlated and can be measured by an improving peripheral CD4 and CD8 count [65]. In another study, although CD4:CD8 ratio remained in the normal range, CD8<sup>+</sup> T lymphocytes were the most improved subsets after treatment [66]. While only one study reported that CD4<sup>+</sup> T cell count was independently associated with ICU admission [67], several results highlighted the role of CD8<sup>+</sup> T cells in COVID-19. CD8<sup>+</sup> T cell lymphopenia was analysed as an independent predictor for the prognosis of COVID-19 [26, 46]. Notably, an association of decreased lymphocytes with disease severity, has been observed suggesting that lymphopenia is an important predictive factor for the severity of COVID-19 [57,68,69].

The nature of the association between lymphopenia and failure of viral containment has not been established, however a negative correlation between T cell count and virus detection could indicate that T cells contribute to the limitation of viral load. Peripheral blood lymphocyte counts on admission were significantly and negatively correlated with SARS-CoV-2 nucleic acid-positive duration in 18 patients. Amongst lymphocytes, the T cell count but not B cell or NK cell count that negatively correlated with nucleic acid-positive duration [70]. Another study which analysed T cells in 66 recovered COVID-19 patients, found that CD4<sup>+</sup> T cell count was predictive of the duration of viral RNA detection in the stool sample [71]. These data suggest that depletion of T lymphocytes is associated with a delay in viral clearance; however, the direction of causality is yet to be established.

**Table 1.** Raw data of T cell subsets in patients with severe and non-severe COVID-19

Paper	Location	N (Non-severe; severe)	CD3 <sup>+</sup> T cell count (×10 <sup>6</sup> /L)		CD4 <sup>+</sup> T cell count (×10 <sup>6</sup> /L)		CD8 <sup>+</sup> T cell count (×10 <sup>6</sup> /L)		CD4:CD8 Ratio	Reference number (DOI)	
			Non severe	Severe	Non severe	Severe	Non severe	Severe			Non severe
Calvet, J. 2020 [19]	Spain	17:13	725 (497–1119)	647 (375–1113)	545 (445–767)	278 (178–663)	253 (145–319)	237 (87–586)	3.12 (1.58–3.99)	1.72 (0.78–2.52)	10.3390/v12111277
Cantenys-Molina, S. 2020 [20]	Spain	590:112	662 (464–890)	363 (251–581)	412 (288–568)	242 (154–353)	213 (137–331)	116 (67–210)	1.90 (1.33–2.71)	1.98 (1.18–3.14)	10.1111/cei.13547
Chen, G. 2020 [21]	China	10:11	640.5 (588.3–789.5)	294.0 (169.3–415.3)	381.5 (255–451)	177.5 (104–249.8)	254 (183.3–312.8)	89 (61.5–130.3)	N/A	N/A	10.1172/JC1137244
Chen, R. 2020 [22]	China	345:155	662.00 (452.00–950.00)	367.5 (210.00–556.00)	386 (287.50–691.00)	226.5 (144.25–362.25)	252.5 (371.75)	126.5 (61.25–164.50)	1.52 (1.17–2.36)	1.94 (1.55–2.58)	10.1016/i.jaci.2020.05.003
Cui, N. 2020 [23]	China	118:13	1047 (760–1330)	122 (57–322)	610 (446–808)	93 (30–225)	336 (245–449)	51 (17–122)	1.88 (1.36–2.52)	2.01 (1.32–4.04)	10.3389/fcimb.2020.595333
Demaret, J. 2020 [24]	France	10:24	1000 (700–1400)	1300 (1000–1800)	700 (600–900)	700 (600–1100)	300 (200–500)	500 (400–600)	N/A	N/A	10.1002/cti2.1217
Diao, B. 2020 [25]	China	479:20	652 (351–977)	261 (157–457)	342 (192–559)	198 (100–279)	208 (118–356)	64.3 (40.7–160)	1.60 (1.17–2.28)	2.43 (1.50–4.25)	10.3389/fimmu.2020.00827
Du, R. H. 2020 [26]	China	158:21	N/A	N/A	128.3 (73.5–201.7)	68 (55.1–148.8)	104.5 (58.5–142.7)	47.9 (25.4–73.8)	NA	NA	10.1183/13993003.00524-2020
Fu, Y. Q. 2020 [27]	China	71:14	609.00 (410.00–905.00)	339.50 (217.50–524.25)	368.00 (246.00–549.00)	203.00 (126.50–284.25)	205.00 (303.00)	145.00 (70.00–213.00)	1.93 (1.26–2.68)	1.59 (1.13–2.47)	10.1371/journal.pone.0240751
Gutierrez-Bautista, J. F. 2020 [28]	Spain	100:17	859 (549–1278)	630 (500–876)	387 (258–573)	313 (262–467)	172 (101–303)	167 (123–334)	2.41 (1.50–3.53)	1.96 (1.04–3.03)	10.3389/fimmu.2020.596553
Han, M. 2020 [29]	China	122:32	864 (598–1125)	477 (337.675)	462 (314–621)	221 (185–407)	326 (224–478)	172 (119–269)	1.37 (1.09–1.83)	1.36 (0.95–2.09)	10.1007/s00430-020-00693-z
He, B. 2020 [30]	China	32:21	794 (586–1112)	221 (168–414)	433 (318–651)	146 (107–277)	297 (230–388)	59 (33–109)	1.45 (1.24–1.80)	2.38 (1.62–4.63)	10.3389/fimmu.2020.02075
He, S. 2020 [31]	China	48:25	821.86 (526.19)	465.28 (505.67)	475.68 (263.57)	277.07 (306.09)	302.35 (256.25)	185.75 (166.3)	1.68 (0.9–2.85)	1.46 (0.96–3.13)	10.1016/i.jid.2020.06.059
Kalicenska, E. 2020 [32]	Poland	11:16	530 (360–980)	540 (175–1080)	320 (200–530)	185 (95–525)	200 (98–380)	320 (60–630)	1.65 (1.18–2.75)	1.01 (0.59–1.2)	10.1016/j.tranon.2020.100943
Kalpakci, Y. 2020 [33]	Turkey	20:20	N/A	N/A	958.83 ± 416.24	395.45 ± 237.59	504.15 (313.61–786.22)	192.00 (135.52–261.80)	1.57 (1.38–2.85)	1.81 (1.16–3.13)	10.1590/1806-9282.66.12.1666

