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Effects of severe acute respiratory syndrome (SARS) coronavirus infection on peripheral blood lymphocytes and their subsets

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KEYWORDS

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Summary

Introduction: Severe acute respiratory syndrome (SARS) caused large outbreaks of atypical pneumonia in 2003, with the largest localized outbreak occurring in Beijing, China. Lymphopenia was prominent amongst the laboratory abnormalities reported in acute SARS.

Methods: The effect of SARS on peripheral blood lymphocytes and their subsets was examined in 271 SARS coronavirus-infected individuals.

Results: There was a significant decrease in the CD45+, CD3+, CD4+, CD8+, CD19+ and CD16+/56+ cell counts over the five weeks of the SARS illness although CD4+/CD8+ ratios did not change significantly. The lymphopenia was prolonged, reaching a nadir during days 7–9 in the second week of illness before returning towards normal after five weeks, with the lowest mean CD4+ cell count of 317 cells $\times 10^6/L$ at day 7, and CD8+ cell count of 239 cells $\times 10^6/L$ at day 8. Patients with more severe clinical illness, or patients who died, had significantly more profound CD4+ and CD8+ lymphopenia.

Discussion: Lymphopenia is a prominent part of SARS-CoV infection and lymphocyte counts may be useful in predicting the severity and clinical outcomes. Possible reasons for the SARS-associated lymphopenia may be direct infection of lymphocytes by SARS-

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CoV, lymphocyte sequestration in the lung or cytokine-mediated lymphocyte trafficking. There may also be immune-mediated lymphocyte destruction, bone marrow or thymus suppression, or apoptosis.

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Introduction

Severe acute respiratory syndrome (SARS) is a new emerging disease that has affected many countries, with the World Health Organization (WHO) reporting 8422 probable cases up to 7 August 2003. There have been 916 deaths with a reported mortality of 10.9%.¹ Most cases have occurred in China (5327 cases), Taiwan, Hong Kong SAR, Singapore and Canada. The largest localized outbreak worldwide has been in Beijing, with 2521 cases. Three hundred and four patients fitting the clinical case definition of SARS were hospitalized at the Ditan Hospital in Beijing between 26 March and 31 May 2003.

Most early reports classified cases as SARS on the basis of clinical case definitions, although the recognition of the SARS-CoV as the causative agent allowed specific laboratory confirmation to be made.^{2–10} Approximately 75% of patients presenting with SARS have a laboratory-confirmed SARS-CoV infection,⁵ with the remainder either having other infectious causes of severe atypical pneumonia or undetected SARS-CoV infection. Among the clinical and laboratory features of SARS, a number of hematological abnormalities have been described. Prominent amongst these is a total lymphopenia, although in most studies lymphocyte subset analyses were not reported.^{4,6,8–11}

In this study, an examination of lymphocyte subsets was undertaken in a cohort of 271 laboratory-confirmed cases of SARS.

Methods

The daily clinical and laboratory findings of 304 SARS patients at the Ditan Hospital in Beijing were entered on a pre-designed database. The clinical case definition of probable SARS included a fever of 38 °C or higher, cough or shortness of breath, new pulmonary infiltrates on chest radiography, and close contact with a person who is a suspected or probable case of SARS. Day 1 of illness was defined as the day of onset of fever. Blood was collected for SARS-CoV specific antibody testing from all patients during hospitalization. SARS-CoV specific IgM and IgG were detected using an indirect immunofluorescence assay (IFA, Euroimmun AG, Lubeck, Ger-

many), SARS-CoV RNA was detected in throat washes, stools and blood using a SARS-CoV RNA fluorescence quantitative RT-PCR assay (ShenZhen PJ Company, Shenzhen, Guangdong Province, China). Immunological tests included T, NK and B lymphocyte cell counts by flow cytometry (MultiTEST CD45Percp/CD3FITC/CD4APC/CD8PE TruCount Four-Color kit, MultiTEST CD45Percp/CD3FITC/CD16+56PE/CD19APC TruCount Four-Color kit, BD Biosciences, San Jose, CA, USA). Lymphocyte counts were performed as controls on 51 non-SARS-affected and otherwise healthy individuals. All analyses were performed at a single laboratory. The study was approved by the Ethics Committee of Ditan Hospital, Beijing, China.

