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The evaluation of the immune status of COVID-19 recovered subjects with persistent abnormal lung CT after one year: A longitudinal cohort study

Hongbo Chi [a,1], Kai Zhou [a,1], Liping Shen [a], Jiaqin Xu [a], Jun Li [a], Shiyong Chen [a], Xiaomai Wu [b], Tao-Hsin Tung [c], Bo Shen [a,*], Hongguo Zhu [a,*]

[a] Department of Clinical Laboratory, Taizhou Hospital of Zhejiang Province affiliated to Wenzhou Medical University, Linhai, Zhejiang, China
[b] Department of Respiratory Medicine, Taizhou Hospital of Zhejiang Province affiliated to Wenzhou Medical University, Linhai, Zhejiang, China
[c] Evidence-based Medicine Center, Taizhou Hospital of Zhejiang Province affiliated to Wenzhou Medical University, Linhai, Zhejiang, China

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ABSTRACT

Objectives: COVID-19 is an immune-related disease caused by novel Coronavirus SARS-COV-2. Lung lesions persist in some recovered patients, making long-term follow-up monitoring of their health necessary. The mechanism of these abnormalities is still unclear. In this study, the immune status was observed to explore the immune mechanism of persistent lung CT abnormalities in one-year COVID-19 recovered subjects.

Methods: One-year follow-up of 73 recovered patients from COVID-19 confirmed in Taizhou City, Zhejiang Province, was conducted to collect laboratory indicators such as blood immune cells, cytokines, complement series, immunoglobulin, and lung imaging; According to the results of lung CT, 60 patients were divided into normal CT group (n = 40) and abnormal CT group (n = 20). We compared the dynamic changes of immune indexes at three timepoints namely onset (T1), discharge (T2), and 1-year follow-up (T3), and studied the relationship between immune indexes and pulmonary sequelae.

Results: Compared with the healthy control, there was no significant difference in immune-related indexes, and immune levels had recovered. Patients with elder age, high BMI, severe patients, and those with underlying diseases (hypertension or diabetes) had a higher CT abnormal rate after recovery. Longitudinal observation showed that immunoglobulin increased first and then decreased, immune cell TBNK decreased in the onset period and increased in the recovery period, cytokine level increased significantly in the onset period and decreased to the normal level in the recovery period, and complement series C1q, C3 and C4 increased at the onset and decreased during the one-year follow-up. Complement C3 remained at a high level in the CT abnormal group (CT normal group vs CT abnormal group; $P = 0.036$). Correlation analysis showed that C3 negatively correlated restrictive ventilation index (TLC-He (ratio) ($r = -0.302$, $P = 0.017$). The above results suggest that complement C3 is a negative factor correlating abnormal pulmonary function 1 year after the recovery.

Conclusion: After one year recovering from COVID-19, the subjects were with stable immune indicators. High levels of complement C3 were associated with persistent lung abnormalities in COVID-19 recovered subjects.

1. Introduction

So far, WHO has confirmed more than 480 million COVID-19 cases worldwide, with 6.1 million deaths and 370 million cured cases [https://covid19.who.int/]. Although most of them have been discharged and returned to society, the follow-up problems caused by the disease, such as long-term lung damage and post-traumatic stress disorder, still exist[1].

Studies have reported that most of the COVID-19 recovered subjects after being discharged for 3 months suffered from symptoms such as fever, sputum production, fatigue, diarrhea, dyspnea, cough, tightness in the chest, palpitations, and so on, and 42% had mild pulmonary dysfunction [2]. Huang et al. found that the main symptoms of COVID-19 recovered subjects 6 months after acute infection were fatigue or muscle weakness, sleep difficulty, anxiety, or depression. In the latest 1-year follow-up, about 20–30% of severe COVID-19 recovered subjects

* Corresponding authors.
E-mail addresses: shenb@enzemed.com (B. Shen), zhuhg@enzemed.com (H. Zhu).
[1] These authors contributed equally.

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were observed with impaired lung diffuse function, while in critically ill patients, the proportion was as high as 54%[3]. The recovered subjects with severe illness and impaired pulmonary dispersion ability during hospitalization has a high proportion of abnormal chest imaging manifestations [4]. However, related factors and specific mechanisms of persistent pulmonary dysfunction are not fully understood.

There is evidence that complement activation is the pathophysiological basis of many lung diseases, such as asthma and acute respiratory distress syndrome [5], and also leads to immune-mediated lung injury [6]. Normal immune status was found among COVID-19 recovered subjects 2 weeks after the discharge [7]. However, the long-term immune status of COIVD-19 patients has not been reported in the literature. This study retrospectively analyzed related immune indicators of COVID-19 recovered subjects from infection to one-year follow-up to evaluate the immune status, and explored possible factors relating their persistent abnormal lung CT.

2. Materials and methods

2.1. Study cohort

From February 9, 2021, to February 10, 2021, we followed up 144 subjects for one year after they were discharged from Taizhou Hospital where they were formerly confirmed with COVID-19. The following subjects were first excluded: (1) refusal to participate (n = 42); (2) Unable to contact (n = 6); (3) 23 subjects who lived outside Taizhou. Among the remaining 73 subjects, those who had an infection (n = 6), autoimmune diseases (n = 6), or malignant tumor (n = 1) during the follow-up period were also excluded for the sake of evaluating immune status. Eventually, 60 subjects were included, 33 males and 27 females, with a median age of 48 years, and 26.7% of them were severe patients. At the one-year follow-up, lung CT and lung function were performed. The presence of patchy/GGO, consolidation, and fibrosis lesions in each image was recorded. Patients with more than one of the above-mentioned features were determined as lung CT abnormality. Subjects were divided into normal CT group (n = 40) and abnormal CT group (n = 20) (Fig. 1). At the same time, 39 healthy controls from the physical examination center were included by matching age, sex, and health status (no underlying diseases or immune diseases, relevant clinical indicators within the normal range) with subjects.

