Lymphocyte subsets with the lowest decline at baseline and the slow lowest rise during recovery in COVID-19 critical illness patients with diabetes mellitus

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A R T I C L E   I N F O

A B S T R A C T

Background: Host dysregulation of immune response was highly involved in the pathological process of Coronavirus disease 2019 (COVID-19), especially COVID-19 severe cases with DM.

Aim: In this study we aimed at the dynamic change of peripheral lymphocyte and subsets during COVID-19 covery.

Methods: The peripheral lymphocyte and subsets of 95 confirmed cases with COVID-19 from baseline to four weeks were compared between critical illness and non-critical illness cases with or without DM.

Results: The dynamic characteristics of lymphocyte and subsets in COVID-19 patients was that it reduced significantly at one week, rapidly elevated to the peak at two weeks after onset, then gradually declined during recovery. The COVID-19 critical illness patients with DM had the lowest decline at one week and the slow lowest rise at two weeks after onset, while COVID-19 non-critical illness patients with DM had the rapid highest rise at two weeks after onset, both of them had similar lymphocyte and subsets at five weeks after onset and lower than those patients without DM.

Conclusions: These findings provide a reference for clinicians that for COVID-19 patients with DM and the lowest decline of lymphocyte and subsets, immunomodulatory therapy as soon as possible might avoid or slow down disease progression; moreover for COVID-19 critical illness patients with or without DM and non-critical illness patients with DM, continuous immunomodulatory therapy in later stages of disease might speed up virus clearance, shorten hospital stay, improve disease prognosis in COVID-19 critical illness patients with DM.

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1. Introduction

The outbreak of novel coronavirus (2019-nCOV) infection named as coronavirus disease 2019 (COVID-19) is wide spread in the world [1–4].As of April 18, 2020, cases were reported in China and the whole world, a total of cumulative confirmed and death cases were 2,160,207 and 146,088 cases in the whole world [5], 82,735 and 4632 cases in China [6], respectively.

Those COVID-19 patients who is the elderly and those with chronic underlying disease have a poor prognosis. Diabetes mellitus is one of the common underlying diseases [7]. Host dysregulation of immune response was highly involved in the pathological process of COVID-19 [8].Our previous research found that the COVID-19severe cases with diabetes mellitus (DM) had overall decreased lymphocytes and subsets which can affect the diseasese verity, disease progression, viral negative conversion and prognosis [9]. The dynamic changes of lymphocyte and subsets between critical illness case and non-critical illness case of COVID-19 with or without DM are unknown and worth studying in this article.

2. Methods

2.1. Objects

95 patients with COVID-19 was retrospectively recruited from January 16, 2020 to March 16, 2020in hospital isolation ward of the Public and Health Clinic Centre of Chengdu," the specific hospital for the treatment of severe patients with COVID-19 in Chengdu" designated by the government. The study was approved by the Public and Health Clinic Centre of Chengdu Ethics Committee (PJ-K2020-06-01). For emerging infectious diseases the Ethics Commission of the designated hospital agreed to waive written informed consent [9].

The diagnosis criteria, the clinical typing criteria of COVID-19 was judged according to the seventh Trial Version of the Novel Coronavirus Pneumonia Diagnosis and Treatment Guidance [7].

DM diagnostic criteria was judged according to Guidelines for the Prevention and Treatment of Type 2 Diabetes in China (2017 edition) [10].

The participants were divided in two subgroups according to clinical typing: the non-critical illness subgroup (including light and common type) and critical illness subgroup (including severe and critically illness type).

2.2. Clinical data collection

Data including underline disease history, demographic information (age and sex), lymphocyte subsets at baseline, one week and 4 weeks, clinical data and glucose metabolic parameters [FPG levels and hemoglobin A1c (HbA1c) levels] were obtained from the hospital electronic medical record system of the Public and Health Clinic Centre of Chengdu [9].

According to the needs of the research databases were established by two researchers simultaneously collecting and entering, 30% of that data was randomly selected by the researchers to assess data integrity, authenticity, and accuracy.

2.3. Statistical analyses

The Statistical Package for the Social Sciences software version 17.0 (IBM Inc., Armonk, NY, the USA) and GraphPad Prism 8 (GraphPad, CA, the USA) software were used for statistical analysis. The measurement data were expressed as x ± SD, and a multigroup comparison was performed using ANOVA. Further comparison between the two groups was conducted using Student-Newman-Keuls (SNK) analysis. The two groups were compared using an independent-sample t-test. Chi-square test was used for the enumeration data. A p value of <0.05 was considered statistically significant.

3. Results

3.1. Similar baseline conditions except glucose metabolic parameters between four subgroups

Patients in non-critical illness non-DM subgroup were significantly younger than those in the other three subgroups, but similar age was found in latter three subgroups and similar male percentage was found in four subgroups (Table 1). FPG levels and HbA1c level in DM group were obviously higher than that in non-DM group (Table 1). But there was no significant difference between each intra-group (Table 1) [9].

