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Clinica Chimica Acta 508 (2020) 110–114

Contents lists available at ScienceDirect

Clinica Chimica Acta

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

Decreased T cell populations contribute to the increased severity of COVID-19

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ARTICLE INFO

Keywords:
COVID-19
Lymphocyte subsets
$CD3^+$ T cells
$CD4^+$ T cells
$CD8^+$ T cells

ABSTRACT

Background: We observe changes of the main lymphocyte subsets ($CD16^+CD56$、CD19、CD3、CD4、and CD8) in COVID-19-infected patients and explore whether the changes are associated with disease severity.
Methods: One-hundred and fifty-four cases of COVID-19-infected patients were selected and divided into 3 groups (moderate group, severe group and critical group). The flow cytometry assay was performed to examine the numbers of lymphocyte subsets.
Results: $CD3^+$, $CD4^+$ and CD8 + T lymphocyte subsets were decreased in COVID-19-infected patients. Compared with the moderate group and the sever group, $CD3^+$, $CD4^+$ and $CD8^+$ T cells in the critical group decreased greatly ($P < 0.001$, $P = 0.005$ or $P = 0.001$).
Conclusions: Reduced $CD3^+$, $CD4^+$, $CD8^+$ T lymphocyte counts may reflect the severity of the COVID-19. Monitoring T cell changes has important implications for the diagnosis and treatment of severe patients who may become critically ill.

1. Introduction

The COVID-19 is highly contagious and its pathologic mechanism has attracted a lot of attention [1–3]. Most patients eventually made a recovery after careful treatment, but, some had developed into severe and even critical illness [4]. To date, the detailed mechanisms underlying severe respiratory syndrome caused by COVID-19 coronavirus remain unclear [5]. What's worse, there is no vaccine or effective treatment to rescue severe patients who might be turned into patients with critical illness [3]. Therefore, to clarify the pathological differences between moderate, severe, and critical patients is urgent.

Cytokine storm, which is caused by excessive proinflammatory cytokine responses, is associated with a wide variety of infectious and noninfectious diseases [6,7]. It is suggested that a cytokine storm plays an important role in the aggravation of the COVID-19 [8]. One important immune cell type that can be activated by virus and initiate a cytokine storm is T cells. After activation by antigen-presenting cells, T cells undergo proliferation and differentiation into specific effector T cells to clear pathogens through producing a series of pro-inflammatory cytokines including IFN-γ, TNF-a, IL-6 [6,7]. However, whether T cells are involved in the progression of the COVID-19 is unknown.

2. Subjects & methods

2.1. Study population

The study covered 154 cases of novel coronavirus patients from the Renmin Hospital of Wuhan University between 22 January 2020 to 25 February 2020. The patients were divided into 3 groups according to the Diagnosis and Treatment of Novel Coronavirus Patients (the Fifth Pilot Ed.), moderate group (total 49, male 26 and female 23), sever group (total 61, male 34 and female 27), critical group (total 44, male

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https://doi.org/10.1016/j.cca.2020.05.019
Received 24 March 2020; Received in revised form 6 May 2020; Accepted 8 May 2020
Available online 13 May 2020
0009-8981/

24 and female 20). The average age of the moderate group, the sever group, and the critical group is 63 ± 13, 63 ± 14, and 65 ± 15 y, respectively. There is no statistical significance between gender and age among these 3 groups ($P > 0.05$).

All the experiments were performed at the Renmin Hospital of Wuhan University and the research was approved by the Ethics Committee of the Renmin Hospital of Wuhan University. All data were collected anonymously and recorded following the international standards for the protection of privacy and personal information.

2.2. Equipment and reagents

Flow cytometric analysis in our study was performed using a Flow Cytometer BNII (Becton Dickinson). Multitest™ 6-colour TBNK reagents were obtained from BD Biosciences.

2.3. Methods

Fasting blood were collected in heparin on all the patients involved was collected in early morning, all the tests were performed within 2 h. The expression of $CD16^+CD56$、CD19、CD3、CD4、CD8 were analyzed by a Flow Cytometer BNII and the data were analyzed using FACS Diva software (BD Biosciences).