For the dynamic analysis of clinical indicators, we analyzed three time points. The first point was T1: admission, defined as within 7 days after the admission; the second was T2: within 7 days before the discharge and 2 weeks after the discharge; the third was T3: one-year follow-up.

The study was approved by the ethics committee of Taizhou Hospital

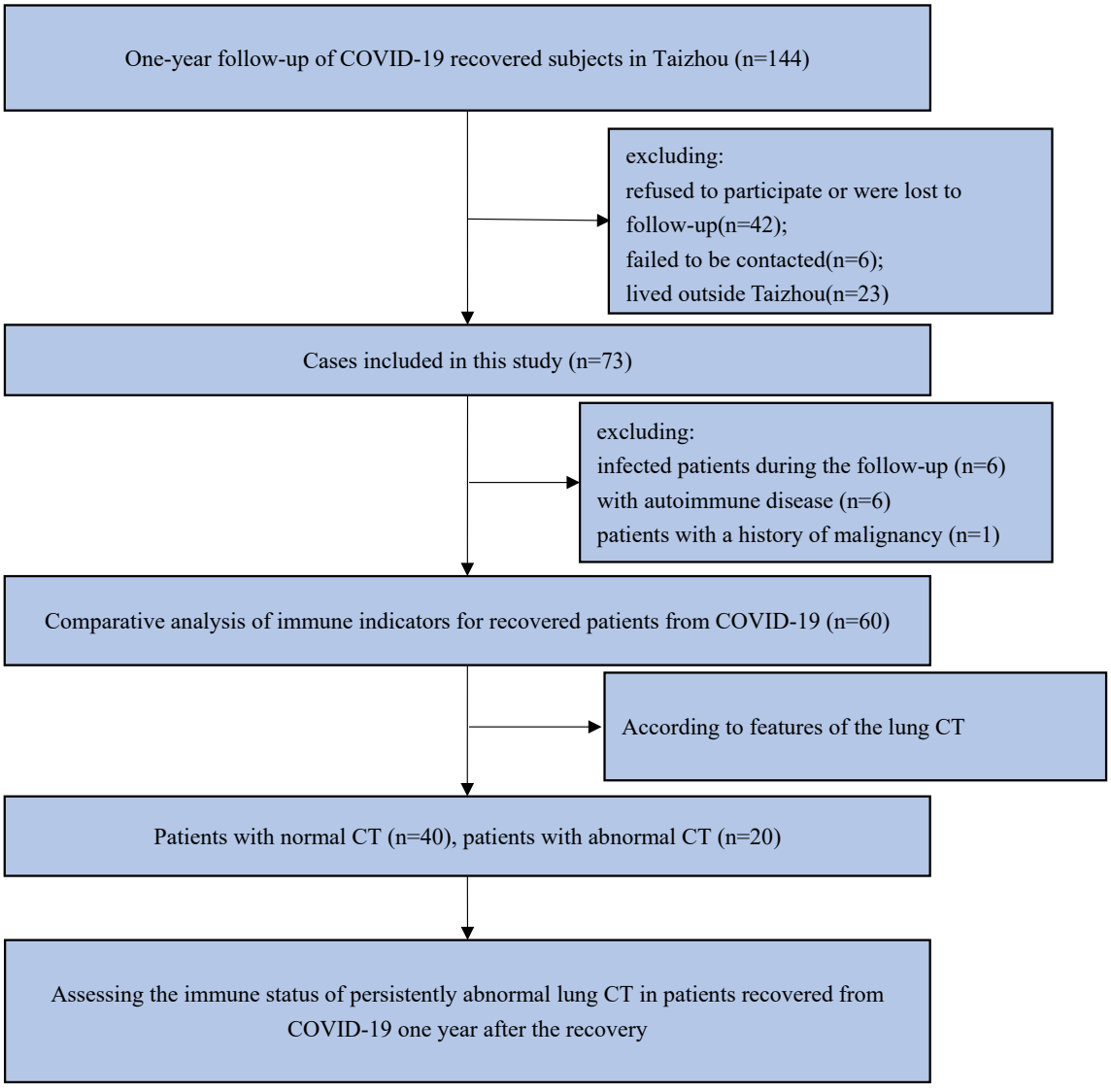

Fig. 1. Study design and workflow.

of Zhejiang Province. It was registered in the Chinese Clinical Trial Registry (registration number: ChiCTR2100048440). Informed consent was obtained from each subject. The minors' participation in the study was approved by their parents and/or legal guardians.

2.2. Clinical indicator analyses

We analyzed the 23 immune indicators including immunoglobulin (Globulin, A/G, IgG, IgA, IgM), lymphocyte subsets (CD3 T cells, CD4 T cells, CD8 T cells, NK cells, and CD19 B cells), complement series (C1q, C3, and C4), whole blood cell count (WBC, neutrophil, lymphocyte, and Monocyte) and cytokines. The immunoglobulin index and complement series were measured by a Beckman Automatic Biochemical analyzer (AU5821, Beckman Coulter, Brea, CA, USA). Cytokine and lymphocyte subsets were detected by flow cytometry (FACS Canto TM II, BD, USA). The whole blood count was analyzed by a Sysmex hematology analyzer (XN, Kobe, Japan).

2.3. CT imaging examination

Chest CT scans were performed using a combined 40-row UCT530 scanner (United Imaging, Shanghai, China). The patients were scanned in supine position with head raised and breath held. Lungs were scanned from top to bottom. CT images obtained were sent to the GE-PACS workstation for double-blind reading by two senior radiologists. The points of CT score are defined by the following rules. 1) Based on the lesion involvement, each infected lobe adds one point [8]. 2) Semi-quantitative assessment of the pulmonary features of all these abnormalities according to CT stages I (patchy/GGO), II (consolidation), and III (fibrosis) [9]. Presence of ground-glass opacity adds one point, two points were added in the presence of consolidation lesions, while three points were added in case of fibrosis lesions. Consistent with previously published studies scoring methodology. A CT score was calculated as follows: numbers of lobes involved × 1 + patchy/GGO × 1 + consolidation × 2 + fibrosis × 3 [10].