Patients satisfying the case definition of probable SARS were retrospectively classified after discharge into non-severe (122) and severe (149) cases. The non-severe and severe groups were defined according to 'The standard of clinical diagnosis for atypical pneumonia' guidelines listed by the Chinese Public Health Ministry on 4 May 2003. The patients in the non-severe group had a fever of 38 °C or higher, a cough or shortness of breath, and new pulmonary infiltrates on chest radiography. The patients in the severe group had in addition at least one of the following features: dyspnea (respiratory rate >30/minute), hypoxemia (PaO₂ <70 mmHg or SpO₂ <93% whilst on oxygen at a rate of 3–5 L/minute), acute lung injury/acute respiratory distress syndrome, a chest radiograph showing multifocal involvement over one third of the lung fields (or that developed to 50% in 48 hours), and shock or multiple organ dysfunction syndrome (MODS). They also had other underlying diseases, developed a secondary infection or were over 50 years old. Patients satisfying the case definition of probable SARS were retrospectively classified after discharge into those who recovered (246 cases) and those who died from SARS (25).

Results

Probable SARS patients were regarded as laboratory confirmed if they had at least one of the following: SARS-CoV IgG and/or IgM antibody detected by IFA three or more weeks after the onset of the illness,

and/or SARS-CoV RNA detected by RT-PCR during the first two weeks of illness.

In this study, 271/304 (89.1%) patients were laboratory confirmed as having SARS, including 148 (55%) with SARS-CoV detected by RT-PCR on respiratory tract or fecal samples. Of the 148 SARS-CoV RT-PCR positive samples, SARS-CoV IgG was detected in 145 (98%) and SARS-CoV IgM in 117 (79%) using IFA.¹² There were 33/304 (10.9%) that were negative on SARS testing. An alternative laboratory diagnosis was made in 27/33, of which the most common were acute influenza B (13 cases) and *Klebsiella pneumoniae* infection (nine cases). The mean age of the 271 laboratory-confirmed SARS cases was 36 ± 16 years, with 51 (18.8%) over 50 years of age and nine (3.3%) under 18 years. There were 157 (57.9%) females and 114 (42.1%) males. There were 92 (33.9%) health care workers, including 51 nurses, 30 physicians and 11 others in the cohort. Thirty-two patients had underlying health problems, including diabetes (18 cases), cardiac disease (eight cases), malignancy (four cases), chronic airways disease (one case) and chronic renal failure (one case). One hundred and twelve individuals (41.3%) acquired SARS in the hospital setting as health care workers, inpatients, or visitors, mostly in the wards of the hospital. A further 62 cases were infected following home exposure, when family members or friends of hospital-associated cases had come into close contact with affected individuals.

Lymphocyte subsets

The lymphocyte subpopulation counts were compared between 696 samples collected from 271 cases of laboratory-confirmed SARS patients and 51 controls (Table 1). The total lymphocyte counts from SARS patients were compared with those from normal individuals, and the lymphocyte counts at each week after the onset of the illness were compared with other weeks of illness and with those from normal individuals. Using nonparametric tests there were significant decreases in the CD45+, CD3+, CD4+, CD8+, CD19+ and CD16/56+ counts over each of the five weeks of the SARS illness compared to healthy controls, although the CD4+/CD8+ ratio did not change significantly over the course of the illness. The various lymphocyte populations (CD45+, CD3+, CD4+ and CD8+) were below the normal ranges in the first week of the clinical illness, reaching a nadir during the second week before returning towards normal levels. There were significant differences in lymphocyte subset counts between weeks 1 and 2, weeks 2 and 3, weeks 4 and 5, and weeks 1 and 5 (Table 1) (Figures 1–3).