2.4. Statistical analysis

Statistical analysis was performed using SPSS25.0, the non-normal distribution data were analyzed using Kruskal-Wallis test, medium values (P25-P75) were used to present the analysis data. The enumeration data were analyzed using χ^2 test or Fisher's test. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics

We collected data on demographic characteristics, comorbidities (diabetes mellitus, hypertension, cardiovascular, and cerebrovascular diseases, chronic liver disease, respiratory system disease and malignant tumor), and the outcome observed. A total of 154 patients hospitalized with COVID-19 were randomly selected, of whom 91 (59.09%) had at least one comorbidity (Table 1). It seems that patients with diabetes or cardiovascular and cerebrovascular diseases were more likely to develop into critically ill patients. While in patients with hypertension, chronic liver disease, and malignant tumor, there was no statistical difference among the moderate group, severe group and critical group. Surprisingly, patients with respiratory system disease also showed no effect on the severity of COVID-19. We also found that the patients in critical groups showed definite higher mortality than that in the other 2 groups. And there were no differences in the outcomes between the moderate group and the severe group. Differences in peripheral blood lymphocyte subsets among three groups of patients with COVID-19.

We examined the distribution of peripheral blood lymphocytes in patients infected with COVID-19 and correlations between the COVID-19 and the lymphocyte subsets. As shown in the following Table 2, the lymphocytes were decreased in most patients (72.73%). Compared to the moderate group (63.27%) and the severe group (73.77%), the lymphocytes numbers decreased significantly in the critical group (81.82%).

In our study (Fig. 1), the absolute value of $CD3^+$ T cells was below the normal range in 120 (77.92%) patients. Compared to the severe group, the median absolute value of $CD3^+$ T cells was significantly lowered ($P < 0.001$) in the critical group, whereas no significant difference was found between the moderate group and the severe group. The absolute value of $CD4^+$ T cells was below the normal range in 117 (75.97%) patients. Almost all the patients in the critical group showed low $CD4^+$ T cell counts (40/total 44, 90.91%). Moreover, a significantly lower median absolute value of $CD4^+$ T cells was observed in the critical group compared to the severe group ($P = 0.005$), but not in the moderate group versus the severe group. The absolute value of $CD8^+$ T cells was below the normal rage in 2/3 patients (105/total 154). Similar to $CD4^+$ T cells, compared to the severe group, the median absolute value of $CD8^+$ T cells was significantly lower in the critical group ($P = 0.005$), while no significant differences were found between the moderate group and the severe group. Meanwhile, the $CD4^+/CD8^+$ T cell ratio was below the normal range in 24 patients (15.58%) and above the normal range in 67 patients (43.51%). No statistical significant difference was observed among the three study groups in the two different disorders.

We also observed a reduction concerning the normal range of NK cells ($CD16^+CD56$) in 62 patients (40.26%) and B cells ($CD19^+$) in 39 patients (25.32%), but no statistical differences were found in absolute values of NK cells or B cells among the 3 groups.

4. Discussion

Whether T cells are involved in the progression of the COVID-19 is not clear. In this study, we found there was a strong correlation between the severity of COVID-19 and the $CD3^+$, $CD4^+$ and $CD8^+$ T lymphocytes. we have shown that the population of $CD3^+$, $CD4^+$ and $CD8^+$ Lymphocyte subsets is decreased when patients went from severe

Table 1
Demographics and baseline characteristics of patients infected with COVID-19.

	All patient (n = 154)	moderate group (n = 49)	severe group (n = 61)	critical group (n = 44)	p value
Age (y)	64 ± 14	63 ± 13	63 ± 14	65 ± 15	NS
Gender (male/Female)	84/70	26/23	34/27	24/20	NS
Chronic medical illness					
Any comorbidity	91 (59.09%)	28 (57.14%)	31 (50.82%)	32 (72.73%)	NS
Diabetes	19 (12.34%)	5 (10.20%)	4 (6.56%)	10 (22.73%)	0.039
Hypertension	48 (31.17%)	13 (26.53%)	16 (26.23%)	19 (43.18%)	NS
Cardiovascular and cerebrovascular diseases	30 (19.48%)	13 (26.53%)	2 (3.28%)	15 (34.09%)	< 0.001
Chronic liver disease	5 (3.25%)	2 (4.08%)	2 (3.28%)	1 (2.27%)	NS
Respiratory systemdisease	15 (9.74%)	2 (4.08%)	6 (9.84%)	7 (15.91%)	NS
Malignant tumor	3 (1.95%)	0 (0.00%)	2 (3.28%)	1 (2.27%)	NS
Clinical outcome					
Remained in hospital	41 (26.62%)	16 (32.65%)	13 (21.31%)	12 (27.27%)	NS
Transferred	10 (6.49%)	6 (12.24%)	4 (6.56%)	0 (0.00%)	NS
Discharged	76 (49.35%)	24 (48.98%)	42 (68.85%)	10 (22.73%)	< 0.001
Died	24 (15.58%)	2 (4.08%)	2 (3.28%)	20 (45.45%)	< 0.001