2.4. Lung function examination

Lung function was measured using a power cube-Body ultrasound lung function instrument (PowerCube-body, GANSHORN, Niederlauer, Germany). Pulmonary function tests were used to assess ventilatory function, diffusion function, and residual air. Ventilatory function tests included the following measures: FVC (forced lung capacity); FEV1 (forced expiratory volume in one second); Peak expiratory flow; Forced expiratory flow (FEF), etc. Parameters of diffusion capacity of Carbon MONOXIDE (DLCO), Alveolar volume (VA), and KCO (DLCO/VA) were related to diffusion function. The standard helium dilution method was used to check for residual gas whose volume was assessed using residual gas volume (RV), total lung capacity (TLC), and RV/TLC.

2.5. Statistical analysis

Continuous and categorical variables were expressed by median (quartile interval) and count (percentage), respectively. Mann-Whitney *U* test was used for comparing continuous variables between two groups, Kruskal-Wallis's test was used for multiple comparisons, and $\chi 2$ and Fisher's test were used for categorical variables. IBM SPSS 22.0 statistical software was used for all statistical analyses. Origin 2019b was used to draw the graphs while variables with *P-value* < 0.05 were considered statistically significant.

3. Results

3.1. Patients' clinical characteristics

60 subjects were eventually included in the study with 33 males and 27 females. Compared with normal CT, we observed that median age (51 years vs. 45 years; P = 0.037), BMI (26.1 vs 23.1; P = 0.038), the proportion of severe patients (60%, P < 0.001), and the symptom of chest tightness (P = 0.038) were higher in the abnormal CT group. The normal CT group had a higher proportion of underlying diseases in hypertension (P = 0.031) or diabetes (P = 0.013) (Table 1).

3.2. Returning to immune homeostasis one year after recovery

To assess the immune status, congenital immune indices (WBC count, lymphocyte count, and monocyte count), adaptive immune indices (CD3 T cell count, CD4 T cell count, and CD8T cell count), and other immune-related indices (Globulin, IgG, IgM) were analyzed among these 60 subjects. Compared with healthy controls, we found no difference in any of these measures (Fig. 2). These results preliminarily suggest that the patient's immune status had returned to normal during the one-year follow-up.

3.3. Dynamic changes of immunity indicator within one year

The immune status of the subjects was normal one year after the discharge, however, there were 20 subjects with CT abnormalities according to lung imaging. To study related factors of lung CT abnormalities, we observed the changes in immune indexes at T1, T2, and T3 in the normal and abnormal CT groups respectively (Fig. 3).

Based on longitudinal immunoglobulin changes, A/G decreased at admission and then gradually increased, while an opposite trend was found in globulin; In the abnormal CT group, IgG increased at the onset

Table 1
Baseline clinical characteristics of one-year follow-up of 60 COVID-19 survivors.

Characteristic	All (60)	Follow-up(n = 60)		P value
		CT-Normal (n = 40)	CT-Abnormal (n = 20)	
Gender(Male/Female)	33/27	22/18	11/9	1.000
Median age (IQR[a]), year	47.5 (40.0–54.5)	45(37–50)	51(41–56)	**0.037**
BMI (IQR[a]), kg/m2	24.3 (22.7–26.5)	23.1 (21.8–25.0)	26.1 (23.4–27.3)	**0.038**
Length of stay, days	22 (13-28)	20(13–27)	25(19–32)	0.239
Severe n[b](%)	16 (26.7)	4(10)	12(60)	**<0.001**
Symptoms and signs-n[b] (%)				
Fever	46 (76.7)	30(75)	16(80)	0.756
Pharyngalgia	7 (11.7)	5(12.5)	2(10)	1.000
Cough	30 (50)	18(45)	12(60)	0.273
Expectoration	13 (21.7)	8(20)	5(25)	0.658
Muscle soreness	3 (5)	2(5)	1(5)	1.000
Headache	10 (16.7)	7(17.5)	3(15)	1.000
Diarrhea	3 (5)	2(5)	1(5)	1.000
Chest tightness	5 (8.3)	1(2.5)	4(20)	**0.038**
Comorbidities-n[b] (%)				
Hypertension	11 (18.3)	4(10)	7(35)	**0.031**
Diabetes	6 (10)	1(2.5)	5(25)	**0.013**
Cardiovascular disease	2 (3.3)	1(2.5)	1(5)	1.000
Cerebrovascular disease	1 (1.7)	1(2.5)	0	1.000
Chronic bronchitis	1 (1.7)	0	1(5)	0.333
Tuberculosis	1 (1.7)	1(2.5)	0	1.000
Thyroid disease	2 (3.3)	1(2.5)	1(5)	1.000
Hepatitis	5 (8.3)	4(10)	1(5)	0.656
Chronic kidney disease	2 (3.3)	1(2.5)	1(5)	1.000
Digestive system disease	1 (1.7)	1(2.5)	0	1.000

IQR[a]: Median (P25-P75).
n[b] (%): number.