Table 1 Changes in lymphocyte subset counts of SARS patients compared with normal individuals over five weeks of illness.

Groups	Samples	Lymphocytes $\times 10^6/L$						
		CD45+	CD3+	CD4+	CD8+	CD4+/CD8+	CD19+	CD16/56+
SARS patients								
1st week	126	1057 \pm 512 ^{3,6}	696 \pm 371 ^{3,6}	386 \pm 244 ³	290 \pm 153 ^{3,6}	1.42 \pm 0.72 ³	170 \pm 105 ³	16 \pm 113 ^{3,5}
2nd week	186	977 \pm 579 ^{3,7}	641 \pm 466 ^{3,7}	360 \pm 275 ^{3,7}	270 \pm 216 ^{3,7}	1.47 \pm 0.82 ^{3,8}	205 \pm 152 ^{3,7}	115 \pm 91 ³
3rd week	163	1403 \pm 835 ³	989 \pm 623 ³	570 \pm 374 ³	389 \pm 269 ³	1.58 \pm 0.73 ⁴	270 \pm 187 ³	122 \pm 133 ³
4th week	111	1471 \pm 872 ^{3,9}	1056 \pm 672 ^{3,9}	593 \pm 394 ^{3,9}	435 \pm 328 ^{3,10}	1.53 \pm 0.66 ⁴	263 \pm 205 ³	117 \pm 94 ³
5th week	110	1727 \pm 881 ^{3,11}	1263 \pm 669 ^{3,11}	733 \pm 453 ^{3,11}	483 \pm 274 ^{3,11}	1.60 \pm 0.66 ^{4,12}	309 \pm 233 ^{4,11}	137 \pm 116 ^{3,11}
Total	696	1298 \pm 785 ¹	897 \pm 606 ¹	510 \pm 372 ¹	362 \pm 263 ¹	1.51 \pm 0.73 ²	236 \pm 181 ¹	131 \pm 111 ¹
Normals	51	2024 \pm 423	1391 \pm 289	795 \pm 129	551 \pm 183	1.57 \pm 0.44	317 \pm 111	279 \pm 162

Counts expressed as cells $\times 10^6/L \pm 1$ standard deviation. Reduction of total lymphocyte counts over five weeks of illness from SARS patients compared with those of normal individuals: ¹ $p < 0.01$, ² $p < 0.05$. Reduction of lymphocyte counts from each week of illness from SARS patients compared with those of normal individuals: ³ $p < 0.01$, ⁴ $p > 0.05$. Reduction of lymphocyte counts in week 2 of illness from SARS patients compared to week 1 of illness: ⁵ $p < 0.01$, ⁶ $p < 0.05$. Reduction of lymphocyte counts in week 3 of illness from SARS patients compared to week 2 of illness: ⁷ $p < 0.01$, ⁸ $p < 0.05$. Reduction of lymphocyte counts in week 4 of illness from SARS patients compared to week 5 of illness: ⁹ $p < 0.01$, ¹⁰ $p < 0.05$. Reduction of lymphocyte counts in week 1 of illness from SARS patients compared to week 5 of illness: ¹¹ $p < 0.01$, ¹² $p < 0.05$.