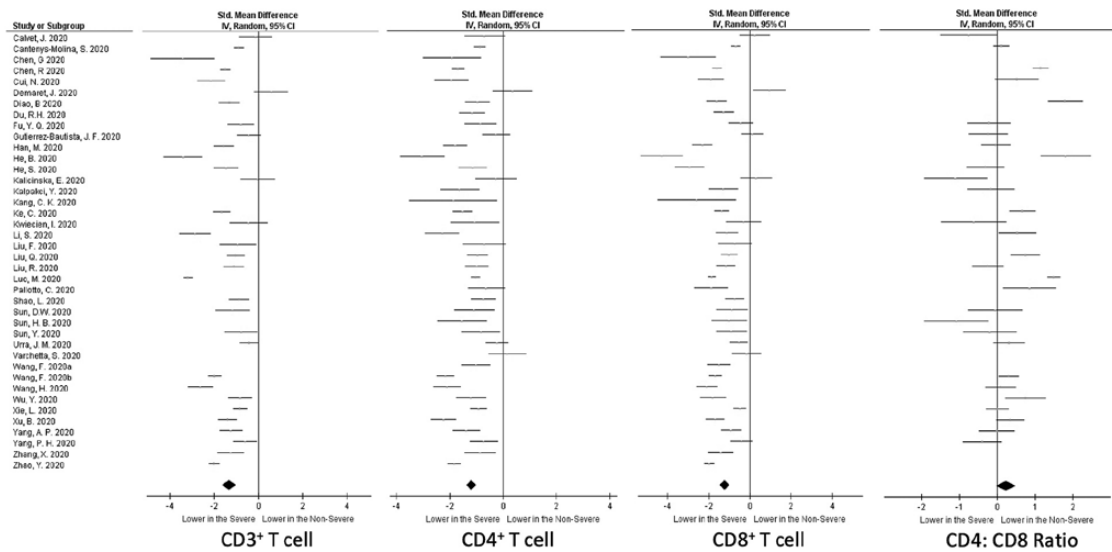
Table 1. Continued

Paper	Location	N (Non-severe: severe)	CD3 <sup>+</sup> T cell count (×10 <sup>6</sup> /L)	CD4 <sup>+</sup> T cell count (×10 <sup>6</sup> /L)	CD8 <sup>+</sup> T cell count (×10 <sup>6</sup> /L)	CD4:CD8 Ratio	Reference number (DOI)	
Kang, C. K. 2020 [34]	Republic of Korea	8:3	N/A	435.5 ± 57.5	296.1 ± 60.9	143.2 ± 13.1	N/A	10.1016/j.ijid.2020.05.106
Ke, C. 2020 [35]	China	148:46	965.06 ± 421.16	612.47 ± 277.33	316.26 ± 179.59	3.33 ± 2.11	10.1016/j.medcli.2020.06.055	
Kwiecien, I. 2020 [36]	Poland	9:14	951 (683–2253)	619 (533–1210)	313 (225–862)	2.1 (1.4–3.6)	10.3390/cells.9122615	
Li, S. 2020 [37]	China	43:26	991 (740–1154)	544 (364–667)	417 (309–539)	1.40 (0.79–2.08)	10.1172/jci.insight.138070	
Liu, F. 2020 [38]	China	32:8	857.74 ± 283.59	454.16 ± 193.24	385.74 ± 142.82	N/A	10.10388/41598-020-70387-2	
Liu, Q. 2020 [39]	China	310:30	773 ± 549	457 ± 342	297 ± 220	1.71 ± 0.894	10.1371/journal.pone.0239695	
Liu, R. 2020 [40]	China	49:61	509 (336.5–873.5)	290 (172.5–506)	161 (101–302.5)	1.75 (1.09–2.75)	10.1016/j.cca.2020.05.019	
Luo, M. 2020 [41]	China	817:201	611.01 (420.12–858.10)	367.99 (242.39–543.00)	203.98 (142.54–313.05)	1.70 (1.30–2.37)	10.1172/jci.insight.139024	
Pallotto, C. 2020 [42]	Italy	25:13	N/A	461 (275–654)	184 (132–334)	2.8 (2.3–4)	10.1080/23744235.2020.1778178	
Shao, L. 2020 [43]	China	104:25	824.54 ± 469.11	504.39 ± 367.90	327.29 ± 212.36	N/A	10.3389/fmed.2020.00246	
Sun, D. W. 2020 [44]	China	25:11	1089.680 ± 290.154	686.960 ± 225.383	359.84 ± 111.279	1.993 ± 0.606	10.1016/j.cca.2020.05.027	
Sun, H. B. 2020 [45]	China	13:12	N/A	576 ± 234	492 ± 214	1.23 ± 0.37	10.1371/journal.pone.0239532	
Sun, Y. 2020 [46]	China	36:10	808.97 ± 371.22	436.8 ± 225.08	355.33 ± 166.86	1.62 ± 1.86	10.1016/j.jaut.2020.102473	
Urra, J. M. 2020 [47]	Spain	145:27	701.0 ± 408.5	395.9 ± 241.0	287.6 ± 223.8	1.9 ± 1.6	10.1016/j.clim.2020.108486	
Varchetta, S. 2020 [48]	Italy	17:15	N/A	280 (144–562)	189 (32–505)	N/A	10.10388/41423-020-00557-9	
Wang, F. 2020a [49]	China	33:32	N/A	363.7 ± 225.5	179.5 ± 110.1	N/A	10.10388/41423-020-0483-y	

Table 1. Continued

Paper	Location	N (Non-severe; severe)	CD3 <sup>+</sup> T cell count (×10 <sup>6</sup> /L)	CD4 <sup>+</sup> T cell count (×10 <sup>6</sup> /L)	CD8 <sup>+</sup> T cell count (×10 <sup>6</sup> /L)	CD4:CD8 Ratio	Reference number (DOI)
Wang, F. 2020b [50]	China	253:70	1071 (772.5–1399)	529 (387.0–712.5)	596.5 (452.5–757.0)	302.0 (204.5–383.0)	1.48 (1.12–1.96) 1.61 (1.02–1.94) 10.1186/s12967-020-02423-8
Wang, H. 2020 [51]	China	48:47	774 (572–1095)	324 (195–455)	513 (304–625)	180 (109–274)	1.50 (1.11–2.04) 1.54 (1.04–2.51) 10.1016/j.intimp.2020.106683
Wu, Y. 2020 [52]	China	31:29	399 (324–626)	306 (167–422)	234 (156–401)	153 (102–289)	1.46 (0.78–2.11) 1.99 (1.28–3.75) 10.1128/mSphere.00362-20
Xie, L. 2020 [53]	China	322:51	1342.67 ± 493.06	938.79 ± 429.62	810.72 ± 321.02	530.61 ± 269.47	2.02 ± 0.96 1.87 ± 1.27 10.1177/1753466620942129
Xu, B. 2020 [54]	China	117:28	894.50 (662.75–1192.00)	593.00 (412.00–725.00)	573.50 (426.75–771.00)	299.00 (249.00–460.00)	1.68 (0.96–2.18) 1.96 (1.02–2.70) 10.1016/j.jinf.2020.04.012
Yang, A. P. 2020 [55]	China	69:24	763.8 ± 483.3	222.2 ± 195.2	448.7 ± 254.9	132.6 ± 98.5	2.01 ± 0.98 2.00 ± 0.97 10.18632/aging.103255
Yang, P. H. 2020 [56]	China	22:48	975.00 (685.00–1365.00)	731.00 (377.25–1019.50)	540.00 (364.00–724.00)	377.00 (196.00–513.00)	1.41 (1.07–1.59) 1.13 (0.85–1.53) 10.1186/s40249-020-00780-6
Zhang, X. 2020 [57]	China	293:12	778 (553–1041)	500 (379–705)	455 (314–650)	332 (226–541)	N/A N/A 10.1038/s41586-020-2355-0
Zhao, Y. 2020 [58]	China	414:125	814 (516–1088)	277 (163.5–430)	473 (291–657.75)	172 (99.5–267.5)	N/A N/A 10.1186/s40249-020-00723-1

Data are presented as median (IQR) and/or mean ± SD.



**Figure 2.** Forest plot of T cell subsets in patients with severe and non-severe COVID-19. CD3<sup>+</sup>, CD4<sup>+</sup> and CD8<sup>+</sup> T cell counts are significantly lower in patients with severe COVID-19 compared with those in patients with non-severe COVID-19 ( $P < 0.00001$ ). The effect of severity of disease on the CD4:CD8 ratio was inconclusive ( $P = 0.08$ ). Black diamond represents test for overall effect of 40 studies.

While clinical data indicate T cell lymphopenia is associated with persistent SARS-CoV-2 viraemia, some studies also indicate that infection may alter the quality and phenotype of the CD4<sup>+</sup> T cell response. Surprisingly, a higher than normal naive-to-memory CD4<sup>+</sup> T cell ratio has been observed suggesting an impact on the differentiation of naive to memory T cells in COVID-19 patients [64]. There was a lower frequency of regulatory T cells (T regs) in patients with severe disease compared with those with mild disease [34]. Patients had reduced levels of CD4<sup>+</sup> Th1 cells [72], with a reported Th2 skewed response in peripheral blood smears from ICU patients [73]. An upregulated Th17 response was found in 39 COVID-19 patients [74]. Bioinformatics analysis shows that genes involved in Th17 cell differentiation were enriched in patients with both mild and severe COVID-19 [75]. Altogether these observations of skewed T cell helper phenotypes suggest that the inhibition of Treg-induced anti-inflammatory responses and increased Th2 or Th17 responses, which are inflammatory without necessarily leading to viral control, could be involved in the pathogenesis of COVID-19 [76].

### Possible mechanisms for T cell lymphopenia

Dissection of the mechanism for the universal finding of peripheral T cell lymphopenia in SARS-CoV-2 infection particularly in severe COVID-19, will be important for

the development of treatments and identifying who is at risk of severe disease.