Note: Three patients lost case information and data are mean ± SD, n/n, or n (%). p values comparing moderate group, severe group and critical group are from χ^2 test or Fisher's exact test, or Variance analysis, $P < 0.05$ was defined as statistically significant.

Table 2
The comparison of lymphocyte subsets of patients infected with COVID-19 between different groups.

	All patient (n = 154)	moderate group (n = 49)	severe group (n = 61)	critical group (n = 44)	p value
CD16 + 56	109	118	99	95	NS
count, per ul	(64.75 ~ 170)	(76.5 ~ 184)	(54.5 ~ 160)	(61.25 ~ 181.75)	
< 84	62/154(40.26%)	14/49(28.57%)	27/61(44.26%)	21/44(47.73%)	NS
≥84	92/154(59.74%)	35/49(71.43%)	34/61(55.74%)	23/44(52.27%)	-
CD19	119.5	114	131	106.5	NS
count, per ul	(77.75 ~ 178.75)	(62.5 ~ 197)	(95.5 ~ 194.5)	(70 ~ 165)	
< 80	39/154(25.32%)	14/49(28.57%)	10/61(16.39%)	15/44(34.09%)	NS
≥80	115/154(74.68%)	35/49(71.43%)	51/61(83.61%)	29/44(65.91)	-
CD3	437.5	509	517	341.5	< 0.001
count, per ul	(308.75 ~ 648.25)	(336.5 ~ 873.5)	(376 ~ 651.5)	(226.75 ~ 440.5)	
< 723	120/154(77.92%)	32/49(65.31%)	50/61(81.97%)	38/44(86.36%)	0.031
≥723	34/154(22.08%)	17/49(34.69%)	11/61(18.03%)	6/44(13.64%)	-
CD4	276	290	292	192.5	0.005
count, per ul	(178 ~ 402.25)	(172.5 ~ 506)	(237.5 ~ 399.5)	(125.25 ~ 335.5)	
< 404	117/154(75.97%)	30/49(61.22%)	47/61(77.05%)	40/44(90.91%)	0.004
≥404	37/154(24.03%)	19/49(38.78%)	14/61(22.95%)	4/44(9.09%)	-
CD8	146.5	161	200	98.5	0.001
count, per ul	(89.75 ~ 257.25)	(101 ~ 302.5)	(93 ~ 261)	(54.5 ~ 158.75)	
< 220	105/154(68.18%)	31/49(63.27%)	37/61(60.66%)	37/44(84.09%)	0.026
≥220	49/154(31.82%)	18/49(36.73%)	24/61(39.34%)	7/44(15.91%)	-
CD4 count	1.76	1.89	1.75	1.74	NS
/CD8 count	(1.18 ~ 2.77)	(1.25 ~ 2.64)	(1.09 ~ 2.75)	(1.19 ~ 3.33)	
< 0.9	24/154(15.58%)	9/49(18.37%)	10/61(16.39%)	5/44(11.36%)	NS
0.9-2.0	63/154(40.91%)	18/49(36.73%)	24/61(39.34%)	21/44(47.73%)	-
≥2.0	67/154(43.51%)	22/49(44.90%)	27/61(44.26%)	18/44(40.91%)	-
Lymphocyte count, $\times 10^9$ per L	0.835	0.96	0.91	0.75	0.012
	(0.608 ~ 1.13)	(0.635 ~ 1.35)	(0.67 ~ 1.12)	(0.533 ~ 0.888)	
< 1.1	112/154(72.73%)	31(63.27%)	45(73.77%)	36(81.82%)	0.13
1.1-3.2	42/154(27.27%)	18(36.73%)	16(26.23%)	8(18.18%)	-

Note: Data are median (IQR) or n/N (%), where N is the total number of patients with available data. p values comparing moderate group, severe group and critical group are from χ^2, Fisher's exact test, or Kruskal-Wallis test, $P < 0.05$ was defined as statistically significant.

to critical whereas the populations of T cells are comparable between moderate and severe patients. However, there was no significant changes in the number of NK cells and B cells between these groups. Based on the data, our study has strengthened the significance of T cells in the clearance of the COVID-19 coronavirus.