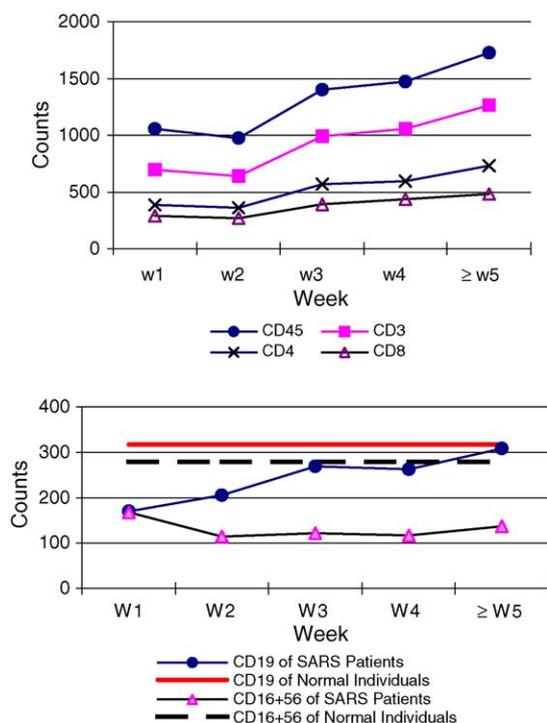


Figure 1 Kinetics of CD45+, CD4+, CD8+, CD3+, CD19+ and CD16+56+ lymphocyte subsets (expressed as mean number of cells $\times 10^6/L$) measured over the first five weeks of illness in laboratory-confirmed SARS patients and in otherwise healthy controls.

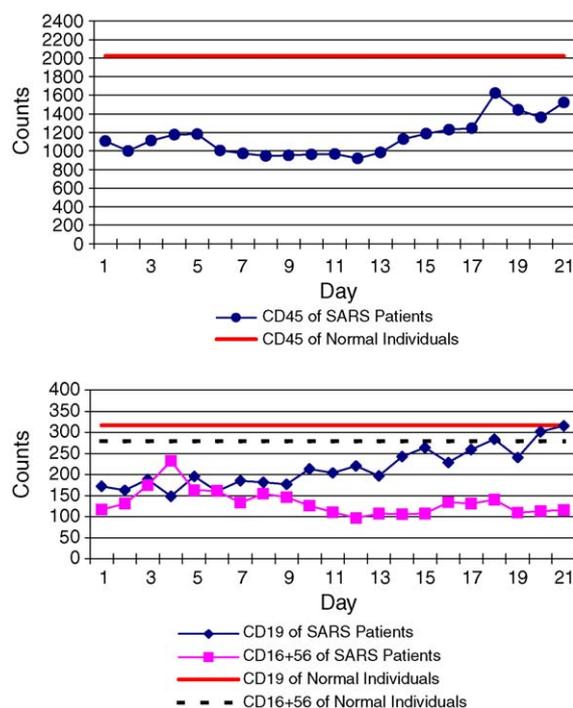


Figure 2 Kinetics of CD45+, CD19+, CD16+56+ lymphocytes (expressed as mean number of cells $\times 10^6/L$) measured over the first 21 days of illness in laboratory-confirmed SARS patients and in otherwise healthy controls.

Table 2 Kinetics of CD45+, CD3+, CD4+, CD8+, CD19+ and CD16/56+ counts (expressed as cells $\times 10^6/L \pm 1$ standard deviation) in SARS patients during the first 21 days of illness.