3.2. The lowest lymphocyte and subsets at baseline in COVID-19 critical illness patients with DM

At baseline in COVID-19critical illness cases with DMlymphocyte count level and percentage value (Fig. 1a and b), CD3+ count level (Fig. 2a), CD3 + CD4+ count level (Fig. 2c), CD3 + CD8+ count level (Fig. 2e), B(CD19+) count level (Fig. 3a) and NK (CD56+) count level (Fig. 4a) were the lowest decline compared with that in critical illness cases without DM and non-critical illness cases with or without DM, all of significant differences were found.

At baseline in COVID-19 critical illness patients lymphocytes count level and percentage value (Fig. 1a and b), CD3 + count level (Fig. 2a), CD3+ CD4+ count level (Fig. 2c), B (CD19+) count level (Fig. 3a) were obviously lower than that in COVID-19 non-critical illness patients, the difference was significant. But no significantly difference of NK (CD56+) count level (Fig. 3a) and all lymphocyte subsets percentage value were found between critical illness and non-critical illness patients whether with or without DM.

At baseline in COVID-19 critical illness patients with DM except B (CD19+) count level (Fig. 3a) was obviously lower than that in COVID-19 critical illness patient without DM, the difference was significant, no statistical difference of the other lymphocytes subsets was found between the same disease severity with and without DM subgroups.

Variable	Non-DM group (n = 76)		DM group(n = 19)		x^2 or F score	P score
	Non-critical illness subgroup (n = 57)	Critical illness subgroup(n = 19)	Non-critical illness subgroup (n = 8)	Critical illness subgroup(n = 11)		
Age (year)	42.67 ± 14.71	58.00 ± 19.24***	61.57 ± 12.01***	59.36 ± 12.31***	8.914	0.000
Male (case, %)	25(43.86)	11(57.89)	3(37.50)	7(63.64)	2.532	0.469
Duration (day)	7.54 ± 6.01	6.16 ± 3.98	8.45 ± 5.53	7.14 ± 5.11	0.423	0.738
FPG (mmol/L)	5.35 ± 0.65	5.81 ± 0.91**	7.80 ± 4.91****	7.35 ± 1.19****	10.02	0.000
HbA1c (%)	5.46 ± 0.73	5.58 ± 0.48	7.49 ± 2.65**	6.89 ± 1.18****	6.380	0.001
Virus negative conversion time	18.02 ± 8.66	19.26 ± 6.84	24.86 ± 11.50*	26.36 ± 8.44***##	4.490	0.006
Prognosis					−3.394	0.001
Cured (case, %)	53 (71.05)		5(26.32)			
Unhealed	21(26.32)		13(68.42)			
Death	2(2.63)		1(5.26)			

Table 1 – Comparison of baseline conditions and glucose metabolic parameters between four subgroups (*n* = 95).