Of the 154 patients with COVID-19 recruited, the median age was 63.90 y and 84 were male. In the cohort, we observed that 59% of patients had at least one underlying disorder including diabetes, hypertension, cardiovascular and cerebrovascular diseases, and chronic liver disease, respiratory system disease and malignant tumor. In accordance with previous reports, we observed that patients with diabetes or cardiovascular and cerebrovascular diseases were more likely to develop into critically ill patients [1,11]. However, there was no statistical difference in disease severity in patients with hypertension, chronic liver disease, malignant tumor, or even respiratory system disease, suggesting that different underlying diseases contribute differently to disease progression of COVID-19.

$CD3^+$ T cells are mainly composed of $CD4^+$ T cells and $CD8^+$ T cells. $CD4^+$ helper T cells have a crucial role in adaptive immune responses [9]. Upon antigen presentation, naïve $CD4^+$ T cells can differentiate into distinct subsets [10]. Among them, Th1 cells, which are induced by IL-12 and produce large quantities of IFN-γ, are involved in enhancing the clearance of certain intracellular pathogens, including viruses [10,11]. Besides, $CD8^+$ T cells restricted by class I major histocompatibility complex molecules are important in establishing immunity to influenza virus because they recognize internal viral proteins that are conserved between multiple viral strains [12]. Both $CD4^+$T cells and $CD8^+$ T cells are critical in defending against influenza viruses [13–15]. Since the sequence of the new coronavirus is highly homologous to SARS and MERS virus [16,17], both of which are severe respiration viruses, probably that $CD4^+$T cells and $CD8^+$ T cells are also responsible for controlling the new coronavirus. Here, we have shown that the reduction of those populations is associated with the enhancement of the severity of patients with the COVID-19. Although further studies are needed to examine the detailed mechanisms of how T cell controlling the COVID-19 coronavirus, our findings broaden our horizons in understanding the pathogenesis of the COVID-19.

Complications or ultimately death caused by COVID-19 are often associated with cytokine storms [18]. It was reported that people with weakened immune systems due to pre-existing diseases, such as cancer, diabetes, liver or kidney disease, are more likely to get infected by the new coronavirus or even more easily turned into severe or critical illness [4,19]. Since depressed immunity is manifested by decreased immune cell populations including T cells, patients can easily cause the onset of cytokine storm when encountering massive virus invasion. Nowadays, it is common to use glucocorticoid [20] or specific neutralization antibodies to fight against cytokine storms [21]. The former causes a lot of complications while the latter is costly [22]. It has been proposed that immuno-modulatory therapy may prevent cytokine storms [14]. Here, we proposed that enhancing T cell populations or improving their functions through medical features or diet may deter the disease from getting worse. Our results further support the concept that boosting your immunity is effective in dealing with viruses [23,24].

5. Conclusion

Taken together, we suggested that T cells may play an important role in regulating the development of COVID-19. Enhancing T cell populations may be effective in preventing severe patients from getting worse.

CRediT authorship contribution statement

Rui Liu: Conceptualization, Writing - original draft. **Ying Wang:** Conceptualization, Writing - original draft. **Jie Li:** Data curation. **Huan**