Day after onset	Cases	CD45+ No. \pm SD	CD3+ No. \pm SD	CD4+ No. \pm SD	CD8+ No. \pm SD	CD19+ No. \pm SD	CD16/56+ No. \pm SD
1	14	1108 \pm 694	810 \pm 525	496 \pm 357	309 \pm 198	172 \pm 109	117 \pm 65
2	13	1000 \pm 525	668 \pm 400	367 \pm 245	293 \pm 211	163 \pm 174	131 \pm 57
3	25	1111 \pm 528	767 \pm 394	412 \pm 202	317 \pm 186	188 \pm 164	174 \pm 105
4	29	1174 \pm 521	777 \pm 376	457 \pm 287	314 \pm 120	148 \pm 78	232 \pm 159
5	33	1181 \pm 666	779 \pm 477	446 \pm 333	299 \pm 163	196 \pm 108	163 \pm 103
6	40	1006 \pm 487	651 \pm 369	349 \pm 217	285 \pm 162	160 \pm 85	162 \pm 108
7	28	973 \pm 495	603 \pm 329	317 \pm 185	275 \pm 168	185 \pm 118	133 \pm 97
8	40	949 \pm 393	582 \pm 268	323 \pm 190	239 \pm 105	182 \pm 107	155 \pm 150
9	39	950 \pm 564	606 \pm 449	322 \pm 256	276 \pm 253	177 \pm 107	146 \pm 152
10	41	964 \pm 589	643 \pm 507	348 \pm 284	282 \pm 237	213 \pm 145	126 \pm 87
11	54	969 \pm 669	632 \pm 484	356 \pm 293	252 \pm 187	204 \pm 160	111 \pm 95
12	38	920 \pm 555	593 \pm 423	330 \pm 266	258 \pm 215	220 \pm 185	96 \pm 63
13	36	983 \pm 500	655 \pm 391	385 \pm 249	251 \pm 141	196 \pm 126	108 \pm 76
14	31	1126 \pm 909	745 \pm 706	437 \pm 435	319 \pm 294	243 \pm 175	106 \pm 108
15	39	1187 \pm 764	782 \pm 516	440 \pm 322	318 \pm 208	263 \pm 235	107 \pm 88
16	33	1227 \pm 836	854 \pm 629	485 \pm 366	361 \pm 298	228 \pm 121	134 \pm 194
17	28	1244 \pm 635	854 \pm 478	514 \pm 330	315 \pm 172	259 \pm 146	130 \pm 121
18	35	1621 \pm 990	1178 \pm 744	662 \pm 407	459 \pm 323	284 \pm 188	139 \pm 138
19	32	1440 \pm 667	1053 \pm 551	603 \pm 345	443 \pm 264	240 \pm 126	110 \pm 86
20	26	1365 \pm 875	958 \pm 691	526 \pm 423	366 \pm 252	301 \pm 212	113 \pm 101
21	27	1521 \pm 1057	1063 \pm 732	622 \pm 436	416 \pm 345	315 \pm 253	115 \pm 135