Abbreviations: FPG, fasting plasma glucose; HbA1c, glycated hemoglobin A1c; DM, diabetes mellitus. Compared with the non-critical illness non-DM subgroup, **P < 0.01, ***P < 0.001, ****P < 0.0001. Comparison of age between the latter three subgroups, P > 0.05.
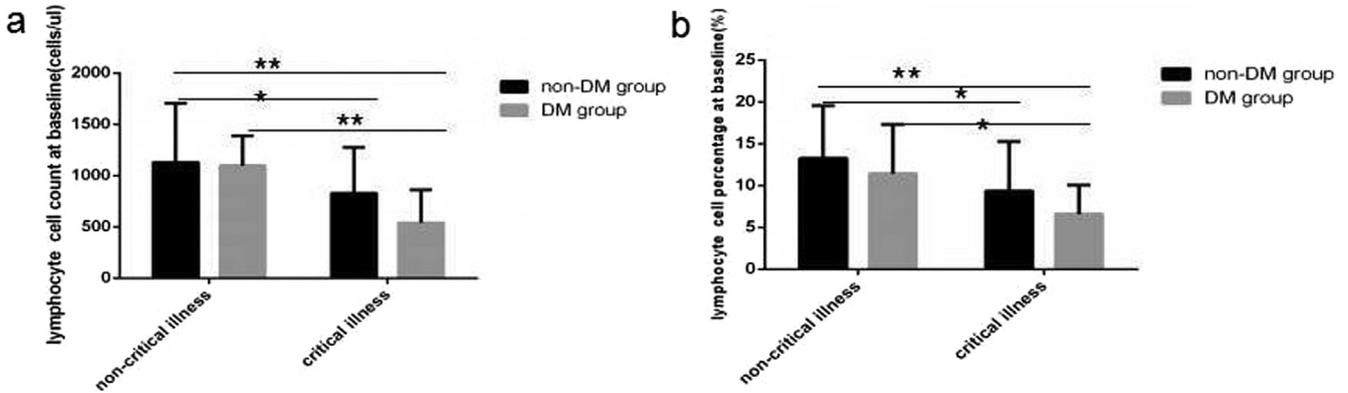
Fig. 1 – Comparison of lymphocyte count levels and percentage values between four subgroup. Abbreviations: DM, diabetes mellitus. a. lymphocyte count. b. lymphocyte percentage. Unpaired one ANOVA were used for intergroup comparison (a,b, p all < 0.01). Unpaired *t*-tests were used for the intra-group comparison.*P < 0.05,P < 0.01.**
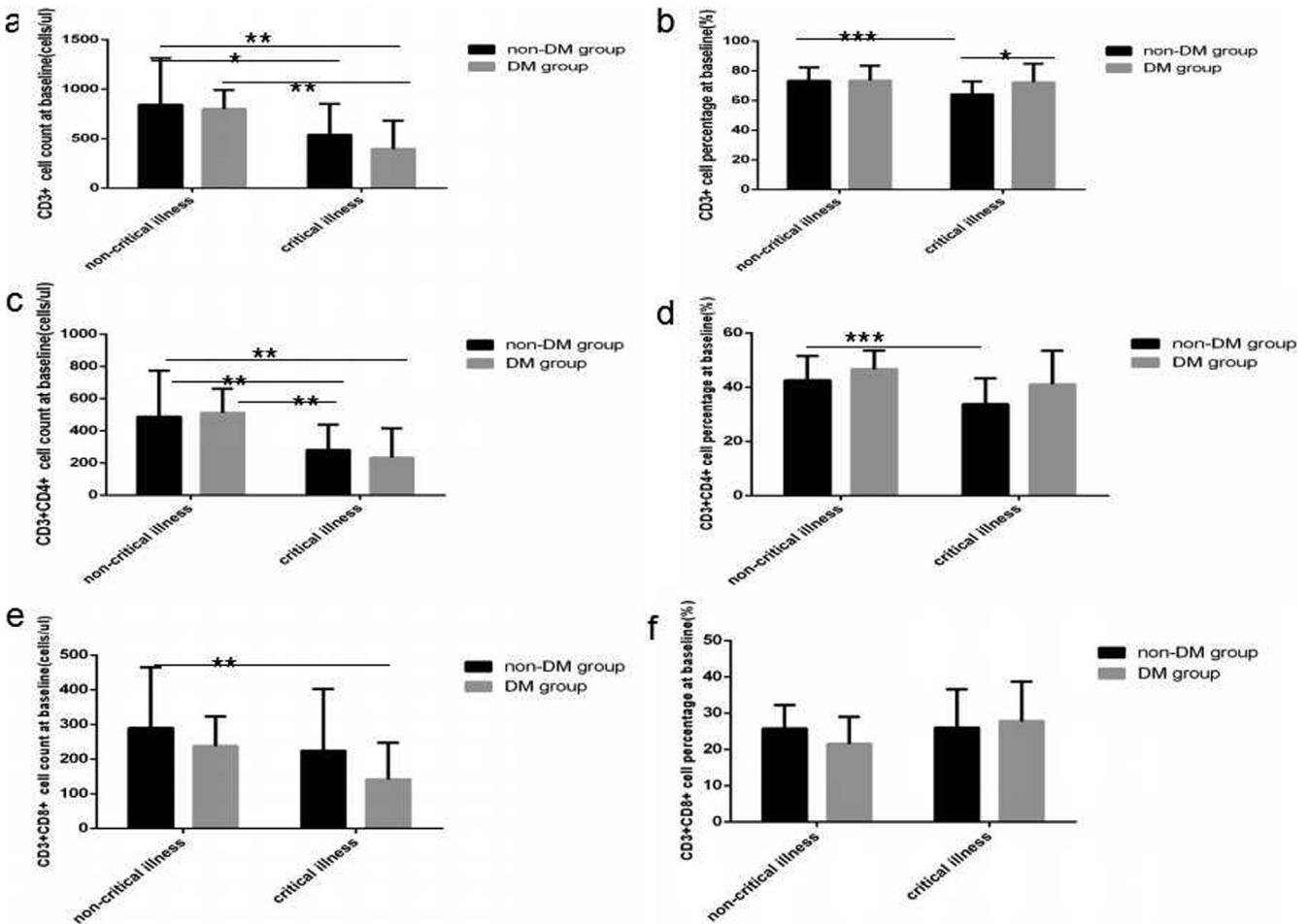