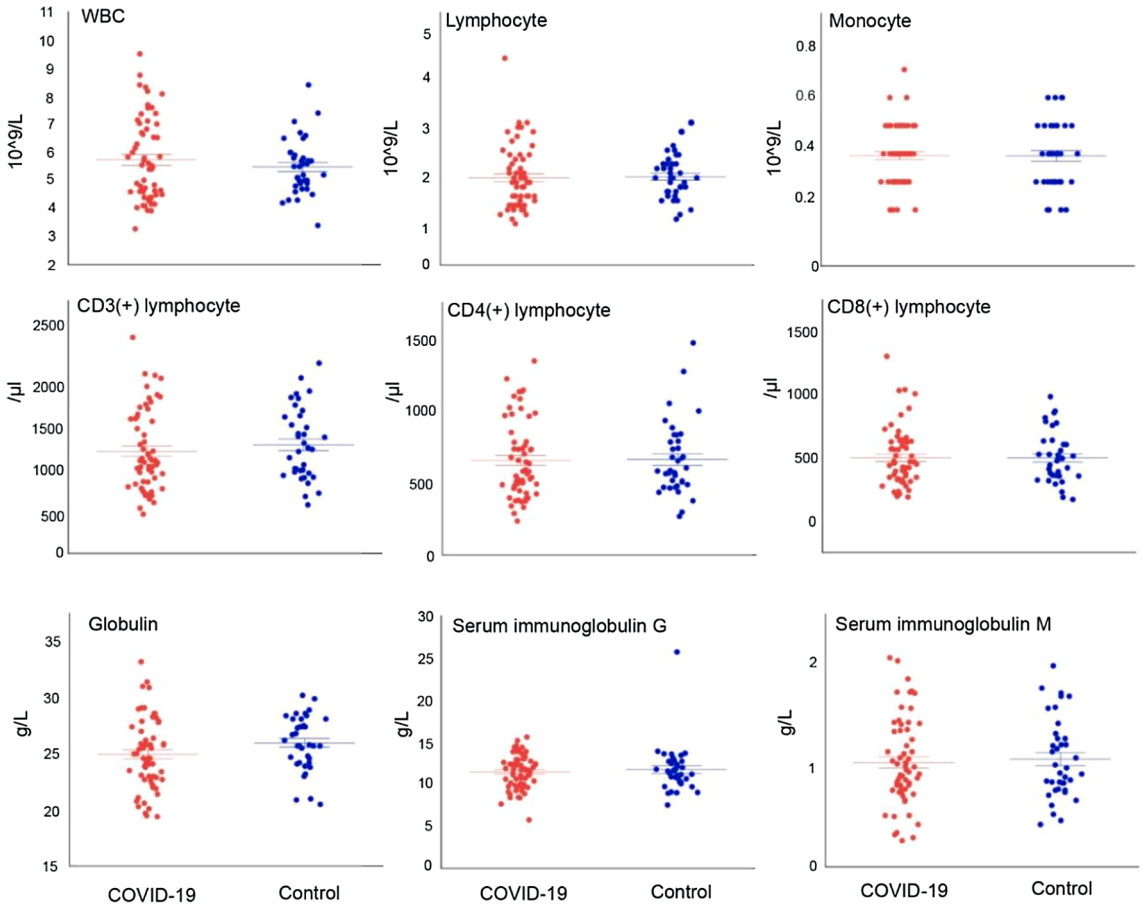

Fig. 2. Recovered immune homeostasis one year after the discharge. Comparison of the number of leukocytes, lymphocytes, monocytes, and lymphocyte subsets (CD3+, CD4+, CD8+) and immune series (globulin, IgG, IgM) between COVID-19 recovered subjects in first-year follow-up and healthy controls.

and returned to the normal level, but there was no difference between IgA and IgM.

Dynamic changes of C1q, C3, and C4 showed that they were all elevated at the onset, and remained elevated at discharge. At one-year follow-up, C3 levels in the abnormal CT group were still higher than those in the healthy control group, and all the others were reduced to normal levels.

Lymphocyte and lymphocyte subgroup TBNK decreased at T1 and increased at T2 and T3, but cytokines showed an opposite trend while CD19+ cells had no difference in T1, T2, and T3. It should be noted that with the recovery from the disease, NK cell counts increased and CD19+ B cell counts decreased in the normal group at one-year follow-up compared with healthy controls, while IL-2 and IFN-γ levels remained high.

3.4. The relation between complement C3 and restrictive ventilation disorders of lung function in COVID-19 recovered subjects

To explore the factors associated with persistent pulmonary imaging abnormalities in the 60 subjects, we compared the immune indices at 1-year follow-up in normal and abnormal groups and found that complement C3 levels were higher in the abnormal group (Table 2). At the same time, the longitudinal analysis showed that the onset of complement C3 increased in the normal and abnormal groups, and complement C3 levels in the abnormal group were still higher than those in the healthy control group at the one-year follow-up (Fig. 3). These results suggested that high levels of complement C3 at the one-year follow-up were associated with abnormal pulmonary effects. To further study the relationship between C3 level and lung function, the 60 subjects were divided into two groups according to the median C3 level and were analyzed on the relationship between C3 level and lung function. The results showed that a high C3 level was associated with lower restrictive ventilation indicators TLC-HE (ratio) and diffuse ventilation indicators (KCO) (Fig. 4A, B). Correlation analysis showed that complement C3 negatively correlated TLC-He (ratio) ($R = -0.302$, $P = 0.017$) (Fig. 4C).

4. Discussion

The outbreak of COVID-19 has brought serious consequences to health all over the world. Management and follow-up of recovered patients are also important to work. Relevant studies suggested that continuing medical observation after discharge is necessary[11]. In this study, 73 cases of one-year COVID-19 recovered subjects in Zhejiang province were followed up, we found that 24/73 (32.8%) still had abnormal lung CT at the one-year follow-up, indicating that it is still necessary to carry out medical management for recovered patients. At the same time, we dynamically conducted a comprehensive evaluation of immune indicators during the follow-up period from admission to one-year recovery and explored the relationship between persistent lung CT abnormalities in COVID-19 recovers and immune indicators.