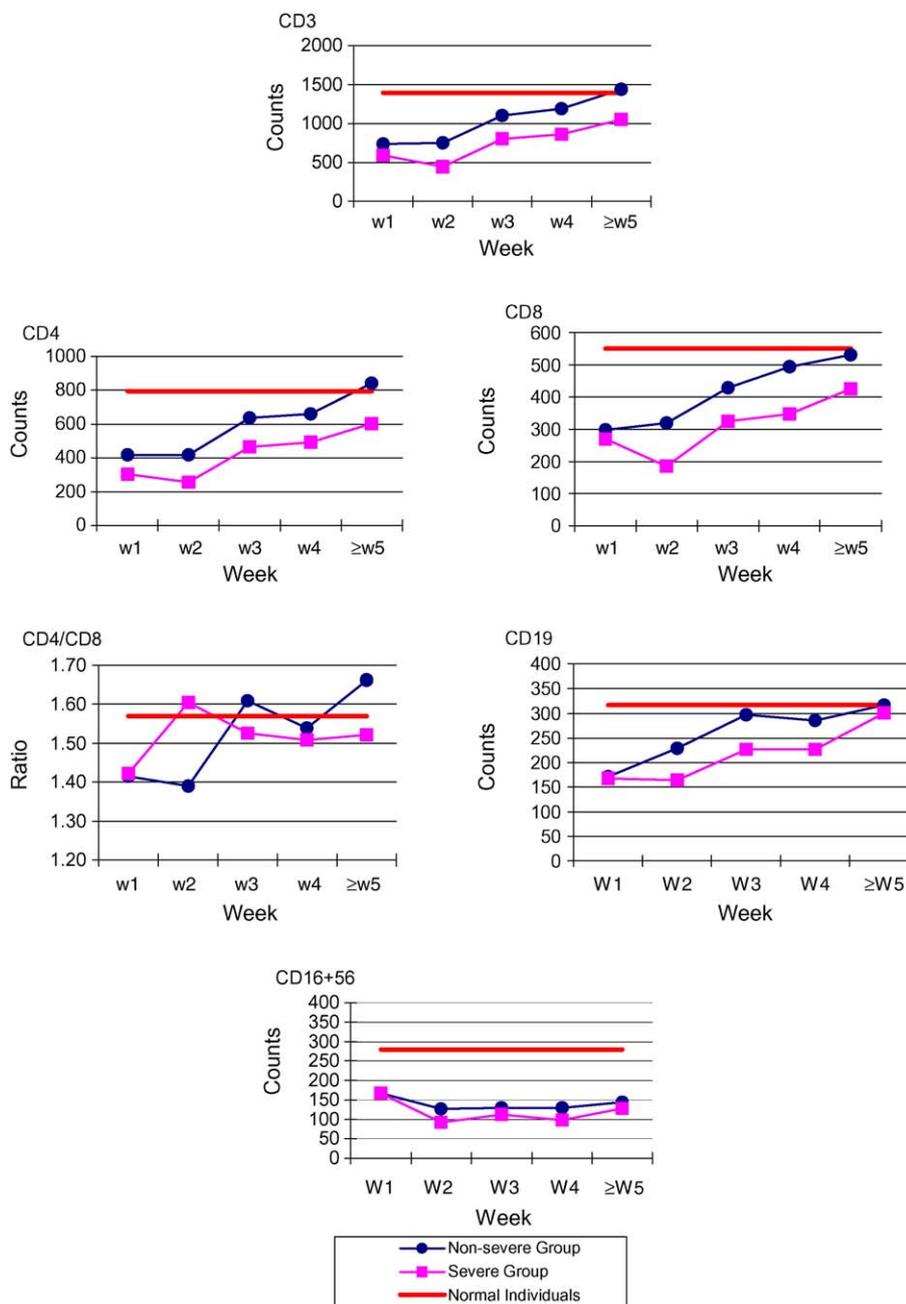


Figure 3 Kinetics of lymphocyte subsets (expressed as mean number of cells $\times 10^6/L$) measured over the first five weeks of illness in non-severe and severe laboratory-confirmed SARS patients, and in otherwise healthy controls.

These observations are further defined in [Table 2](#) where the CD45+, CD3+, CD4+, CD8+, CD19+ and CD16/56+ counts on samples collected daily during the first 21 days of SARS are listed. The total, CD4+ and CD8+ lymphopenia was most marked at days 7–9 in the second week of the illness. In [Table 3](#) the lymphocyte subpopulation counts were compared between those with severe SARS (260 samples from 149 patients), non-severe SARS (436 samples from 122 patients), and those that recovered (613 samples from 246 cases) or died (48 samples from 25 patients) from SARS. The CD45+, CD3+, CD4+, CD8+,

CD19+ and CD16/56+ counts were significantly lower (using nonparametric tests) in those patients that died compared to those who recovered, and in those with severe disease compared to those with non-severe disease.

Discussion

The interaction between the SARS-CoV and the immune system is complex. In this study, lymphocyte subsets were measured over five weeks in 271

Table 3 Lymphocyte subpopulation counts in severe and non-severe SARS cases, and in patients who recovered or died of SARS.