Fig. 2 – Comparison of T lymphocytes and subsets count levels and percentage values between four subgroup. Abbreviations: DM, diabetes mellitus; non-DM, without diabetes mellitus. a. CD3 + cell count. b. CD3 + cell percentage. c. CD3 + CD4 + cell count. d. CD3 + CD4 + cell percentage. e. CD3 + CD8 + cell count. f. CD3 + CD8 + cell percentage. Unpaired one ANOVA were used for intergroup comparison (a,b,c,d,e,f, P < 0.01, 0.05, 0.001, 0.01, >0.05, 0.05, respectively). Unpaired t-tests were used for the intra-group comparison. *P < 0.05, **P < 0.01, ***P < 0.001.
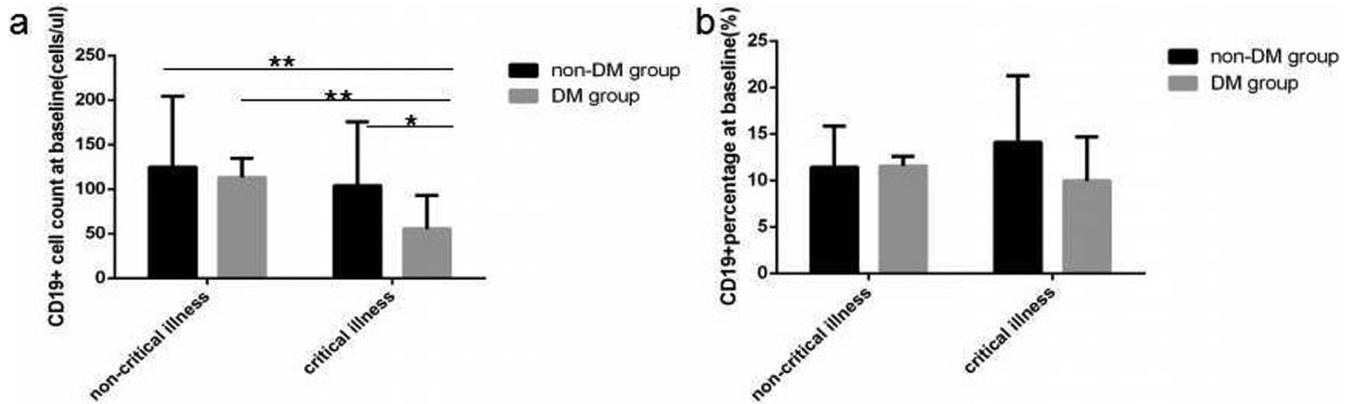
Fig. 3 – Comparison of B lymphocytes count levels and percentage values between four subgroup. Abbreviations: DM, diabetes mellitus; non-DM, without diabetes mellitus. a. B lymphocytes count. b. B lymphocytes percentage. Unpaired one ANOVA were used for intergroup comparison (a,b, P < 0.05, >0.05, respectively). Unpaired *t*-tests were used for the intra-group comparison. *P < 0.05, **P < 0.01.
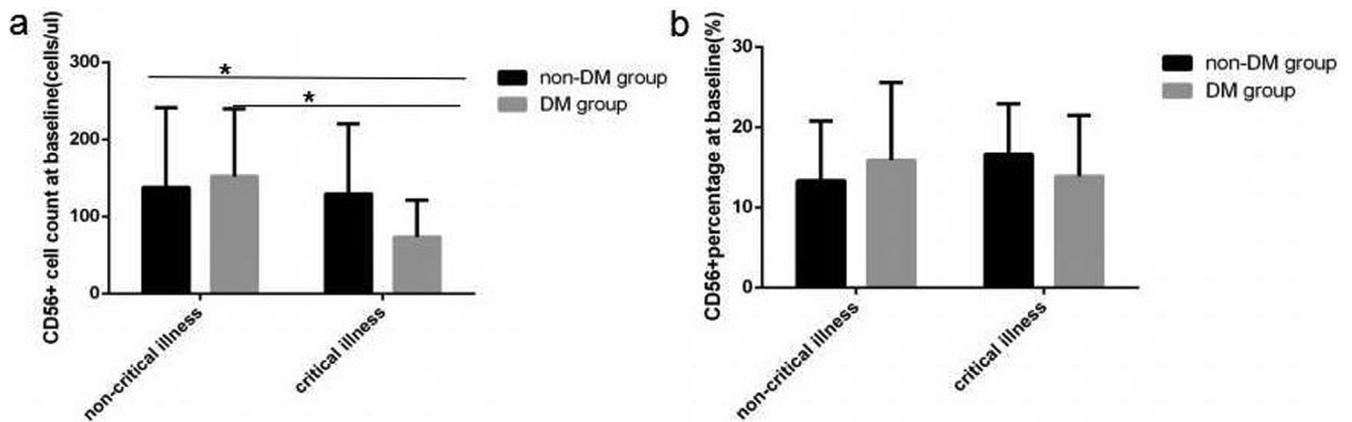

Fig. 4 – Comparison of NK lymphocytes count levels and percentage values between four subgroup. Abbreviations: DM, diabetes mellitus; non-DM, without diabetes mellitus. a. NK lymphocyte count. b. NK lymphocytes percentage. Unpaired one ANOVA were used for intergroup comparison ((a,b, P all > 0.05). Unpaired *t*-tests were used for the intra-group comparison. *P < 0.05.

3.3. The slow lowest rise of lymphocyte and subsets within four weeks in COVID-19 critical illness patients with DM

During recovery in COVID-19 patients whether critical illness or non-critical illness, whether with or without DM, lymphocyte count level and percentage value (Fig. 5a and b), CD3 + CD4+ count level (Fig. 6c) all rapidly raised to the peak at one week, then gradually declined, but still above baseline value at four weeks; simultaneously B (CD19 +) count level (Fig. 7a) also rapidly raised to the peak at one week, then gradually declined under baseline value at four weeks; while CD3 + CD8+ count level (Fig. 6e) gradually raised to the peak at fours week, there were all significant differences (p all < 0.05). In spite of NK (CD56+) count level (Fig. 8a) also rapidly elevated up to the peak at one week then continuously maintained this level within four weeks, but no statistical difference was found between different time points.