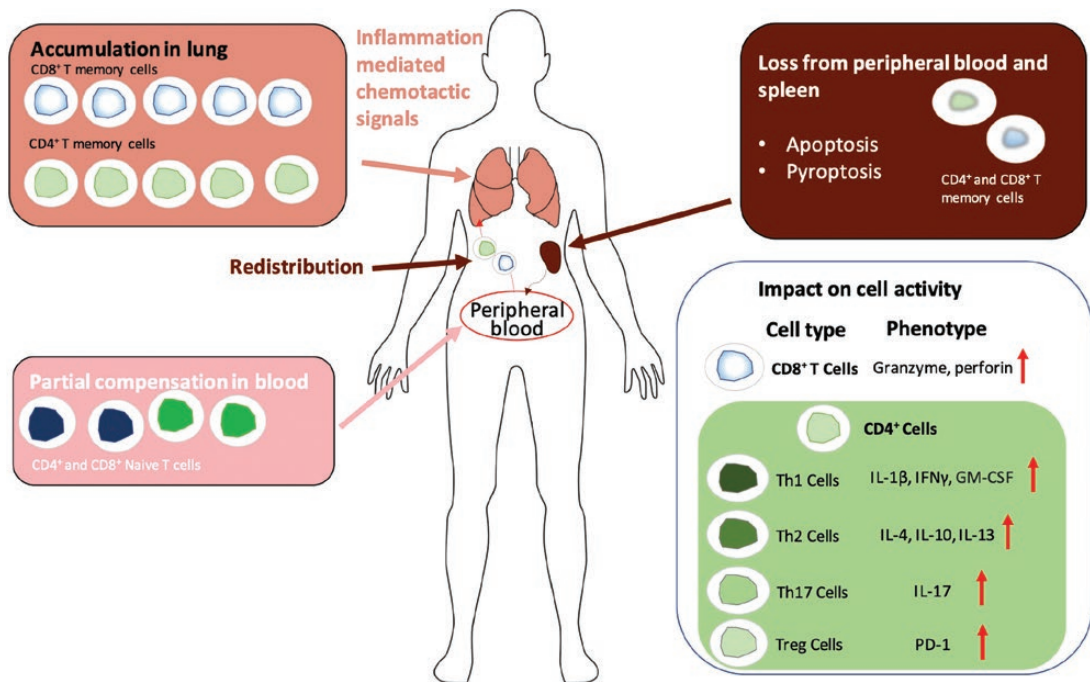
### SARS-CoV-2 infection of T cells

It is not yet clear whether SARS-CoV-2 can cause cytopathology through directly infecting T cells. Viral gene and angiotensin-converting enzyme 2 (ACE2) expression were not detectable in the peripheral blood mononuclear cells (PBMCs) of COVID-19 patients [77]. Findings that the spike protein can bind to CD147 also known as basigin, and mediate viral invasion have not been corroborated [78, 79]. More recently a study has suggested that SARS-CoV-2 could interact with the CD4 molecule and that CD4-positive cells are permissive to viral infection [80]. However *in vivo* infection of CD4<sup>+</sup> but not CD8<sup>+</sup> T cells is not supported by published studies. Given the very early and conflicting nature of the data, caution is needed when interpreting these reports.

### T cell redistribution

Although SARS-CoV-2 replication occurs principally in the lung, in severe cases, patients present with multi-organ failure in the late stage. This begs the question as to whether this is due to direct viral infection of these organs or due to an indirect effect of viral replication in the lung. To investigate this, we evaluated 123 autopsy case series of SARS-CoV-2 patients. In the respiratory tract, lung congestion, patchy lesions, diffuse alveolar damage,





**Figure 3.** Hypothesis for peripheral T cell lymphopenia during SARS-CoV-2 infection and severe disease. According to experimental data from peripheral blood of patients with severe COVID-19, we propose two drivers for peripheral lymphopenia. Firstly, T lymphocytes in the periphery are attracted by chemokines released by infected cells and immune cells at the site of disease and migrate out of the periphery to infected organs, mainly the lungs. Secondly, functionally exhausted T lymphocytes and activation of Th1/Th2/Th17 responses at the site of disease, fail to achieve viral containment, and undergo cell death through a variety of mechanisms including apoptosis and pyroptosis. It is likely that interruption of the normal circulation of T cells is the key component in this cycle.

widespread vascular thrombosis, and new vessel growth were distinct characteristics of COVID-19 [81, 82]. Of significance for the interaction of the virus with T cells, 74 out of 123 studies reported mild-to-prominent infiltration of lymphocytes into organs by H&E staining, 36 out of 74 studies additionally confirmed T cell infiltration by IHC staining (Fig. 1). Both T cell infiltration and viral infection, as confirmed by presence of spike protein and/or viral nucleic acid, was observed in the heart [83], spleen [84], pharynx [82, 85], liver [83], and kidney [86]. Activated T cells in lymph nodes have also been reported [87]. In the spleen, the commonly reported lymphoid hypoplasia and lymphocytic depletion, especially CD8<sup>+</sup> T cells indicates a decrease in the source of circulating lymphocytes [88]. The absence of germinal centres in hilar and posterior mediastinal lymph nodes suggests that the differentiation and maturation of B cells is also impacted [87].

The movement of T cells into tissues could be driving some of the observed damage. Cardiovascular changes reported were cardiomyocyte hypertrophy, degeneration,

necrosis, congestion, and oedema of interstitial tissue [89]. H&E staining and caspase 3 staining support a model of inflammatory infiltration consistent with a pattern of endothelial apoptosis [90]. CD8<sup>+</sup> T cell activation could contribute to cardiac injury in patients with severe disease [91]. The myocarditis found in histopathological studies could result from hyper inflammation of pathological T cells and cytokine storm [92]. Finally, the intense inflammation observed in severe COVID-19 could be associated with aberrant T-cell endothelial cell interactions leading to altered tethering and adhesion of cells [93]. Taken together, these autopsy findings indicate that normal T cell circulation is interrupted during severe disease due to SARS-CoV-2 infection (Fig. 3).

One potential driver for T cell redistribution contributing to the observed lymphopenia is the cytokine environment. Type I interferons are associated with SARS-CoV-2 infection, and in mouse models, lymphopenia was dependent on IFN signalling [94]. This may be a greater problem in the prolonged viral infection associated with severe COVID-19.

## T cell activation, exhaustion, and apoptosis

Given that lymphopenia was associated with higher viral loads, dysregulation of T cell circulation could be associated with antigen-driven over-activation and exhaustion, which may in turn lead to their absence in peripheral circulation. Data to support this hypothesis are scarce. The abnormal cytokine profile in COVID-19 has been well described and also in association with expression of apoptosis pathway transcripts in PBMC but more data are needed to demonstrate whether these are linked [77, 95]. Several studies have indicated expression of exhaustion and activation markers in severe COVID-19. Kinetic studies found that CD4<sup>+</sup> and CD8<sup>+</sup> T cells expressed higher levels of the exhaustion markers PD-1, Tim-3, and NKG2A in the symptomatic stage, compared with the prodromal and recovery stages [25, 96]. Analysis of a peripheral blood sample taken from a deceased patient showed that the remaining CD4<sup>+</sup> and CD8<sup>+</sup> T cells were hyperactivated, indicated by the expression of both CD38 and HLA-DR. The increased frequency of CCR6<sup>+</sup> Th17 CD4<sup>+</sup> T cells and perforin and granulysin positive CD8<sup>+</sup> T cells suggests that T cell activation accounted for severe immune injury in this patient [97]. Downregulation of the costimulatory molecule CD28 in patients with severe disease also suggests activation of T cells might contribute to aberrant signalling [98]. Different levels of activation markers were observed in different classes of T cells, with a very high level of activation in CD8<sup>+</sup> T cells observed compared to CD4<sup>+</sup> T cells [99]. An incompetent or aberrant CD8<sup>+</sup> T-cell response could limit antigen-specific immunity, and there is some evidence this might be occurring in older people, although our review has not demonstrated lymphopenia to be uniquely CD8<sup>+</sup> T cell biased [100, 101]. It was notable that in clonal analysis of CD8<sup>+</sup> T cells, they were highly activated but not exhausted in COVID-19 patients compared with healthy controls [102]. While data are accumulating indicating T cell hyperactivation in COVID-19, whether this is mechanistically linked to lymphopenia remains to be seen.

## Cell death

Finally, T cell lymphopenia could also be a function of SARS-CoV-2 infection-induced cell death. The cytokine storm produced by T cells and other inflammatory cells can promote apoptosis, pyroptosis, and necrosis of T cells in turn [25, 103]. A study of SARS-CoV found higher plasma Fas-ligand level in patients, which is associated with a higher level of caspase-3, which plays a key role in cell apoptosis, in CD4<sup>+</sup> and CD8<sup>+</sup> lymphocytes [104]. Since there are similarities between SARS-CoV-1 and SARS-CoV-2, it was proposed

that lymphocyte apoptosis is one of the causes of lymphopenia in COVID-19. Genes involved in apoptosis and P53 signalling pathways were enriched in PBMCs and cells of bronchoalveolar lavage fluid sample in three COVID-19 patients, indicating cell apoptosis could contribute to lymphopenia [77].

Another form of inflammation induced cell death is pyroptosis, which is caspase-1 triggered cell death via cleavage of gasdermin family members. Pyroptosis is triggered by inflammatory cytokines. While no studies have directly reported T cell pyroptosis during COVID-19 infection, one study proposed a mechanism for cytokine induced cell death [105]. This cell death was linked to IFN $\gamma$  and TNF, both of which are elevated in patients with severe COVID-19, so it could potentially be a mechanism. Type I interferons have also been shown to prime cells for Fas-mediated apoptosis [106] which may drive the cell death seen.