Lymphocytes	Groups	1st week	2nd week	3rd week	4th week	5th week
		NS = 91, S = 35 R = 113, D = 8	NS = 118, S = 68 R = 158, D = 19	NS = 101, S = 62 R = 144, D = 11	NS = 66, S = 45 R = 98, D = 6	NS = 60, S = 50 R = 100, D = 4
CD45+	Non-severe (NS)	1104 ± 520 ¹	1123 ± 627 ¹	1550 ± 823 ¹	1624 ± 828 ¹	1922 ± 911 ¹
	Severe (S)	936 ± 478	723 ± 366	1162 ± 805	1247 ± 897	1493 ± 791
	Recovery (R)	1100 ± 518 ³	1039 ± 593 ³	1462 ± 793 ³	1542 ± 857 ³	1802 ± 862 ³
	Death (D)	609 ± 201	552 ± 285	742 ± 892	481 ± 470	437 ± 237
CD3+	Non-severe	737 ± 373 ¹	752 ± 514 ¹	1101 ± 600 ¹	1189 ± 646 ¹	1439 ± 688 ¹
	Severe	591 ± 350	447 ± 280	805 ± 621	860 ± 669	1052 ± 586
	Recovery	726 ± 375 ³	688 ± 482 ³	1033 ± 598 ³	1115 ± 664 ³	1324 ± 652 ³
	Death	394 ± 193	310 ± 178	521 ± 693	303 ± 264	283 ± 181
CD4+	Non-severe	418 ± 261 ¹	419 ± 303 ¹	635 ± 361 ¹	661 ± 353 ¹	843 ± 485 ¹
	Severe	303 ± 167	257 ± 179	463 ± 373	493 ± 432	601 ± 374
	Recovery	401 ± 248 ³	386 ± 285 ³	596 ± 365 ³	627 ± 390 ³	771 ± 450 ³
	Death	223 ± 124	170 ± 104	276 ± 340	185 ± 153	160 ± 111
CD8+	Non-severe	299 ± 138 ¹	319 ± 244 ¹	429 ± 264 ¹	494 ± 334 ¹	532 ± 284 ¹
	Severe	269 ± 188	185 ± 118	325 ± 268	347 ± 301	425 ± 252
	Recovery	302 ± 155 ³	291 ± 226 ³	406 ± 260 ³	462 ± 329 ³	505 ± 268 ³
	Death	168 ± 98	133 ± 88	195 ± 216	119 ± 115	116 ± 67
CD4+/CD8+	Non-severe	1.42 ± 0.59 ²	1.39 ± 0.61 ¹	1.61 ± 0.71 ²	1.54 ± 0.65 ²	1.66 ± 0.70 ²
	Severe	1.42 ± 1.00	1.61 ± 1.09	1.53 ± 0.77	1.50 ± 0.67	1.52 ± 0.60
	Recovery	1.39 ± 0.58 ⁴	1.44 ± 0.74 ⁴	1.59 ± 1.70 ⁴	1.52 ± 0.68 ⁴	1.62 ± 0.68 ⁴
	Death	1.85 ± 1.85	1.73 ± 1.40	1.41 ± 1.05	1.72 ± 0.49	1.32 ± 0.19
CD19+	Non-severe	171 ± 101 ²	228 ± 173 ¹	297 ± 209 ²	286 ± 225 ²	316 ± 255 ²
	Severe	167 ± 118	164 ± 94	226 ± 138	226 ± 164	300 ± 206
	Recovery	175 ± 107 ³	216 ± 157 ³	283 ± 187 ³	291 ± 219 ³	291 ± 219 ³
	Death	114 ± 62	107 ± 54	159 ± 173	170 ± 211	170 ± 211
CD16/56+	Non-severe	167 ± 113 ²	127 ± 99 ¹	129 ± 118 ²	129 ± 99 ²	144 ± 108 ²
	Severe	167 ± 113	93 ± 69	113 ± 155	98 ± 83	129 ± 125
	Recovery	172 ± 115 ³	117 ± 92 ³	130 ± 138 ³	131 ± 105 ³	131 ± 105 ³
	Death	93 ± 47	97 ± 84	45 ± 35	54 ± 91	54 ± 91

NS = non-severe cases; S = severe cases; R = recovered cases; D = cases that died. Counts expressed as cells × 10⁶/L ± 1 standard deviation. Comparison of lymphocyte counts between the severe and non-severe SARS cases at each week (1–5) of illness: ¹*p* < 0.05, ²*p* > 0.05. Comparison of lymphocyte counts between cases who died and those cases who survived at each week (1–5) of illness: ³*p* < 0.01, ⁴*p* > 0.05.

laboratory-proven non-severe and severe cases of SARS, where patients either recovered or died. Total lymphocyte counts decreased in the first two weeks of illness (the nadir was in week 2) before increasing in the third week and returning to normal levels by the fifth week. Peripheral blood lymphocyte subsets (CD45+, CD3+, CD4+, CD8+) were quantitated by dynamic methods in a large cohort of 271 laboratory-proven cases of SARS.