At one week COVID-19non-critical illness cases with DM had the rapid highest rise of lymphocyte count level and per-

centage value (Fig. 5a and b), CD3+ count level (Fig. 6a), CD3 + CD4+ count level (Fig. 6c), CD3 + CD8+ count level (Fig. 6e), B (CD19 +)count level (Fig. 7a), NK (CD56+) count level (Fig. 8a). On the contrary COVID-19 critical illness cases with DM had the slow lowest rise of corresponding lymphocyte and subsets. Simultaneously COVID-19 non-critical illness cases without DM had higher lymphocyte and subsets than COVID-19critical illness cases without DM.

At 4 weeks COVID-19 patients without DM had higher lymphocyte and subsets than those with DM, but the lymphocyte and subsets was similar between critical illness cases and non-critical illness cases whether with or without DM.

3.4. Dynamic lymphocyte and subsets influencing on the virus negative conversion time and the prognosis in COVID-19 patients

Pearson correlation analysisshowed that B (CD19+) count leveland percentage value at five weeks were negatively related to viral negative conversion time (Table 2). The
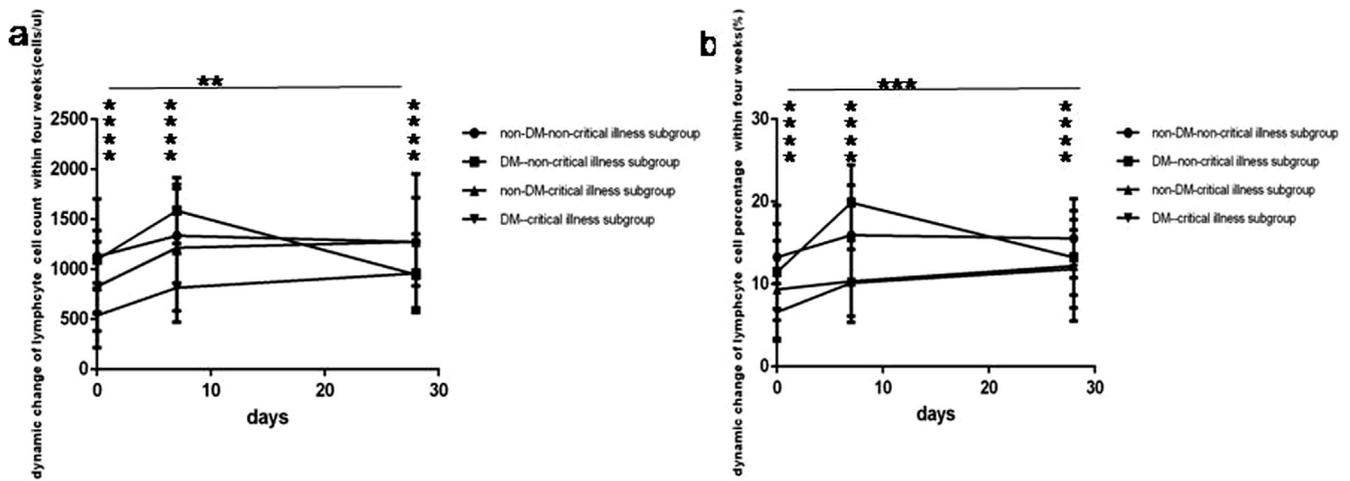
Fig. 5 – Comparison of dynamic change of lymphocytes count levels and percentage values between four subgroup within four weeks. Abbreviations: DM, diabetes mellitus; non-DM, without diabetes mellitus. a. lymphocytes count. b. lymphocytes percentage. Unpaired one ANOVA were used for intergroup comparison. Unpaired t-tests were used for the intra-group comparison. **P < 0.01, ***P < 0.001, ****P < 0.0001.