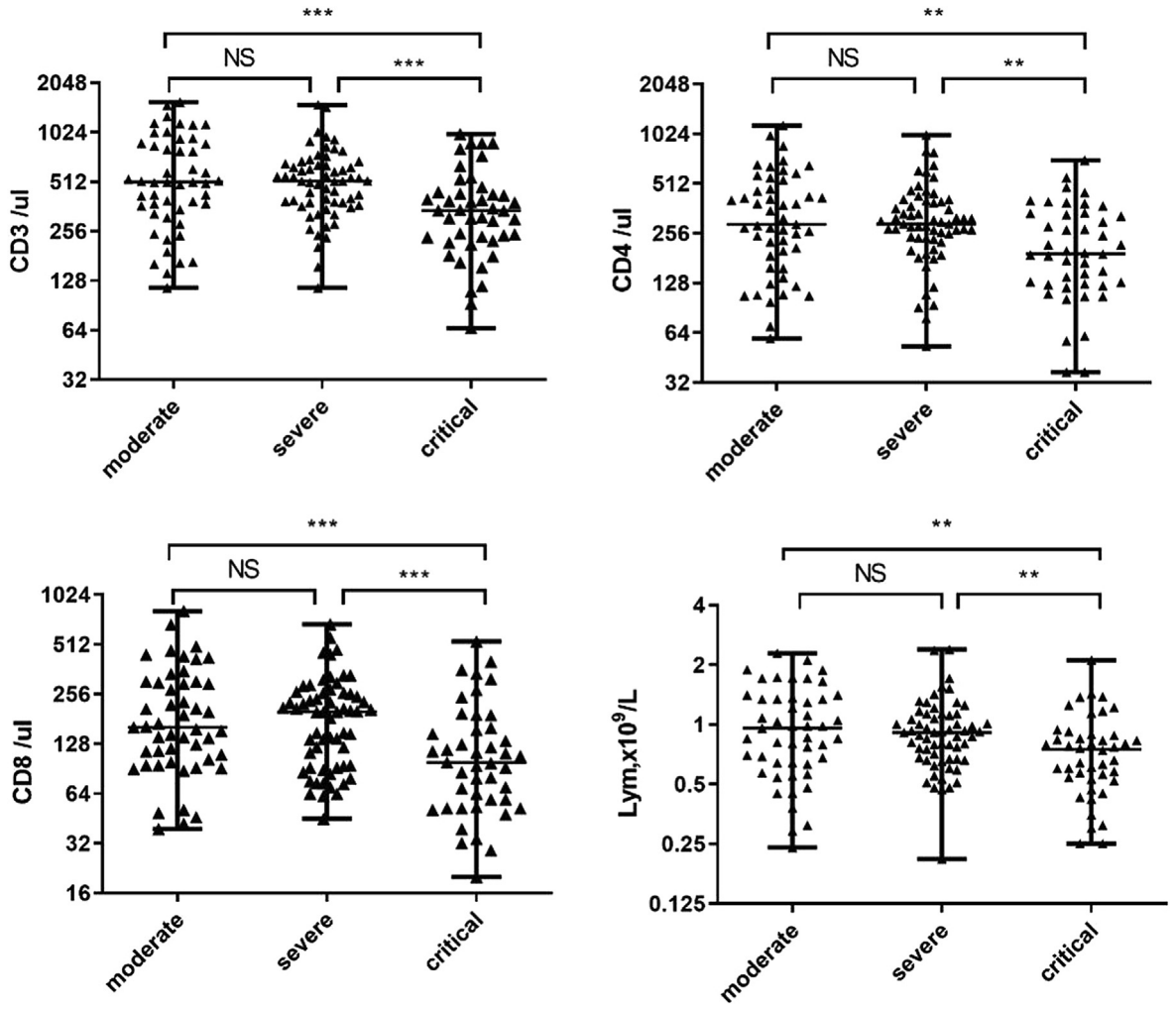

Fig. 1. Absolute values of $CD3^+$, $CD4^+$, and $CD8^+$ lymphocytes, in patients with moderate, severe or critical COVID-19 infection. The longer horizontal line indicates the median value for each group. *** indicates $P < 0.01$, ** indicates $P < 0.05$.

Han: Data curation. **Zunen Xia:** Data curation. **Fang Liu:** Investigation. **Kailang Wu:** Investigation. **Lan Yang:** Investigation. **Xinghui Liu:** Supervision, Writing - review & editing. **Chengliang Zhu:** Supervision, Writing - review & editing.

Acknowledgement

This work was supported by The National Natural Science Foundation of China, the National Mega Project on Major Infectious Disease Prevention, the Open Research Program of the State Key Laboratory of Virology of China, the Outstanding Leaders Training Program of Pudong Health Bureau of Shanghai, the Key Disciplines Group Construction Project of Pudong Health Bureau of Shanghai and Postdoctoral Sustentation Fund of Shanghai Gongli Hospital, Secondary Military Medical University.

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