Aging can lead to decreased lung function, while advanced age has been identified as a major risk factor for the development of severe COVID-19 [11,12], and age is also a risk factor for lung recovery[13,14]. Overweight and obese tend to lead to be severe and have a poor prognosis [15]. This study found that subjects with abnormal CT in the 1-year follow-up were older and with higher BMI. The most common comorbidities among 73 COVID-19 recovered subjects were hypertension (11/73, 15%) and diabetes (6/73, 8.2%), both of which were higher

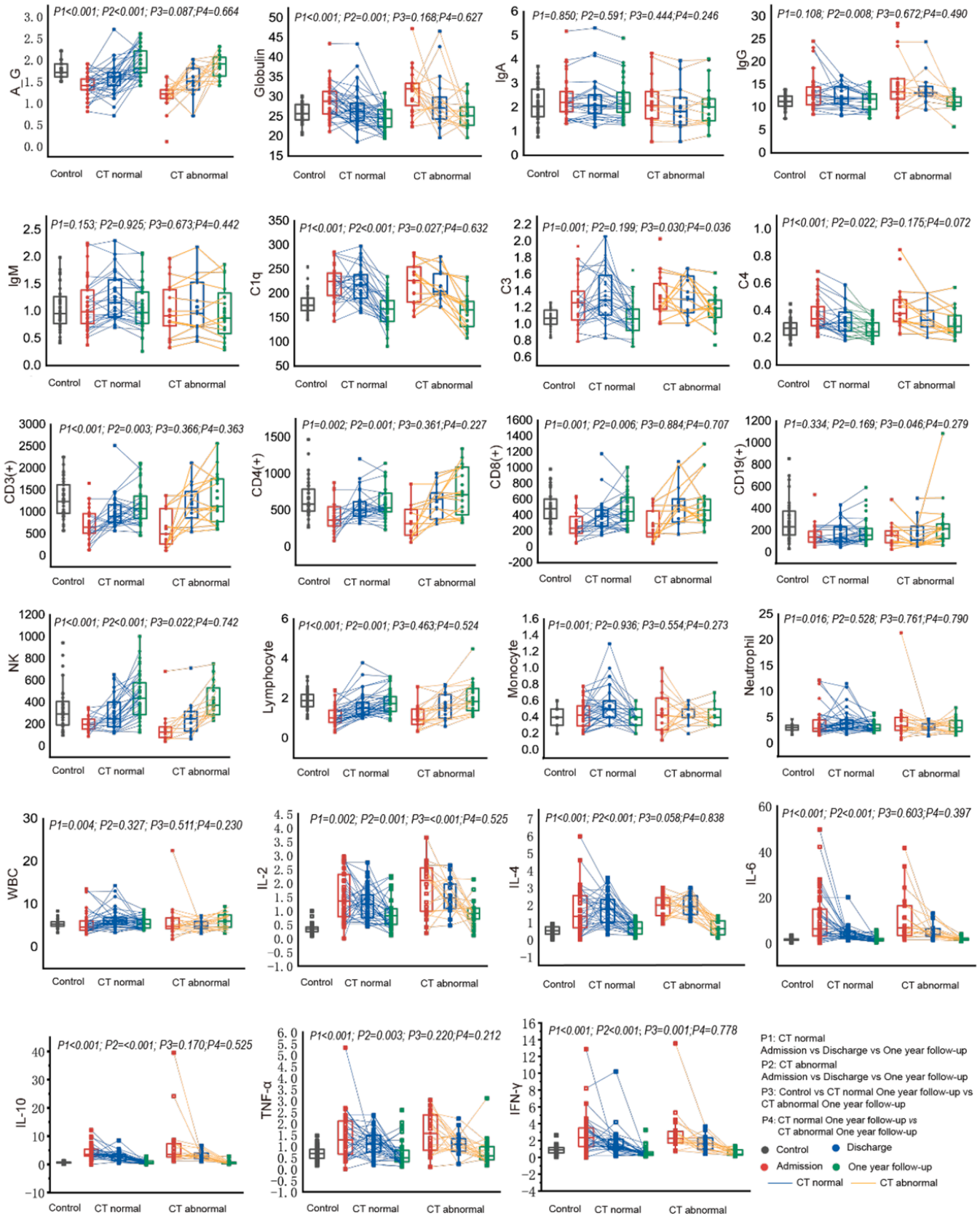

Fig. 3. Dynamic changes of immune indexes of COVID-19 subjects within one year after the discharge. P1: the immune indexes comparison at T1, T2, and T3 in the normal CT group for; P2: the immune indexes comparison at T1, T2, and T3 in the abnormal CT group; P3: the immune indexes comparison at T3 in the healthy control group, normal CT group, and abnormal CT group; P4: the immune indexes comparison at T3 in the normal CT group and abnormal CT group. The Y-axis represents the value of immune indicators, The X-axis represents groups, The color gray represents healthy control, red represents T1, blue represents T2, and the green represents T3. The blue line represents the CT normal group and the yellow line represents the CT abnormal group.

Table 2
Immune indexs of one year follow-up 60 COVID-19 surviors.

Variables	CT Normal (n = 40)	CT Abnormal (n = 20)	P
Albumin /globulin ration	1.8 (1.7–2.2)	1.9 (1.6–2.0)	0.642
Globulin	24.6 (22.5–26.5)	25.2 (22.9–27.2)	0.627
IgA	2.2 (1.8–2.6)	2.0 (1.5–2.3)	0.246
IgG	11.9 (9.7–13.0)	11.1 (10.3–12.3)	0.490
IgM	1.0 (0.8–1.4)	0.9 (0.6–1.3)	0.442
Complement C1q	167.7 (142.9–184.2)	166.3 (132.6–182.3)	0.632
Complement C3	1.1 (0.9–1.2)	1.2 (1.1–1.3)	**0.036**
Complement C4	0.25 (0.22–0.31)	0.29 (0.24–0.36)	0.072
CD3(+) lymphocyte counts	1076.6 (852.7–1344.9)	1129.8 (786.5–1745.7)	0.363
CD4(+) lymphocyte counts	534.2 (485.6–734.3)	716.4 (460.1–1088.1)	0.227
CD8(+) lymphocyte counts	444.3 (331.5–624.7)	463.9 (346.0–587.7)	0.707
NK cell counts	438.9 (289.0–578.8)	375.1 (289.1–522.0)	0.742
CD19(+) lymphocyte counts	156.4 (119.5–218.0)	215.3 (131.5–255.6)	0.279
Interleukin-2	0.82 (0.50–1.06)	0.91 (0.72–1.09)	0.525
Interleukin-4	0.65 (0.32–1.00)	0.62 (0.28–1.08)	0.838
Interleukin-6	1.39 (0.94–1.85)	1.56 (1.17–2.02)	0.397
Interleukin-10	0.50 (0.25–1.16)	0.49 (0.24–0.67)	0.525
Tumor necrosis factor-α	0.49 (0.32–0.79)	0.58 (0.41–0.97)	0.212
Interferon-γ	0.42 (0.25–0.64)	0.37 (0.27–0.89)	0.778
WBC	5.44 (4.47–6.36)	6.0 (4.6–7.4)	0.230
Neutrophil	3.0 (2.5–3.8)	3.4 (2.3–4.6)	0.790
Lymphocyte	1.8 (1.4–2.1)	1.89 (1.5–2.5)	0.542
Monocyte	0.4 (0.3–0.5)	0.4 (0.3–0.5)	0.273