Fig. 6 – Comparison of the dynamic change of T lymphocytes count levels and percentage values between four subgroup within four weeks. Abbreviations: DM, diabetes mellitus; non-DM, without diabetes mellitus. a. CD3 + cell count. b. CD3 + cell percentage. c. CD3 + CD4 + cell count. d. CD3 + CD4 + cell percentage. e. CD3 + CD8 + cell count. f. CD3 + CD8 + cell percentage. g. CD4/CD8. Unpaired two ANOVA were used for intergroup comparison. *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001.
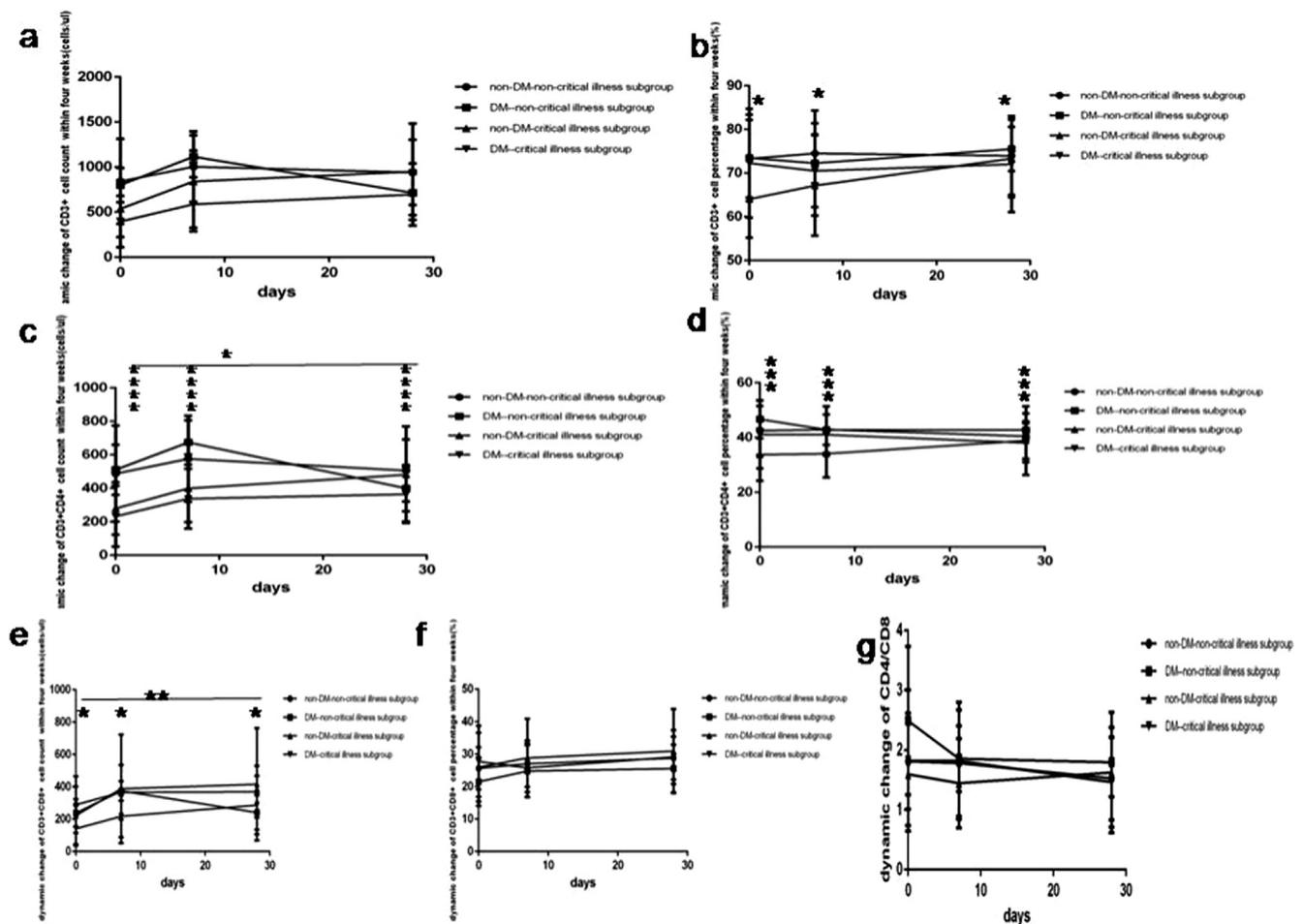
Fig. 7 – Comparison of the dynamic change of B lymphocytes count levels and percentage values between four subgroup within four weeks. Abbreviations: DM, diabetes mellitus; non-DM, without diabetes mellitus. a. B lymphocytes count. b. B lymphocyte percentage. Unpaired two ANOVA were used for intergroup comparison. **P < 0.01, ***P < 0.001, ****P < 0.0001.
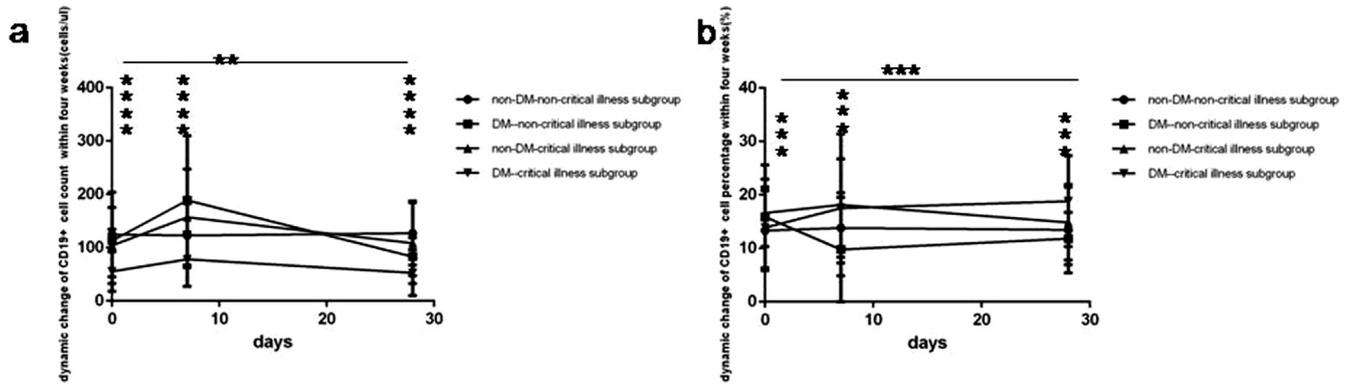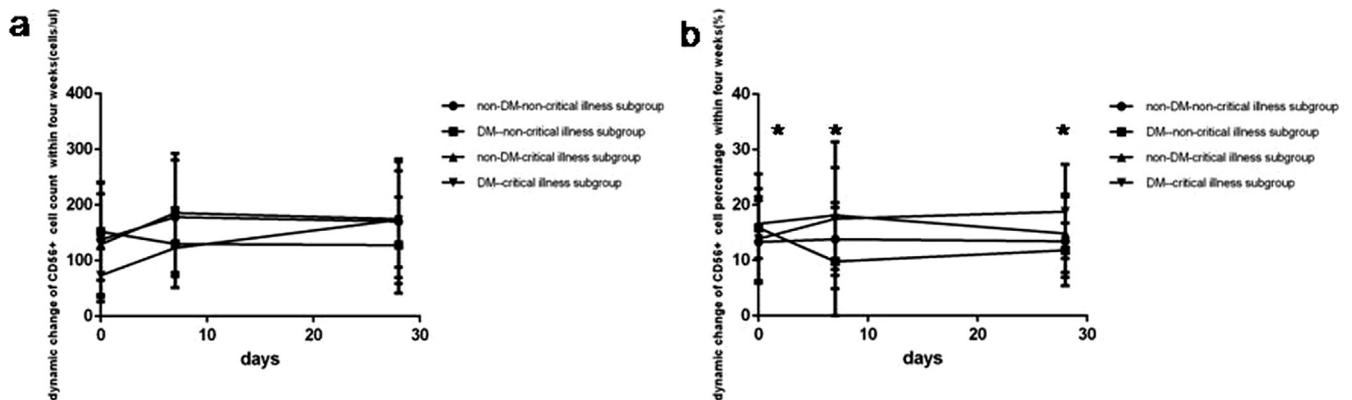