## Treatment strategies and ongoing clinical trials targeting T cells

The link between lymphopenia and severe disease opens up a number of therapeutic strategies, to target the different mechanisms driving the lymphopenia. Treatment strategies that have been considered include blocking SARS-CoV-2 from infecting T cells [78], inhibition of cytokine secretion [107–109], mitigation of T cell exhaustion [110, 111], blockade of the chemokine receptor CCR5 [112, 113], and normalisation of Th1/Th2/Th17 differentiation [114, 115]. Despite limited understanding of the pathogenesis and processes involving T cells in SARS-CoV-2 infection, some of these have already entered clinical trials (Table 2). Anti-IL-6 treatment has been tested in a number of different settings, with mixed results. A recently published study indicates that in critically ill patients anti-IL-6 receptor drugs can improve outcomes [116] but in other settings it has been less effective.

Dexamethasone, which suppresses the immune response via the glucocorticoid receptor, is the only drug so far to have shown to have consistent efficacy against COVID-19 [117]. Randomised clinical trials have shown that intravenous dexamethasone treatment significantly prolonged ventilator-free days [118] and reduced mortality [119]. A meta-analysis demonstrated lower 28-day all-cause mortality in the corticosteroid treatment group [120]. Despite clinical improvements, the side effect of dexamethasone including dampening viral clearance, suppressing bone marrow, and interrupting metabolism need attention [121]. The

impact of dexamethasone on T cell circulation and function in COVID-19 will be important to study. Why dexamethasone, which acts pleiotropically has been more effective than targeted cytokine blocking drugs is not clear, there may be a goldilocks effect, where

both too little and too great a cytokine response is detrimental, so dexamethasone dampens but does not completely block inflammation while specific cytokine drugs remove the beneficial role of the cytokine as well as the excess inflammation.

**Table 2.** Clinical trials using therapeutics targeting T cells

Rationale	Target	Drug	ClinicalTrials.gov Identifier
Proposed viral entry (mechanism to be confirmed)	CD147	Meplazumab (Anti-CD147 antibody)	NCT04275245 Phase 1, 2
			NCT04586153 Phase 2, 3
Target a downstream component of aberrant immune cell communication Reduce cytokine-storm, inflammation and exhaustion	IL-6	Tocilizumab (Anti-IL-6R antibody)	ChiCTR2000029765
			NCT04320615 Phase 3
			NCT04330638 Phase 3
			NCT04345445 Phase 3
			NCT04347031 Phase 2, 3
			NCT04349410 Phase 2, 3
			NCT04356937 Phase 3
			NCT04359095 Phase 2, 3
			NCT04361032 Phase 3
			NCT04372186 Phase 3
			NCT04377750 Phase 4
			NCT04380519 Phase 2, 3
			NCT04381936 Phase 2, 3
			NCT04403685 Phase 3
			NCT04409262 Phase 3
			NCT04412772 Phase 3
			NCT04423042 Phase 3
			NCT04424056 Phase 3
			NCT04577534 Phase 3
			NCT04600141 Phase 3
NCT04678739 Phase 3			
NCT04730323 Phase 4			
Siltuximab (Anti-IL-6 antibody)	NCT04322188 Not shown		
	NCT04329650 Phase 2		
	NCT04330638 Phase 3		
Clazakizumab (Anti-IL-6 antibody)	NCT04486521 Not shown		
	NCT04381052 Phase 2		
	NCT04343989 Phase 2		
	NCT04363502 Phase 2		
	NCT04348500 Phase 2		
Sarilumab (Anti-IL-6 Receptor antibody)	NCT04494724 Phase 2		
	NCT04659772 Phase 2		
	NCT04315298 Phase 2, 3		
	NCT04324073 Phase 2, 3		
	NCT04322773 Phase 2		
	NCT04327388 Phase 3		
	NCT04341870 Phase 2, 3		
	NCT04357808 Phase 2		
	NCT04357860 Phase 2		
	NCT04359901 Phase 2		
NCT04661527 Phase 2			
Fluoxetine (SSRI inhibitor)	NCT04377308 Phase 4		

Rationale	Target	Drug	ClinicalTrials.gov Identifier
		Ruxolitinib (JAK inhibitor)	NCT04331665 Not shown NCT04334044 Phase 1, 2 NCT04338958 Phase 2 NCT04348071 Phase 2, 3 NCT04348695 Phase 2 NCT04355793 Not shown NCT04359290 Phase 2 NCT04361903 Not shown NCT04362137 Phase 3 NCT04374149 Phase 2 NCT04377620 Phase 3 NCT04403243 Phase 2 NCT04414098 Phase 2 NCT04424056 Phase 3 NCT04477993 Phase 2, 3 NCT04581954 Phase 1, 2
Reduce aberrant T cell migration	CCR5	Maraviroc (CCR5 antagonist)	NCT04441385 Phase 2 NCT04475991 Phase 2 NCT04710199 Phase 2
		Leronlimab (Anti-CCR5 antibody)	NCT04343651 Phase 2 NCT04347239 Phase 2 NCT04678830 Phase 2
Limit T cell exhaustion	PD-1	PD-1 blocking antibody Nivolumab (Anti-PD1 antibody)	NCT04268537 Phase 2 NCT04356508 Phase 2 NCT04413838 Phase 2
Limit T cell exhaustion	mTOR	Rapamycin/ Sirolimus (mTOR inhibitor)	NCT04341675 Phase 2 NCT04482712 Phase 1, 2 NCT04461340 Phase 2
		RTB101 (PI3K/ mTOR) inhibitor	NCT04584710 Phase 2 NCT04409327 Phase 2

## Vaccines that induce a T cell response

Priming the T cell response prior to infection with vaccination is one strategy to improve protection from disease. To date, the published human clinical vaccine studies including T cell data have been largely phase I/II trials and are not designed to evaluate the protective role of T cells. Several of the studies have reported T cell responses after vaccination [122]. The mRNA vaccine BNT162b1-induced receptor binding domain-specific CD4<sup>+</sup> and CD8<sup>+</sup> Th1 responses with IFN  $\gamma$  production [123]. A combination of rAd26 and rAd5 vector-based vaccines induced proliferation of antigen-specific CD4<sup>+</sup> and CD8<sup>+</sup> T cells [124]. Adenovirus type-5-vectored COVID-19 vaccine successfully induced IFN  $\gamma$ -producing T cells in phase 1 and phase 2 clinical trial [125, 126]. ChAdOx1 nCoV-19 vaccine also elicited IFN  $\gamma$ -producing T cells to a similar degree [127]. Induction of a robust SARS-CoV-2-specific T cell memory response may be different in natural infection compared with immunisation, and the frequency

of SARS-CoV-2-specific T cells may be contingent upon both vaccine design and whether the initial response to the prime dose has been boosted [128]. Larger, follow-up studies will be required to identify the role of vaccine-induced T cells in protection from infection and disease.

## Long COVID-19

The sequelae of infection with SARS-CoV-2 can be chronic and leave symptoms even in recovered nucleic-negative individuals such as fatigue, chest heaviness, and breathlessness [129]. These symptoms have been grouped together as long COVID. Although data are at present limited, persistence of symptoms is common, particularly in patients who are hospitalised, with only 13% of 143 patients symptom-free after discharge in one Italian study [130]. The role of T cells in this condition is yet to be identified, but aberrant T cell circulation, tissue infiltration, and immune damage during

acute infection may all be important in determining longer-term outcomes.

## Conclusion

Peripheral circulation T cell lymphopenia affecting both CD4<sup>+</sup> and CD8<sup>+</sup> T cells is a universal finding in case series of COVID-19 and is associated with severe disease. Our findings are in line with other publications [131–134]. Current evidence from autopsy and *in vivo* studies indicates the most likely mechanism is the interruption of normal lymphocyte circulation and organ-based, and/or endothelial sequestration of T cells. This may be due to the intense inflammation caused by SARS-CoV-2 replication. Coupled with aberrant T cell function, T cell exhaustion, and persistent failure of viral containment, these findings indicate a self-amplifying inflammatory cycle in severe COVID-19, which should be prevented or interrupted with rationally designed vaccines and therapeutics.

## Supplementary material

Supplementary data are available at *Immunotherapy Advances* online.

Supplementary Table 1. Summary of studies included

Supplementary Table 2. Lymphocyte count of patients with SARS-CoV, MERS-CoV and Influenza. Cell count was shown as mean  $\pm$  SD and/or median (IQR).

## Acknowledgements

The Editor-in-Chief, Tim Elliott, would like to thank Tao Dong and Laura Denney for their contribution to the peer review of this article.

## Author contributions

*Conceptualisation:* K.P.; *Writing-Original Draft:* S.Z.; *Figures and tables:* S.Z., J.S.T., and K.P.; *Writing-Review and Editing:* S.Z., J.S.T., B.A., R.S., and K.P.

## Funding

This research was supported by the National Institute for Health Research (NIHR) Imperial Biomedical Research Centre and the NIHR Imperial Clinical Research Facility. The views expressed are those of the author(s) and not necessarily those of the National Health Service, the NIHR or the Department of Health and Social Care.