in the pulmonary dysfunction group, and diabetic patients were more likely to receive invasive mechanical ventilation and intensive care unit (ICU) care [16]. It was also confirmed that the proportion of severe COVID-19 patients in the abnormal CT group reached 60% [4].

Compared with healthy controls, we observed that the total number of leukocytes, lymphocyte counts, monocyte counts, lymphocyte subsets, and immunoglobulins were not significantly different indicating that the immune status was recovered. Longitudinal observation of immune indicators in recovered patients showed that compared with the 2-week follow-up after discharge, lymphocytes and lymphocyte subsets increased, cytokines decreased, and complement series decreased to normal levels at one-year follow-up, except for the abnormal CT group. This is an addition to previous studies reporting that the immune system gradually recovered to a steady state after two weeks of discharge [7,17,18], and also reflects the need for long-term follow-up. Interestingly, compared with healthy controls, the normal group had higher NK cell count levels at one-year follow-up, which also suggested that NK cells were a prognostic factor for good recovery of lung function [13].

In addition, the longitudinal analysis in this study found that a high level of complement C3 might be a related factor for pulmonary abnormality at one-year follow-up, and correlation analysis confirmed that a high level of complement C3 was negatively correlated with pulmonary ventilation function, suggesting that complement C3 might be a risk factor for pulmonary recovery. Complement C3 activation is upstream of pro-inflammatory innate immune circuits that contribute to thrombotic inflammation and organ damage in COVID-19[19,20]. It has been reported that blocking C3 activation or the generation of downstream effects can significantly attenuate the directed pro-inflammatory sequelae of coronavirus (CoV) infection in the lung, including MERS-CoV or SARS-CoV [6,21]. However, the prognostic function of complement C3 on pulmonary recovery during 1-year follow-up of COVID-19 survivors has not been reported. A recent report suggests that complement activation has been found in lung biopsies of COVID-19 patients. Italian researchers also reported the first case of COVID-19 treated with amy101, a complement C3 inhibitor [22]. In conclusion, a sustained high level of complement C3 in COVID-19 survivors is a risk factor for