Fig. 8 – Comparison of the dynamic change of NK lymphocytes count levels and percentage values between four subgroup within four weeks. Abbreviations: DM, diabetes mellitus; non-DM, without diabetes mellitus. a. NK lymphocyte count. b. NK lymphocyte percentage. Unpaired two ANOVA were used for intergroup comparison. **P < 0.01, ***P < 0.001, ****P < 0.0001.

important factors influencing the viral negative conversion time by multiple stepwise regression analysis was only B (CD19+) count level or percentage value at five weeks (Table 3).

Related to theprognosis negative factorswerelymphocyte-count level, CD3+ count level, CD3 + CD4+ count level, CD3 + CD8+ count levelat two weeks after onset, and lympho-cytecount level, CD3+ count level, CD3 + CD4+ count level, CD3 + CD8+ count level, B (CD19+)count level and percentage value at five weeks (Table 2). Influencing factors of the prognosis by multiple stepwise regression analysis was CD3 + CD8+ count level and B (CD19+) percentage value at five weeks (Table 3).

4. Discussion

Our previous research found that the COVID-19 severe cases with DM had the lowest lymphocytes, especially T lympho-cytes and B lymphocytes. Overall decreased lymphocytes sub-sets and DM maybe aggravated the prognosis by aggravating the disease severity and prolonging the viral negative conver-sion time [9]. In this study we analyzed the dynamic charac-teristics of lymphocyte and subsets in coronavirus disease 2019 (COVID-19) patients, found that lymphocyte and subsets reduced significantly at baseline, rapidly rised to the peak at one week of hospitalization, then gradually declined during recovery, at four weeks of hospitalization B lymphocyte sub-set even below baseline, while NK lymphocyte subset contin-uously maintained the peak level. The average disease course from onset to admission of COVID-19 patients in this study was one week, that is to say the lymphocyte and subsets were decreased to the lowest decline at one week, and rised to the highest topat two weeks after the onset of disease, then grad-ually decreased again, this dynamic characteristics is incon-sistent with that in severe acute respiratory syndrome (SARS) patients. Literature report that in SARS patients the CD3+, CD4 + and CD8 + T cells, especially CD4 + T cells decreased at the first two-week of the disease course and reached to the lowest level at the second week, and began to increase from the third week in all patients, the change pattern of CD3+, CD4+ and CD8 + T cells in the severe type of SARS was the same as that of the mild type of SARS, but with more serious extent and longer time [11]. 2019-nCOV infection affects host immune function earlier and faster than SARS coronavirus infection.

In this study we also found that the COVID-19 critical ill-ness patients with DM had the lowest decline at baseline and the slow lowest rise of lymphocyte and subsets at one

Table 2 – Pearson correlation analysis between the virus negative conversion time and lymphocyte subsets at two weeks and five weeks after onset (n = 95).

Time point	Variable	Virus negative conversion time (days)		Prognosis (1 = cured, 2 = unhealed, 3 = death	
		r	p	r	p
At two weeks	CD3+(cells/ul)			−0.324	0.016
	CD3 + CD8+(cells/ul)			−0.288	0.033
	LY(cells/ul)			−0.326	0.015
At five weeks	CD3+(cells/ul)			−0.400	0.005
	CD3 + CD4+(cells/ul)			−0.300	0.038
	CD3 + CD8+(cells/ul)			−0.398	0.005
	LY(cells/ul)			−0.448	0.001
	B(CD19 +)	−0.322	0.015	−0.404	0.005
	B(CD19 +)%	−0.337	0.010	−0.296	0.046

Table 3 – Multiple stepwise regression analysis of influencing factors of the coronavirus negative conversion time (n = 95).