## Conflict of interest

K.P. reports grants from the National Institute for Health Research and the Medical Research Council UK Research and Innovation. K.P. is chief investigator for the Imperial College London COVID-19 vaccine development programme and

principal investigator for the University of Oxford COVID-19 vaccine development trials, personal fees from Sanofi, outside the submitted work; and honoraria received for Vaccines for COVID-19 e-Learning course; British Society for Antimicrobial Therapy and ITV PLC.

## Data availability

No new datasets were generated for this manuscript.

## References

- Zhou R, To KK, Wong YC *et al.* Acute SARS-CoV-2 infection impairs dendritic cell and T cell responses. *Immunity* 2020;53(4):864–77.e5. <https://doi.org/10.1016/j.immuni.2020.07.026>
- 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):1489–501.e15. <https://doi.org/10.1016/j.cell.2020.05.015>
- Ackermann M, Verleden SE, Kuehnel M *et al.* Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med* 2020;383(2):120–8. <https://doi.org/10.1056/NEJMoa2015432>
- Fenwick C, Joo V, Jacquier P *et al.* T-cell exhaustion in HIV infection. *Immunol Rev* 2019;292(1):149–63. <https://doi.org/10.1111/imr.12823>
- Douek DC, Brenchley JM, Betts MR *et al.* HIV preferentially infects HIV-specific CD4<sup>+</sup> T cells. *Nature* 2002;417(6884):95–8. <https://doi.org/10.1038/417095a>
- Gougeon ML. To kill or be killed: how HIV exhausts the immune system. *Cell Death Differ* 2005;12 Suppl 1:845–54. <https://doi.org/10.1038/sj.cdd.4401616>
- Younan P, Santos RI, Ramanathan P *et al.* Ebola virus-mediated T-lymphocyte depletion is the result of an abortive infection. *PLoS Pathog* 2019;15(10):e1008068. <https://doi.org/10.1371/journal.ppat.1008068>
- Malacarne F, Webster GJ, Reingnat S *et al.* Tracking the source of the hepatitis B virus-specific CD8 T cells during lamivudine treatment. *J Infect Dis* 2003;187(4):679–82. <https://doi.org/10.1086/368369>
- McSharry BP, Samer C, McWilliam HEG *et al.* Virus-mediated suppression of the antigen presentation molecule MR1. *Cell Rep* 2020;30(9):2948–62.e2944. <https://doi.org/10.1016/j.celrep.2020.02.017>
- Ho MR, Tsai TT, Chen CL *et al.* Blockade of dengue virus infection and viral cytotoxicity in neuronal cells in vitro and in vivo by targeting endocytic pathways. *Sci Rep* 2017;7(1):6910. <https://doi.org/10.1038/s41598-017-07023-z>
- Li J, Wang J, Kang AS *et al.* Mapping the T cell response to COVID-19. *Signal Transduct Target Ther* 2020;5(1):112. <https://doi.org/10.1038/s41392-020-00228-1>
- Gomez-Mora E, Garcia E, Urrea V *et al.* Preserved immune functionality and high CMV-specific T-cell responses in HIV-infected individuals with poor CD4<sup>+</sup> T-cell

- immune recovery. *Sci Rep* 2017;7(1):11711. <https://doi.org/10.1038/s41598-017-12013-2>
13. Bajwa M, Vita S, Vescovini R *et al.* CMV-specific T-cell responses at older ages: broad responses with a large central memory component may be key to long-term survival. *J Infect Dis* 2017;215(8):1212–20. <https://doi.org/10.1093/infdis/jix080>
  14. Papagno L, Appay V, Sutton J *et al.* Comparison between HIV- and CMV-specific T cell responses in long-term HIV infected donors. *Clin Exp Immunol* 2002;130(3):509–17. <https://doi.org/10.1046/j.1365-2249.2002.02005.x>
  15. Nicolai L, Leunig A, Brambs S *et al.* Immunothrombotic dysregulation in COVID-19 pneumonia is associated with respiratory failure and coagulopathy. *Circulation* 2020;142(12):1176–89. <https://doi.org/10.1161/CIRCULATIONAHA.120.048488>
  16. Yang L, Liu S, Liu J *et al.* COVID-19: immunopathogenesis and immunotherapeutics. *Signal Transduct Target Ther* 2020;5(1):128. <https://doi.org/10.1038/s41392-020-00243-2>
  17. Commission CNH. *Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment (7th edition)*. 2020. <http://kjfy.meetingchina.org/msite/news/show/cn/3337.html>
  18. Wan X, Wang W, Liu J *et al.* Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014;14:135. <https://doi.org/10.1186/1471-2288-14-135>
  19. Calvet J, Gratacos J, Amengual MJ *et al.* CD4 and CD8 lymphocyte counts as surrogate early markers for progression in SARS-CoV-2 pneumonia: a prospective study. *Viruses* 2020;12(11):1277. <https://doi.org/10.3390/v12111277>
  20. Cantenys-Molina S, Fernandez-Cruz E, Francos P *et al.* Lymphocyte subsets early predict mortality in a large series of hospitalized COVID-19 patients in Spain. *Clin Exp Immunol* 2021;203(3):424–32. <https://doi.org/10.1111/cei.13547>
  21. Chen G, Wu D, Guo W *et al.* Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest* 2020;130(5):2620–9. <https://doi.org/10.1172/JCI137244>
  22. Chen R, Sang L, Jiang M *et al.* Longitudinal hematologic and immunologic variations associated with the progression of COVID-19 patients in China. *J Allergy Clin Immunol* 2020;146(1):89–100. <https://doi.org/10.1016/j.jaci.2020.05.003>
  23. Cui N, Yan R, Qin C *et al.* Clinical characteristics and immune responses of 137 deceased patients with COVID-19: a retrospective study. *Front Cell Infect Microbiol* 2020;10:595333. <https://doi.org/10.3389/fcimb.2020.595333>
  24. Demaret J, Lefevre G, Vuotto F *et al.*; Lille Covid Research Network (LICORNE). Severe SARS-CoV-2 patients develop a higher specific T-cell response. *Clin Transl Immunology* 2020;9(12):e1217. <https://doi.org/10.1002/cti2.1217>
  25. 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;11:827. <https://doi.org/10.3389/fimmu.2020.00827>
  26. Du RH, Liang LR, Yang CQ *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):2000524. <https://doi.org/10.1183/13993003.00524-2020>
  27. Fu YQ, Sun YL, Lu SW *et al.* Effect of blood analysis and immune function on the prognosis of patients with COVID-19. *PLoS One* 2020;15(10):e0240751. <https://doi.org/10.1371/journal.pone.0240751>
  28. Gutiérrez-Bautista JF, Rodríguez-Nicolas A, Rosales-Castillo A *et al.* Negative clinical evolution in COVID-19 patients is frequently accompanied with an increased proportion of undifferentiated Th cells and a strong underrepresentation of the Th1 subset. *Front Immunol* 2020;11:596553. <https://doi.org/10.3389/fimmu.2020.596553>
  29. Han M, Xu M, Zhang Y *et al.* Assessing SARS-CoV-2 RNA levels and lymphocyte/T cell counts in COVID-19 patients revealed initial immune status as a major determinant of disease severity. *Med Microbiol Immunol* 2020;209(6):657–68. <https://doi.org/10.1007/s00430-020-00693-z>
  30. He B, Wang J, Wang Y *et al.* The metabolic changes and immune profiles in patients with COVID-19. *Front Immunol* 2020;11:2075. <https://doi.org/10.3389/fimmu.2020.02075>
  31. He S, Zhou C, Lu D *et al.* Relationship between chest CT manifestations and immune response in COVID-19 patients. *Int J Infect Dis* 2020;98:125–9. <https://doi.org/10.1016/j.ijid.2020.06.059>
  32. Kalicińska E, Szymczak D, Andrasiak I *et al.* Lymphocyte subsets in haematological patients with COVID-19: multicentre prospective study. *Transl Oncol* 2021;14(1):100943. <https://doi.org/10.1016/j.tranon.2020.100943>
  33. Kalpakci Y, Hacibekiroglu T, Trak G *et al.* Comparative evaluation of memory T cells in COVID-19 patients and the predictive role of CD4<sup>+</sup>CD8<sup>+</sup> double positive T lymphocytes as a new marker. *Rev Assoc Med Bras (1992)* 2020;66(12):1666–72. <https://doi.org/10.1590/1806-9282.66.12.1666>
  34. Kang CK, Han GC, Kim M *et al.* Aberrant hyperactivation of cytotoxic T-cell as a potential determinant of COVID-19 severity. *Int J Infect Dis* 2020;97:313–21. <https://doi.org/10.1016/j.ijid.2020.05.106>
  35. Ke C, Yu C, Yue D, Zeng X, Hu Z, Yang C. Clinical characteristics of confirmed and clinically diagnosed patients with 2019 novel coronavirus pneumonia: a single-center, retrospective, case-control study. *Med Clin (Barc)* 2020;155(8):327–34. <https://doi.org/10.1016/j.medcli.2020.06.055>
  36. Kwiecien I, Rutkowska E, Klos K *et al.* Maturation of T and B lymphocytes in the assessment of the immune status in COVID-19 patients. *Cells* 2020;9(12):2615. <https://doi.org/10.3390/cells9122615>
  37. Li S, Jiang L, Li X, *et al.* Clinical and pathological investigation of patients with severe COVID-19. *JCI Insight*. 2020;5(12):e138070. <https://doi.org/10.1172/jci.insight.138070>