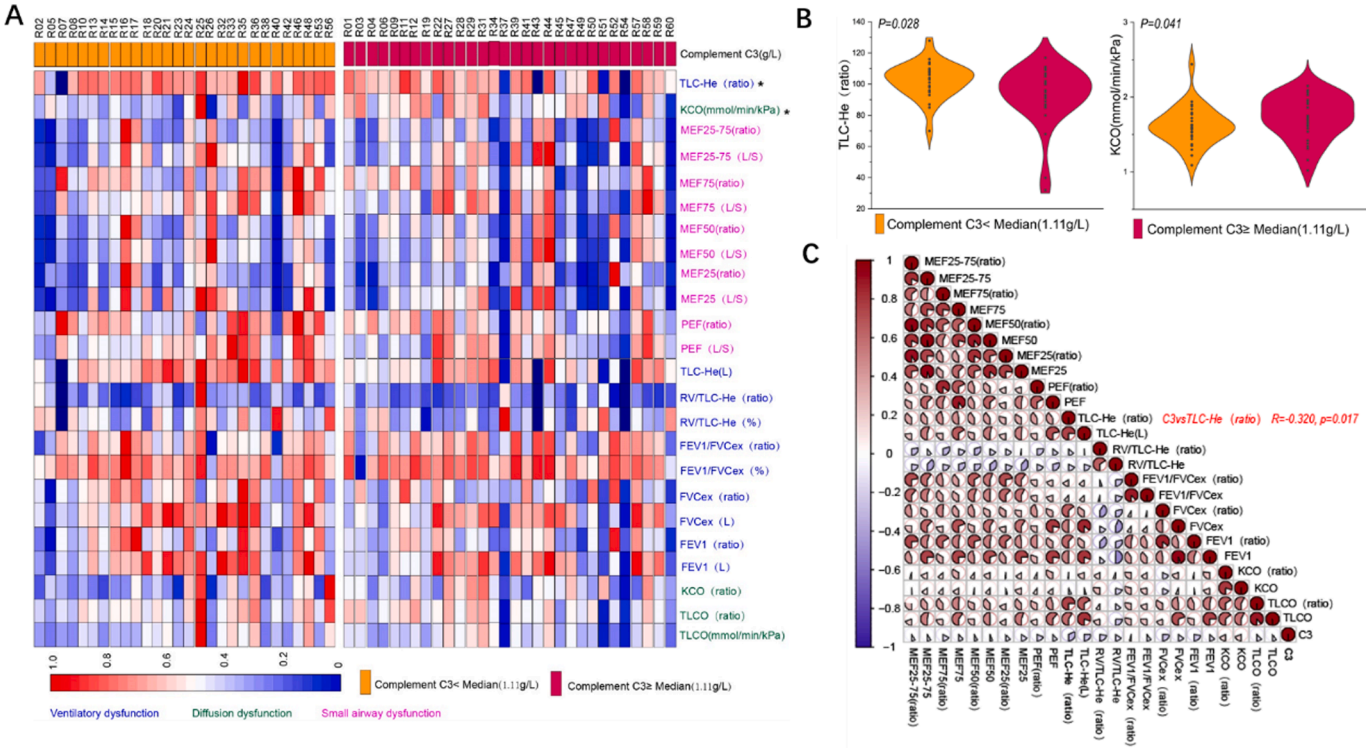

Fig. 4. Complement C3 is a correlative factor of pulmonary function-restrictive ventilatory disorders in COVID-19 patients. A. Heat maps of lung function indicators between groups with complement C3 < median (1.1 g/L) and complement C3 ≥ median (1.1 g/L). B. Difference analysis of restrictive ventilation indicators TLC-HE (Ratio) and diffuse ventilation indicators (KCO) between the two groups. C. The correlation coefficient heat map showed that complement C3 and TLC-He (ratio) were negatively correlated.

persistent lung abnormalities.

Limitations

Several limitations should be considered when interpreting the results of this study. First, the research object of this study is limited to one city, and there may be differences between cities or regions. Second, the sample size is not large enough, which may weaken the statistical power. Therefore, it is necessary to further study inductive validity and external validity to further clarify its internal mechanism. In future studies, it is important to consider a larger sample size and longitudinal studies with wider regions and populations.

5. Conclusion

In conclusion, our findings suggested that the higher the complement C3 level at one-year follow-up, the greater the likelihood of pulmonary imaging abnormalities. In addition, complement C3 negatively correlated with the lung restrictive ventilation index. These findings could be useful for medical institutions and governments to provide further therapy to the COVID-19 recovered subjects.

Author contributions

Hongguo Zhu and Bo Shen supervised the project. Hongguo Zhu, Bo Shen, Hongbo Chi, and Kai Zhou designed the study. Kai Zhou and Hongbo Chi organized the data and wrote the manuscript. Kai Zhou, Hongbo Chi, Liping Shen, Jiaqin Xu, Jun Li, and Shiyong Chen collected clinical data and provided clinical supervision. Xiaomai Wu assisted in completing the face-to-face follow-up. Tao-Hsin Tung provided guidance in the rigor of experimental design and statistics.

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CRediT authorship contribution statement

Hongbo Chi: Conceptualization, Writing – original draft, Writing – review & editing. **Kai Zhou:** Conceptualization, Writing – review & editing. **Liping Shen:** Methodology, Formal analysis. **Jiaqin Xu:** Investigation. **Jun Li:** Investigation. **Shiyong Chen:** Investigation. **Xiaomai Wu:** Investigation. **Tao-Hsin Tung:** Conceptualization, Writing – review & editing. **Bo Shen:** Conceptualization, Writing – review & editing, Supervision, Project administration. **Hongguo Zhu:** Conceptualization, Writing – review & editing, Supervision, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] Z. Zheng, Z. Yao, K. Wu, J. Zheng, Patient follow-up after discharge after COVID-19 pneumonia: considerations for infectious control, J. Med. Virol. 92 (11) (2020) 2412–2419.

[2] L. Liang, B. Yang, N. Jiang, W. Fu, X. He, Y. Zhou, W.L. Ma, X. Wang, Three-month follow-up study of survivors of coronavirus disease 2019 after discharge, J. Korean Med. Sci. 35 (47) (2020), e418.

[3] L. Huang, Q. Yao, X. Gu, Q. Wang, L. Ren, Y. Wang, P. Hu, L. Guo, M. Liu, J. Xu, X. Zhang, Y. Qu, Y. Fan, X. Li, C. Li, T. Yu, J. Xia, M. Wei, L. Chen, Y. Li, F. Xiao, D. Liu, J. Wang, X. Wang, B. Cao, 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study, Lancet 398 (10302) (2021) 747–758.

[4] C. Huang, L. Huang, Y. Wang, X. Li, L. Ren, X. Gu, L. Kang, L. Guo, M. Liu, X. Zhou, J. Luo, Z. Huang, S. Tu, Y. Zhao, L. Chen, D. Xu, Y. Li, C. Li, L. Peng, Y. Li, W. Xie, D. Cui, L. Shang, G. Fan, J. Xu, G. Wang, Y. Wang, J. Zhong, C. Wang, J. Wang, D. Zhang, B. Cao, 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study, Lancet 397 (10270) (2021) 220–232.

[5] V.J. Sarma, M. Huber-Lang, P.A. Ward, Complement in lung disease, Autoimmunity 39 (5) (2006) 387–394.

[6] L.E. Gralinski, T.P. Sheahan, T.E. Morrison, V.D. Menachery, K. Jensen, S.R. Leist, A. Whitmore, M.T. Heise, R.S. Baric, Complement Activation Contributes to Severe Acute Respiratory Syndrome Coronavirus Pathogenesis, mBio 9 (5) (2018).

[7] X.H. Jin, H.L. Zhou, L.L. Chen, G.F. Wang, Q.Y. Han, J.G. Zhang, X. Zhang, Q. Y. Chen, Y.H. Ye, A. Lin, W.H. Yan, Peripheral immunological features of COVID-19 patients in Taizhou, China: a retrospective study, Clin. Immunol. 222 (2021), 108642.

[8] F. Pan, T. Ye, P. Sun, S. Gui, B. Liang, L. Li, D. Zheng, J. Wang, R.L. Hesketh, L. Yang, C. Zheng, Time course of Lung changes at Chest CT during recovery from coronavirus disease 2019 (COVID-19), Radiology 295 (3) (2020) 715–721.