Independent variable		B	Std. Error	Beta	t	p
The coronavirus negative conversion time	constant	24.703	2.146	–	11.514	0.000
	B (CD19 +) (%)	−0.044	0.180	−0.322	−2.533	0.015
Prognosis	constant	2.134	0.207		10.333	0.000
	CD3 + CD8+(cells/ul)	−0.021	0.000	−0.373	−2.780	0.008
	B(CD19 +)%	−0.037	0.017	−0.286	−2.128	0.039

week after admission, while COVID-19 non-critical illness patients with DM had the highest rise of lymphocyte and subsets at one week after admission, both of them had similar lymphocyte and subsets at 4 weeks of hospitalization, all lower than those patients without DM whose also had similar lymphocyte and subsets between non-critical illness and critical illness cases. Important antiviral effects of T cells, CD4 + T cells, and CD8 + T cells are achieved by balancing the risk of fighting pathogens with the risk of developing autoimmunity or excessive inflammation [12]. CD4 + T cells activate T-dependent B cells to produce virus-specific antibodies. However, CD8 + T cells can kill virus-infected cells by cytotoxicity. CD8 + T cells account for about 80% of pulmonary stromal inflammatory cells in SARS-COV infected patients and play an important role in clearing COVs from infected cells and inducing immune damage [13–14]. T cells rather than B cells play an important role in the control of pathogenesis of MERS-COV infection. A cross-reactive T cell response leads to a decrease in MERS-CoV [15]. CD4 + T cells are more susceptible to SARS-COV infection, resulting in itself reduction or even depletion, which reduces the recruitment of lymphocytes in the lungs and the neutralization of antibody and cytokine production, resulting in strong immune-mediated interstitial pneumonia and delay the clearance of SARS-COV in the lungs. But the depletion of CD8 + T cells does not affect or delay viral replication [16–18]. From this we speculate that for COVID-19 patients with DM in early stage of disease, the rapid highest rise of lymphocyte and subsets in some patients avoid disease progression to critical illness cases or slow down disease progression, while the slow lowest rise of lymphocyte and subsets in the others promote disease progression to critical illness cases.

Additionally, T helper cells produce proinflammatory cytokines via the NF-kB signalling pathway [19]. IL-17 cytoki-

nes recruit monocytes and neutrophils to the site of infection with inflammation and activate other downstream cytokine and chemokine cascades, such as IL-1, LL-6, IL-8, IL-21, TNF-β, and MCP-1 [20,21]. On the other hand, MERS-COV induces T cell apoptosis by activating the intrinsic and extrinsic apoptosis pathways. A novel BH3-like region located in the C-terminal cytosolic domain of SARS-COV protein mediates its binding to Bcl-xL and induced T-cell apoptosis [22].

In this study we also found that only B cell subset at five weeks after onset can influence the virus negative conversion time, CD3 + CD8 + T cell and B cell subsets at five weeks after onset can influence the prognosis. This is inconsistent with that in literature that during the later stage of infection, depletion of T cells having antiviral effects may prolong the infection and promote viral survival [23]. This cannot explain our previous research findings why the virus negative conversion time and the in hospital time of COVID-19 patients with DM were longer than that of those without DM.

5. Conclusions

Lymphocyte and subsets in COVID-19 patients reduced the lowest decline at one week, rapidly elevated up to the peak at two weeks after onset, then gradually declined during recovery. The COVID-19 critical illness patients with DM had the lowest decline at one week and the slow lowest rise at two weeks after onset, while COVID-19 non-critical illness patients with DM had the rapid highest rise at two weeks after onset, both of them had similar lymphocyte and subsets at five weeks after onset, all lower than those patients without DM whose also had similar lymphocyte and subsets between non-critical illness and critical illness cases. These findings provide a reference for clinicians that for patients with COVID-19 and DM coexistence and the lowest decline of lym-

phocyte and subsets at one week after onset early application of immunomodulatory therapy as soon as possible might avoid or slow down disease progression, moreover for COVID-19 patients with DM whether critical illness or not, and critical illness cases without DM, then continuous application of immunomodulatory therapy in later stages of disease might speed up virus clearance, shorten hospital stay, improve disease prognosis in COVID-19 critical illness patients with DM.

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Declaration of Competing Interest

The authors declare that they have no competing interests.

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Authors' contributions

Concept and design: Dafeng Liu, Lijuan Lan, Dongxia Luo, Bennan Zhao, Guo Wei, Yinsheng He; Data acquisition: Dafeng Liu, Lijuan Lan, Dongxia Luo, Bennan Zhao, Guo Wei, Yinsheng He; data analysis and interpretation: Dafeng Liu, Lijuan Lan, Dongxia Luo, Bennan Zhao; Drafting the manuscript: Dafeng Liu, Lijuan Lan, Dongxia Luo, Bennan Zhao; administrative, technical, or material support: Dafeng Liu, Lijuan Lan, Dongxia Luo, Bennan Zhao; study supervision: Renqing Zhang, Yalin Liu.

Data availability statement

All data, models, or code generated or used during the study are available from the corresponding author by request: Dafeng Liu, E-mail:liudf312@126.com

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