38. Liu F, Ji C, Luo J *et al.* Clinical characteristics and corticosteroids application of different clinical types in patients with corona virus disease 2019. *Sci Rep* 2020;10(1):13689. <https://doi.org/10.1038/s41598-020-70387-2>
39. Liu Q, Fang X, Tokuno S *et al.* A web visualization tool using T cell subsets as the predictor to evaluate COVID-19 patient's severity. *PLoS One* 2020;15(9):e0239695. <https://doi.org/10.1371/journal.pone.0239695>
40. Liu R, Wang Y, Li J *et al.* Decreased T cell populations contribute to the increased severity of COVID-19. *Clin Chim Acta* 2020;508:110–14. <https://doi.org/10.1016/j.cca.2020.05.019>
41. Luo M, Liu J, Jiang W, Yue S, Liu H, Wei S. IL-6 and CD8<sup>+</sup> T cell counts combined are an early predictor of in-hospital mortality of patients with COVID-19. *JCI Insight* 2020;5(13):e139024. <https://doi.org/10.1172/jci.insight.139024>
42. Pallotto C, Suardi LR, Esperti S *et al.* Increased CD4/CD8 ratio as a risk factor for critical illness in coronavirus disease 2019 (COVID-19): a retrospective multicentre study. *Infect Dis (Lond)* 2020; 52(9): 675–7. <https://doi.org/10.1080/23744235.2020.1778178>
43. Shao L, Li X, Zhou Y *et al.* Novel insights into illness progression and risk profiles for mortality in non-survivors of COVID-19. *Front Med (Lausanne)* 2020;7:246. <https://doi.org/10.3389/fmed.2020.00246>
44. Sun DW, Zhang D, Tian RH *et al.* The underlying changes and predicting role of peripheral blood inflammatory cells in severe COVID-19 patients: A sentinel? *Clin Chim Acta* 2020;508:122–9. <https://doi.org/10.1016/j.cca.2020.05.027>
45. Sun HB, Zhang YM, Huang LG *et al.* The changes of the peripheral CD4<sup>+</sup> lymphocytes and inflammatory cytokines in Patients with COVID-19. *PLoS One* 2020;15(9):e0239532. <https://doi.org/10.1371/journal.pone.0239532>
46. Sun Y, Dong Y, Wang L *et al.* Characteristics and prognostic factors of disease severity in patients with COVID-19: the Beijing experience. *J Autoimmun* 2020;112:102473. <https://doi.org/10.1016/j.jaut.2020.102473>
47. Urra JM, Cabrera CM, Porras L *et al.* Selective CD8 cell reduction by SARS-CoV-2 is associated with a worse prognosis and systemic inflammation in COVID-19 patients. *Clin Immunol* 2020;217:108486. <https://doi.org/10.1016/j.clim.2020.108486>
48. Varchetta S, Mele D, Oliviero B *et al.* Unique immunological profile in patients with COVID-19. *Cell Mol Immunol* 2021;18(3):604–12. <https://doi.org/10.1038/s41423-020-00557-9>
49. Wang F, Hou H, Yao Y *et al.* Systemically comparing host immunity between survived and deceased COVID-19 patients. *Cell Mol Immunol* 2020; 17(8):875–7. <https://doi.org/10.1038/s41423-020-0483-y>
50. Wang F, Qu M, Zhou X *et al.* The timeline and risk factors of clinical progression of COVID-19 in Shenzhen, China. *J Transl Med* 2020;18(1):270. <https://doi.org/10.1186/s12967-020-02423-8>
51. Wang H, Zhang Y, Mo P *et al.* Neutrophil to CD4<sup>+</sup> lymphocyte ratio as a potential biomarker in predicting virus negative conversion time in COVID-19. *Int Immunopharmacol* 2020;85:106683. <https://doi.org/10.1016/j.intimp.2020.106683>
52. Wu Y, Huang X, Sun J *et al.* Clinical characteristics and immune injury mechanisms in 71 patients with COVID-19. *mSphere* 2020;5(4):e00362–20. <https://doi.org/10.1128/mSphere.00362-20>
53. Xie L, Wu Q, Lin Q *et al.* Dysfunction of adaptive immunity is related to severity of COVID-19: a retrospective study. *Ther Adv Respir Dis* 2020;14:1753466620942129. <https://doi.org/10.1177/1753466620942129>
54. Xu B, Fan CY, Wang AL *et al.* Suppressed T cell-mediated immunity in patients with COVID 19: A clinical retrospective study in Wuhan, China. *J Infect* 2020;81(1):e51–e60. <https://doi.org/10.1016/j.jinf.2020.04.012>
55. Yang AP, Li HM, Tao WQ *et al.* Infection with SARS-CoV-2 causes abnormal laboratory results of multiple organs in patients. *Aging (Albany NY)* 2020;12(11):10059–69. <https://doi.org/10.18632/aging.103255>
56. Yang PH, Ding YB, Xu Z *et al.* Increased circulating level of interleukin-6 and CD8<sup>+</sup> T cell exhaustion are associated with progression of COVID-19. *Infect Dis Poverty* 2020;9(1):161. <https://doi.org/10.1186/s40249-020-00780-6>
57. Zhang X, Tan Y, Ling Y *et al.* Viral and host factors related to the clinical outcome of COVID-19. *Nature* 2020;583(7816):437–40. <https://doi.org/10.1038/s41586-020-2355-0>
58. Zhao Y, Nie HX, Hu K *et al.* Abnormal immunity of nonsurvivors with COVID-19: predictors for mortality. *Infect Dis Poverty* 2020;9(1):108. <https://doi.org/10.1186/s40249-020-00723-1>
59. Francis-Morris A, Mackie NE, Eliahoo J *et al.* Compromised CD4:CD8 ratio recovery in people living with HIV aged over 50 years: an observational study. *HIV Med* 2020;21(2):109–18. <https://doi.org/10.1111/hiv.12800>
60. Wang N, Liu X, Zhang Y, Xie Y, Zhao W. Hematologic markers of influenza A H1N1 for early laboratory diagnosis and treatment assessment. *Laboratory Medicine* 2011;42(10):607–11. <https://doi.org/10.1309/lmrvlj3brxlzge3>
61. He Z, Zhao C, Dong Q *et al.* Effects of severe acute respiratory syndrome (SARS) coronavirus infection on peripheral blood lymphocytes and their subsets. *Int J Infect Dis* 2005;9(6):323–30. <https://doi.org/10.1016/j.ijid.2004.07.014>
62. Qian F, Gao G, Song Y *et al.* Specific dynamic variations in the peripheral blood lymphocyte subsets in COVID-19 and severe influenza A patients: a retrospective observational study. *BMC Infect Dis* 2020;720(1):910. <https://doi.org/10.1186/s12879-020-05637-9>
63. Bao J, Li C, Zhang K, Kang H, Chen W, Gu B. Comparative analysis of laboratory indexes of severe and non-severe patients infected with COVID-19. *Clin Chim Acta* 2020;509:180–94. <https://doi.org/10.1016/j.cca.2020.06.009>
64. Qin C, Zhou L, Hu Z *et al.* Dysregulation of immune response in patients with COVID-19 in Wuhan, China. *Clin*