[9] H. Dai, X. Zhang, J. Xia, T. Zhang, Y. Shang, R. Huang, R. Liu, D. Wang, M. Li, J. Wu, Q. Xu, Y. Li, High-resolution chest CT features and clinical characteristics of patients Infected with COVID-19 in jiangsu, China, Int. J. Infect. Dis. 95 (2020) 106–112.

[10] K. Zhou, Y. Sun, L. Li, Z. Zang, J. Wang, J. Li, J. Liang, F. Zhang, Q. Zhang, W. Ge, H. Chen, X. Sun, L. Yue, X. Wu, B. Shen, J. Xu, H. Zhu, S. Chen, H. Yang, S. Huang, M. Peng, D. Lv, C. Zhang, H. Zhao, L. Hong, Z. Zhou, H. Chen, X. Dong, C. Tu, M. Li, Y. Zhu, B. Chen, S.Z. Li, T. Guo, Eleven routine clinical features predict COVID-19 severity uncovered by machine learning of longitudinal measurements, Comput. Struct. Biotechnol. J. 19 (2021) 3640–3649.

[11] V. Balachandar, I. Mahalaxmi, M. Subramaniam, J. Kaavya, N. Senthil Kumar, G. Laldinmawii, A. Narayanasamy, P. Janardhana, Kumar Reddy, P. Sivaprakash, S. Kanchana, G. Vivekanandhan, S.G. Cho, Follow-up studies in COVID-19 recovered patients - is it mandatory? Sci. Total Environ. 729 (2020), 139021.

[12] F. Zhou, T. Yu, R. Du, G. Fan, Y. Liu, Z. Liu, J. Xiang, Y. Wang, B. Song, X. Gu, L. Guan, Y. Wei, H. Li, X. Wu, J. Xu, S. Tu, Y. Zhang, H. Chen, B. Cao, Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study, Lancet 395 (10229) (2020) 1054–1062.

[13] S. Dai, B. Zhao, D. Liu, Y. Zhou, Y. Liu, L. Lan, Y. Li, W. Luo, Y. Zeng, W. Li, Follow-up study of the cardiopulmonary and psychological outcomes of COVID-19 survivors six months after discharge in Sichuan, China, Int. J. Gen. Med. 14 (2021) 7207–7217.

[14] Y. Chen, C. Ding, L. Yu, W. Guo, X. Feng, L. Yu, J. Su, T. Xu, C. Ren, D. Shi, W. Wu, P. Yi, J. Liu, J. Tao, G. Lang, Y. Li, M. Xu, J. Sheng, L. Li, K. Xu, One-year follow-up of chest CT findings in patients after SARS-CoV-2 infection, BMC Med. 19 (1) (2021) 191.

[15] G. Caci, A. Albini, M. Malerba, D.M. Noonan, P. Pochetti, R. Polosa, COVID-19 and obesity: dangerous liaisons, J. Clin. Med. 9 (8) (2020).

[16] S. Richardson, J.S. Hirsch, M. Narasimhan, J.M. Crawford, T. McGinn, K. W. Davidson, C.-R.C. the Northwell, D.P. Barnaby, L.B. Becker, J.D. Chelico, S. L. Cohen, J. Cookingham, K. Coppa, M.A. Diefenbach, A.J. Dominello, J. Duer-Hefele, L. Falzon, J. Gitlin, N. Hajizadeh, T.G. Harvin, D.A. Hirschwerk, E.J. Kim, Z. M. Kozel, L.M. Marrast, J.N. Mogavero, G.A. Osorio, M. Qiu, T.P. Zanos, Presenting characteristics comorbidities and outcomes among 5700 patients hospitalized With COVID-19 in the new york city area, JAMA 323 (20) (2020) 2052–2059.

[17] X. Hasichaolu, X. Zhang, X. Li, D. Li, Li, Circulating Cytokines and Lymphocyte Subsets in Patients Who Have Recovered from COVID-19, Biomed. Res. Int. 2020 (2020) 7570981.

[18] L.B Rodda, J Netland, L Shehata, K.B Pruner, P.A Morawski, C.D Thouvenel, K. K Takehara, J Eggenberger, E.A Hemann, H.R Waterman, M.L Fahning, Y Chen, M Hale, J Rathe, C Stokes, S Wrenn, B Fiala, L Carter, J.A Hamerman, N.P King, M Gale Jr, D.J Campbell, D.J Rawlings, M Pepper, Functional SARS-CoV-2-Specific immune memory persists after mild COVID-19, Cell 184 (1) (2021) 169–183, e17.

[19] A.M. Risitano, D.C. Mastellos, M. Huber-Lang, D. Yancopoulou, C. Garlanda, F. Ciceri, J.D. Lambris, Complement as a target in COVID-19? Nat. Rev. Immunol. 20 (6) (2020) 343–344.

[20] F. Ciceri, L. Beretta, A.M. Scandroglio, S. Colombo, G. Landoni, A. Ruggeri, J. Peccatori, A. D'Angelo, F. De Cobelli, P. Rovere-Querini, M. Tresoldi, L. Dagna, A. Zangrillo, Microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome (MicroCLOTS): an atypical acute respiratory distress syndrome working hypothesis, Crit. Care Resusc. 22 (2) (2020) 95–97.

[21] Y. Jiang, G. Zhao, N. Song, P. Li, Y. Chen, Y. Guo, J. Li, L. Du, S. Jiang, R. Guo, S. Sun, Y. Zhou, Blockade of the C5a–C5aR axis alleviates lung damage in hDPP4-transgenic mice infected with MERS-CoV, Emerg. Microbes Infect 7 (1) (2018) 77.

[22] S. Mastaglio, A. Ruggeri, A.M. Risitano, P. Angelillo, D. Yancopoulou, D. C. Mastellos, M. Huber-Lang, S. Piemontese, A. Assanelli, C. Garlanda, J. D. Lambris, F. Ciceri, The first case of COVID-19 treated with the complement C3 inhibitor AMY-101, Clin. Immunol. 215 (2020), 108450.