This study confirms observations of lymphopenia noted in most other series of SARS cases.^{4,6,8–11} A study in Hong Kong reported an absolute lymphopenia (<1000 × 10⁶/L) in 98% of patients during the course of their illness, most marked in the second week.¹¹ The data discussed here extend these observations (and provide the first data from mainland China), showing that the total lymphocyte counts of SARS patients were lower than those of normal individuals throughout the clinical course, and that this was more marked in severe

disease compared to less severe illness, and in those who died compared to the survivors. A study of 75 patients from the Amoy Gardens outbreak in Hong Kong did not find an association of total lymphocyte counts and progression to ventilatory support and intensive care,¹⁰ although there are differences in the progression to acute respiratory distress syndrome (ARDS), oxygen saturation and gastrointestinal symptoms in these two cohorts. However, an association of lymphopenia with more severe disease was seen in another cohort of SARS cases from Hong Kong.⁶ In contrast with other series of adult SARS cases, in the study reported here all patients had laboratory evidence of SARS-CoV infection. In two series totalling 25 children with probable or suspect SARS (although only four children had laboratory-proven SARS), total lymphopenia was common and more prominent in older children with more severe disease.^{13,14}

Lymphocyte subsets (CD4+, CD8+, CD19+ and CD16/56+) were also counted in all patients. A significant CD4+ and CD8+ T cell lymphopenia has been observed in the first two weeks of the SARS illness in 31 patients,¹¹ but in this study, a more prolonged CD4+ and CD8+ lymphopenia was noted. CD4+ and CD8+ cells fell by approximately one half in the second week of the illness before returning to near normal by the end of week 5. In addition, patients with more severe disease had lower counts that took longer to rise. The data show that the CD4+ and CD8+ counts were lower in more severely ill patients and in those that died. The CD4+/CD8+ ratios were not significantly different in the various patient groups. CD19+ B lymphocytes were the first lymphocytes to numerically recover after two weeks and their recovery was associated with the appearance of SARS-CoV specific IgG and IgM. CD16/56+ NK cells also began to decrease in the first week (although there was a rise in NK cells towards the end of week 1) to their lowest levels during week 4, and had not returned to normal by week 5.

Lymphopenia is a prominent part of SARS-CoV infection and lymphocyte counts may be useful in predicting the severity and clinical outcomes. Total and subset lymphopenia occurs in other acute (e.g. measles, cytomegalovirus) and chronic (e.g. HIV) viral infections in humans and animals, but lymphopenia has not been a feature of other human coronavirus infections in adults.^{15–17} Lymphopenia has been described in some cases of experimental coronavirus 229E infections in humans.¹⁸ A possible reason for the lymphopenia may be that lymphocytes are directly infected and destroyed by SARS-CoV. However, angiotensin-converting enzyme 2 has been identified as a functional cellular receptor for the SARS-CoV, a protein that is not expressed on B or T lymphocytes.^{19,20} This would suggest that direct viral invasion and destruction of lymphocytes is not a major cause of the acute lymphopenia in SARS, but this requires further study.

Other possible explanations for the lymphopenia are lymphocyte sequestration in the lung where SARS-CoV damage is most evident, or cytokine-mediated altered lymphocyte trafficking. There may be immune-mediated lymphocyte destruction (lymphocyte depletion has been noted in autopsies of lymph nodes from SARS cases),²¹ bone marrow or thymus suppression, or apoptosis. Apoptosis has been observed in vitro in measles-induced lymphopenia,²² and coronavirus 229E can cause in vitro apoptosis in monocytes/macrophages.²³ Whether different strains of SARS-CoV have variable effects on immune responses and clinical disease (as occurs with experimental measles in macaques)²⁴ is unknown. It is possible that the SARS-CoV-induced

immune suppression predisposes to secondary infections, especially in the more severely ill patients, and it is unknown if there are any longer term effects on humoral or cell-mediated immunity following SARS.

Conflict of interest: No conflict of interest to declare.

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