- Infect Dis* 2020;71(15):762–8. <https://doi.org/10.1093/cid/ciaa248>
65. Ni M, Tian FB, Xiang DD *et al.* Characteristics of inflammatory factors and lymphocyte subsets in patients with severe COVID-19. *J Med Virol* 2020;92(11):2600–06. <https://doi.org/10.1002/jmv.26070>
  66. Ganji A, Farahani I, Khansarinejad B *et al.* Increased expression of CD8 marker on T-cells in COVID-19 patients. *Blood Cells Mol Dis* 2020;83:102437. <https://doi.org/10.1016/j.bcmd.2020.102437>
  67. Chen J, Qi T, Liu L *et al.* Clinical progression of patients with COVID-19 in Shanghai, China. *J Infect* 2020;80(5):e1–e6. <https://doi.org/10.1016/j.jinf.2020.03.004>
  68. Tan L, Wang Q, Zhang D *et al.* Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. *Signal Transduct Target Ther* 2020;5(1):33. <https://doi.org/10.1038/s41392-020-0148-4>
  69. Tan L, Kang X, Ji X *et al.* Validation of predictors of disease severity and outcomes in COVID-19 patients: a descriptive and retrospective study. *Med (NY)* 2020;1(1):128–38-e123. <https://doi.org/10.1016/j.medj.2020.05.002>
  70. Dong X, Wang M, Liu S *et al.* Immune characteristics of patients with coronavirus disease 2019 (COVID-19). *Aging Dis* 2020;11(3):642–8. <https://doi.org/10.14336/AD.2020.0317>
  71. Ling Y, Xu SB, Lin YX *et al.* Persistence and clearance of viral RNA in 2019 novel coronavirus disease rehabilitation patients. *Chin Med J (Engl)* 2020;133(9):1039–43. <https://doi.org/10.1097/CM9.0000000000000774>
  72. Cao M, Zhang D, Wang Y *et al.* Clinical features of patients infected with the 2019 novel coronavirus (COVID-19) in Shanghai, China. *medRxiv* 2020;2020.03.04.20030395. <https://doi.org/10.1101/2020.03.04.20030395>
  73. Roncati L, Nasillo V, Lusenti B *et al.* Signals of Th2 immune response from COVID-19 patients requiring intensive care. *Ann Hematol* 2020;99(6):1419–20. <https://doi.org/10.1007/s00277-020-04066-7>
  74. De Biasi S, Meschiari M, Gibellini L *et al.* Marked T cell activation, senescence, exhaustion and skewing towards TH17 in patients with COVID-19 pneumonia. *Nat Commun* 2020;11(1):3434. <https://doi.org/10.1038/s41467-020-17292-4>
  75. Ouyang Y, Yin J, Wang W *et al.* Down-regulated gene expression spectrum and immune responses changed during the disease progression in COVID-19 patients. *Clin Infect Dis* 2020;71(16):2052–60. <https://doi.org/10.1093/cid/ciaa462>
  76. Muyayalo KP, Huang DH, Zhao SJ *et al.* COVID-19 and Treg/Th17 imbalance: Potential relationship to pregnancy outcomes. *Am J Reprod Immunol* 2020;84(5):e13304. <https://doi.org/10.1111/aji.13304>
  77. Xiong Y, Liu Y, Cao L *et al.* Transcriptomic characteristics of bronchoalveolar lavage fluid and peripheral blood mononuclear cells in COVID-19 patients. *Emerg Microbes Infect* 2020;9(1):761–70. <https://doi.org/10.1080/22221751.2020.1747363>
  78. Wang K, Chen W, Zhang Z, *et al.* CD147-spike protein is a novel route for SARS-CoV-2 infection to host cells. *Signal Transduct Target Ther* 2020;5(1):283. <https://doi.org/10.1038/s41392-020-00426-x>
  79. Shilts J, Crozier TW, Greenwood EJD, Lehner PJ, Wright GJ. No evidence for basigin/CD147 as a direct SARS-CoV-2 spike binding receptor. *Sci Rep* 2021;11(1):413. <https://doi.org/10.1038/s41598-020-80464-1>
  80. Davanzo GG, Codo AC, Brunetti NS *et al.* SARS-CoV-2 Uses CD4 to infect T helper lymphocytes. *medRxiv* 2020;2009.2025.20200329. <https://doi.org/10.1101/2020.09.25.20200329>
  81. Liu Q, Wang RS, Qu GQ *et al.* Gross examination report of a COVID-19 death autopsy. *Fa Yi Xue Za Zhi* 2020;36(1):21–3. <https://doi.org/10.12116/j.jissn.1004-5619.2020.01.005>
  82. Wichmann D, Sperhake JP, Lutgehetmann M *et al.* Autopsy findings and venous thromboembolism in patients with COVID-19: a prospective cohort study. *Ann Intern Med* 2020;173(4):268–77. <https://doi.org/10.7326/M20-2003>
  83. Schaller T, Hirschtbuhl K, Burkhardt K *et al.* Postmortem examination of patients with COVID-19. *Jama* 2020;323(24):2518–20. <https://doi.org/10.1001/jama.2020.8907>
  84. Buja LM, Wolf DA, Zhao B *et al.* The emerging spectrum of cardiopulmonary pathology of the coronavirus disease 2019 (COVID-19): report of 3 autopsies from Houston, Texas, and review of autopsy findings from other United States cities. *Cardiovasc Pathol* 2020;48:107233. <https://doi.org/10.1016/j.carpath.2020.107233>
  85. Edler C, Schroder AS, Aepfelbacher M *et al.* Correction to: dying with SARS-CoV-2 infection-an autopsy study of the first consecutive 80 cases in Hamburg, Germany. *Int J Legal Med* 2020; 134(5):1977. <https://doi.org/10.1007/s00414-020-02336-7>
  86. Su H, Yang M, Wan C *et al.* Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. *Kidney Int* 2020;98(1):219–27. <https://doi.org/10.1016/j.kint.2020.04.003>
  87. Lax SF, Skok K, Zechner P *et al.* Pulmonary arterial thrombosis in COVID-19 with fatal outcome: results from a prospective, single-center, clinicopathologic case series. *Ann Intern Med* 2020;173(5):350–61. <https://doi.org/10.7326/M20-2566>
  88. Gu J, Korteweg C. Pathology and pathogenesis of severe acute respiratory syndrome. *Am J Pathol* 2007;170(4):1136–47. <https://doi.org/10.2353/ajpath.2007.061088>
  89. Yao XH, Li TY, He ZC *et al.* A pathological report of three COVID-19 cases by minimally invasive autopsies. *Zhonghua Bing Li Xue Za Zhi* 2020;49(5):411–7. <https://doi.org/10.3760/cma.j.cn112151-20200312-00193>
  90. Varga Z, Flammer AJ, Steiger P *et al.* Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020;395(10234):1417–8. [https://doi.org/10.1016/S0140-6736\(20\)30937-5](https://doi.org/10.1016/S0140-6736(20)30937-5)
  91. Zhang C, Wang FS, Silvestre JS *et al.* Is aberrant CD8<sup>+</sup> T cell activation by hypertension associated with cardiac injury in severe cases of COVID-19? *Cell Mol Immunol* 2020;17(6):675–6. <https://doi.org/10.1038/s41423-020-0454-3>



92. Bavishi C, Bonow RO, Trivedi V, Abbott JD, Messerli FH, Bhatt DL. Acute myocardial injury in patients hospitalized with COVID-19 infection: a review. *Prog Cardiovasc Dis* 2020;63(5):682–9. <https://doi.org/10.1016/j.pcad.2020.05.013>
93. Muller WA. Leukocyte-endothelial-cell interactions in leukocyte transmigration and the inflammatory response. *Trends Immunol* 2003;24(6):327–34. [https://doi.org/10.1016/s1471-4906\(03\)00117-0](https://doi.org/10.1016/s1471-4906(03)00117-0)
94. Kamphuis E, Junt T, Waibler Z *et al.* Type I interferons directly regulate lymphocyte recirculation and cause transient blood lymphopenia. *Blood* 2006;108(10):3253–61. <https://doi.org/10.1182/blood-2006-06-027599>
95. Lucas C, Wong P, Klein J *et al.* Yale IMPACT Team. Longitudinal analyses reveal immunological misfiring in severe COVID-19. *Nature* 2020;584(7821):463–9. <https://doi.org/10.1038/s41586-020-2588-y>
96. Zheng M, Gao Y, Wang G *et al.* Functional exhaustion of antiviral lymphocytes in COVID-19 patients. *Cell Mol Immunol* 2020;17(5):533–5. <https://doi.org/10.1038/s41423-020-0402-2>
97. 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):420–2. [https://doi.org/10.1016/S2213-2600\(20\)30076-X](https://doi.org/10.1016/S2213-2600(20)30076-X)
98. 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. <https://doi.org/10.1172/jci.insight.137799>
99. Zheng HY, Zhang M, Yang CX *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):541–3. <https://doi.org/10.1038/s41423-020-0401-3>
100. Westmeier J, Paniskaki K, Karakose Z *et al.* Impaired cytotoxic CD8<sup>(+)</sup> T cell response in elderly COVID-19 patients. *mBio* 2020;11(5):e02243–20. <https://doi.org/10.1128/mBio.02243-20>
101. Chen Z, John Wherry E. T cell responses in patients with COVID-19. *Nat Rev Immunol* 2020;20(9): 529–36. <https://doi.org/10.1038/s41577-020-0402-6>
102. Liu C, Martins AJ, Lau WW *et al.* NIAID COVID Consortium; COVID Clinicians. Time-resolved systems immunology reveals a late juncture linked to fatal COVID-19. *Cell* 2021;184(7): 1836–57:e1822. <https://doi.org/10.1016/j.cell.2021.02.018>
103. Li S, Zhang Y, Guan Z *et al.* SARS-CoV-2 triggers inflammatory responses and cell death through caspase-8 activation. *Signal Transduct Target Ther* 2020;5(1):235. <https://doi.org/10.1038/s41392-020-00334-0>
104. Chen RF, Chang JC, Yeh WT *et al.* Role of vascular cell adhesion molecules and leukocyte apoptosis in the lymphopenia and thrombocytopenia of patients with severe acute respiratory syndrome (SARS). *Microbes Infect* 2006;8(1):122–7. <https://doi.org/10.1016/j.micinf.2005.06.007>
105. Karki R, Sharma BR, Tuladhar S *et al.* Synergism of TNF- $\alpha$  and IFN- $\gamma$  triggers inflammatory cell death, tissue damage, and mortality in SARS-CoV-2 infection and cytokine shock syndromes. *Cell* 2021;184(1), 149–168 e117. <https://doi.org/10.1016/j.cell.2020.11.025>
106. Dondi E, Roué G, Yuste VJ *et al.* A dual role of IFN- $\alpha$  in the balance between proliferation and death of human CD4<sup>+</sup> T lymphocytes during primary response. *J Immunol* 2004;173(6):3740–47. <https://doi.org/10.4049/jimmunol.173.6.3740>
107. Gonzalez-Gay MA, Mayo J, Castaneda S, Cifrian JM, Hernandez-Rodriguez J. Tocilizumab: from the rheumatology practice to the fight against COVID-19, a virus infection with multiple faces. *Expert Opin Biol Ther* 2020;20(7):717–23. <https://doi.org/10.1080/14712598.2020.1770222>
108. Benucci M, Giannasi G, Cecchini P *et al.* COVID-19 pneumonia treated with Sarilumab: A clinical series of eight patients. *J Med Virol* 2020;92(11):2368–70. <https://doi.org/10.1002/jmv.26062>
109. Addeo A, Obeid M, Friedlaender A. COVID-19 and lung cancer: risks, mechanisms and treatment interactions. *J Immunother Cancer* 2020;8(1):e000892. <https://doi.org/10.1136/jitc-2020-000892>
110. Liu Y, Pang Y, Hu Z *et al.* Thymosin alpha 1 (Talpha1) reduces the mortality of severe COVID-19 by restoration of lymphocytopenia and reversion of exhausted T cells. *Clin Infect Dis* 2020;71(16):2150–7. <https://doi.org/10.1093/cid/ciaa630>
111. Riva G, Nasillo V, Tagliafico E *et al.* COVID-19: room for treating T cell exhaustion? *Crit Care* 2020;24(1):229. <https://doi.org/10.1186/s13054-020-02960-0>
112. Patterson BK, Seethamraju H, Dhody K *et al.* Disruption of the CCL5/RANTES-CCR5 pathway restores immune homeostasis and reduces plasma viral load in critical COVID-19. *medRxiv* 2020;2020.05.02.20084673. <https://doi.org/10.1101/2020.05.02.20084673>
113. Chua RL, Lukassen S, Trump S *et al.* COVID-19 severity correlates with airway epithelium-immune cell interactions identified by single-cell analysis. *Nat Biotechnol* 2020;38(8):970–9. <https://doi.org/10.1038/s41587-020-0602-4>
114. Omarjee L, Janin I, Perrot F *et al.* Targeting T-cell senescence and cytokine storm with rapamycin to prevent severe progression in COVID-19. *Clin Immunol* 2020;216:108464. <https://doi.org/10.1016/j.clim.2020.108464>
115. Zhou Y, Hou Y, Shen J *et al.* Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2. *Cell Discov* 2020;6:14. <https://doi.org/10.1038/s41421-020-0153-3>
116. Gordon AC, Mouncey PR, Al-Beidh F *et al.*; REMAPCAP Investigators. Interleukin-6 receptor antagonists in critically ill patients with covid-19. *N Engl J Med* 2021;384(16):1491–502. <https://doi.org/10.1056/NEJMoa2100433>
117. Andreaskos E, Papadaki M, Serhan CN. Dexamethasone, pro-resolving lipid mediators and resolution of inflammation in COVID-19. *Allergy* 2020;76(3):626–8. <https://doi.org/10.1111/all.14595>

118. Tomazini BM, Maia IS, Cavalcanti AB *et al.* COALITION COVID-19 Brazil III Investigators. 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(13):1307–16. <https://doi.org/10.1001/jama.2020.17021>
119. Group RC, Horby P, Lim WS *et al.* Dexamethasone in hospitalized patients with covid-19 - preliminary report. *N Engl J Med* 2020;384(8):693–704. <https://doi.org/10.1056/NEJMoa2021436>
120. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Cain DW, Cidlowski JA. After 62 years of regulating immunity, dexamethasone meets COVID-19. *Nat Rev Immunol* 2020;324(13):1330–41. <https://doi.org/10.1001/jama.2020.17023>
121. Cain DW, Cidlowski JA. After 62 years of regulating immunity, dexamethasone meets COVID-19. *Nat Rev Immunol* 2020;20(10):587–8. <https://doi.org/10.1038/s41577-020-00421-x>
122. Tregoning JS, Brown ES, Cheeseman HM *et al.* Vaccines for COVID-19. *Clin Exp Immunol* 2020;202(2):162–92. <https://doi.org/10.1111/cei.13517>
123. Sahin U, Muik A, Derhovanessian E *et al.* COVID-19 vaccine BNT162b1 elicits human antibody and TH1 T cell responses. *Nature* 2020;586(7830):594–9. <https://doi.org/10.1038/s41586-020-2814-7>
124. Logunov DY, Dolzhikova IV, Zubkova OV *et al.* Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in formulations: two open, non randomised phase 1/2 studies from Russia. *Lancet* 2020; 396(10255):887–97. [https://doi.org/10.1016/S0140-6736\(20\)31866-3](https://doi.org/10.1016/S0140-6736(20)31866-3)
125. Zhu FC, Li YH, Guan XH *et al.* Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial. *Lancet* 2020;395(10240):1845–54. [https://doi.org/10.1016/S0140-6736\(20\)31208-3](https://doi.org/10.1016/S0140-6736(20)31208-3)
126. Zhu FC, Guan XH, Li YH *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. *Lancet* 2020;396(10249):479–88. [https://doi.org/10.1016/S0140-6736\(20\)31605-6](https://doi.org/10.1016/S0140-6736(20)31605-6)
127. Folegatti PM, Ewer KJ, Aley PK *et al.*; Oxford COVID Vaccine Trial Group. 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. *Lancet* 2020;396(10249):467–78. [https://doi.org/10.1016/S0140-6736\(20\)31604-4](https://doi.org/10.1016/S0140-6736(20)31604-4)
128. Prendecki M, Clarke C, Brown J *et al.* Effect of previous SARS-CoV-2 infection on humoral and T-cell responses to single-dose BNT162b2 vaccine. *Lancet* 2021;397(10280):1178–81. [https://doi.org/10.1016/S0140-6736\(21\)00502-X](https://doi.org/10.1016/S0140-6736(21)00502-X)
129. Mahase E. Covid-19: what do we know about “long covid”? *BMJ* 2020;370:m2815. <https://doi.org/10.1136/bmj.m2815>
130. Carfi A, Bernabei R, Landi F; Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent symptoms in patients after acute COVID-19. *JAMA* 2020;324(6):603–5. <https://doi.org/10.1001/jama.2020.12603>
131. Zhang H, Wu T. CD4<sup>+</sup>T, CD8<sup>+</sup>T counts and severe COVID-19: a meta-analysis. *J Infect* 2020; 81(3):e82–e84. <https://doi.org/10.1016/j.jinf.2020.06.036>
132. Hu D, Li L, Shi W *et al.* Less expression of CD4<sup>+</sup> and CD8<sup>+</sup> T cells might reflect the severity of infection and predict worse prognosis in patients with COVID-19: Evidence from a pooled analysis. *Clin Chim Acta* 2020;510:1–4. <https://doi.org/10.1016/j.cca.2020.06.040>
133. Huang W, Berube J, McNamara M *et al.* Lymphocyte subset counts in COVID-19 patients: a meta-analysis. *Cytometry A* 2020;97(8):772–6. <https://doi.org/10.1002/cyto.a.24172>
134. Akbari H, Tabrizi R, Lankarani KB *et al.* The role of cytokine profile and lymphocyte subsets in the severity of coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. *Life Sci* 2020;258:118167. <https://doi.org/10.1016/j.lfs.2020.118167>