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Clinical course of persistent viral positivity in lymphoma patients with COVID-19 infection: a retrospective study

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Abstract

Background Patients with lymphoma are at high risk of persistent positive COVID-19 detection and intractable pneumonia. The treatment process for these patients is both difficult and lengthy. In this situation, it is urgent to manage effective treatment strategy for this vulnerable group.

Methods We analyzed 24 lymphoma patients hospitalized due to COVID-19 infection. Clinical characteristics, treatment processes, co-infections, and risk factors of severe/critical COVID-19 infection were analyzed. We conducted univariate and multivariate analyses to evaluate the risk factors associated with persistent viral detection.

Results A total of 24 lymphoma individuals with a COVID-19 diagnosis were identified. The median age of these patients was 63 years old, and 54% of them were male. The median duration of persistent viral detection was 40 days. Patients with persistent viral detection often experienced repeated fever and had a long and hard treatment process. Their imaging evolution manifested as organizing pneumonia, pulmonary fibrosis, or the recurrence of ground-glass opacity. Compared to PCR tests, the metagenomic next-generation sequencing or target next-generation sequencing tests can better detect COVID-19 and co-infection pathogens. The 6 patients who had severe/critical COVID-19 outcomes differed from patients with mild/moderate COVID-19 infection in terms of white blood cells and prealbumin and took a longer duration of viral positivity. Lymphocyte count reduction and prealbumin decrease were observed in patients with persistent viral detection, suggesting possible associations that require confirmation in larger studies.

Conclusion Lymphoma patients with COVID-19 infection may experience a persistent positive viral detection time, which causes persistent symptoms and repeated hospitalization. Their chest CT images may exhibit atypical evolution such as organizing pneumonia, pulmonary fibrosis, or the recurrence of ground-glass opacity. In this exploratory case series, lymphopenia and low prealbumin were possibly associated with persistent viral detection and severe/critical COVID-19. The treatment process for these patients is both difficult and lengthy, especially in the application of antiviral drugs and steroids. However, due to the high individual variability in treatment options, we were unable to draw a clear conclusion of antiviral treatmentduration or glucocorticoid strategy. More studies are needed to formulate a standard treatment scheme for these patients.

Keywords Clinical course · COVID-19 · Lymphoma · Persistent viral detection · Treatment

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic, which lasted from December 2019 and December 2023, has resulted in approximately 6.8 million deaths worldwide [1]. Given their underlying disease and anti-cancer therapy, patients with lymphoma may be immunocompromised and are considered to have a higher risk of severe outcomes after contraction COVID-19, compared to the general population [2, 3].

Emerging evidence has identified multiple demographic and clinical predictors of increased COVID-19-related morbidity and mortality, particularly among individuals aged over 60 years, males, and those with chronic conditions such as hypertension, diabetes, heart disease, cerebrovascular disease, chronic lung disease, chronic kidney disease, obesity, immunosuppression, and cancer [4, 5].

Many previous studies have indicated that oncology patients are at high risk for severe COVID-19.[6,8] COVID-19-associated prognosis appears to be worse for hematological malignancies compared to solid tumors [9, 10]. There are many reasons for these poor outcomes, such as immunocompromise due to disease, anti-cancer treatment and concurrent immunosuppressive therapy [3]. Lymphomas are a group of different types of malignant tumors of lymphocytes that can involve lymphoid tissue, bone marrow and other body organs, and are classified into Hodgkin lymphomas(10–15% of cases) and non-Hodgkin lymphomas [11, 12]. Because of their immunocompromised states, lymphoma patients face a high risk of prolonged COVID-19 viral shedding and hard-to-cure pneumonia [13]. Patients in this situation often experience recurrent fever, resulting in repeated hospitalizations. Their COVID-19 nucleic acid results were repeatedly positive and even failed to turn negative for a long time. The treatment process for these patients is both difficult and lengthy. In this situation, it is urgent to manage effective treatment strategy for this vulnerable group [13].

In this study, we reviewed all lymphoma patients hospitalized in Beijing Chaoyang Hospital due to COVID-19, aiming to describe the clinical characteristics and treatment experiences of COVID-19 in patients with lymphoma.

Methods

Study design

Between December 2022 and December 2023, 24 lymphoma patients with COVID-19 infection were hospitalized in Respiratory and Critical Care Medicine, Beijing Chaoyang Hospital. All 24 patients were included in our study to analyze their viral shedding time, clinical characteristics, treatment processes, co-infections, and risk factors for severe/critical COVID-19 infection. We conducted univariate and multivariate analyses to evaluate the risk factors associated with persistent viral detection. Given the small sample size, the primary analysis was descriptive. Univariate and multivariable analyses were performed only for hypothesis generation and should be interpreted with caution. The COVID-19 infections were tested by PCR, metagenomic next-generation sequencing (mNGS), or target next-generation sequencing (tNGS).

Persistent/prolonged viral detection was defined as a duration of positive COVID-19 RNA testing of more than 20 days, based on PCR, mNGS, or tNGS results. The duration of persistent viral detection was defined as the interval from the first positive COVID-19 test to the first of two consecutive negative tests, or to the last positive test before discharge if the patient remained positive. When throat swab PCR was negative but sputum mNGS/tNGS was positive, the latter was used to determine viral persistence.

The study was approved by the Ethics Committee of Beijing Chao-Yang Hospital, Beijing, China (# 2024-ke-406). The raw sequencing data from the NGS testing in this study have been deposited in the Genome Sequence Archive of the BIG Data Center (https://bigd.big.ac.cn/), Beijing Institute of Genomics (BIG), Chinese Academy of Sciences, with the accession number: CRA015983.

Data sources and assessment of variables

Data of the patients were extracted from their medical records. We collected every patient's demographic data, lymphoma type, lymphoma history, and anti-tumor therapy. Covid-19-related data was also collected including symptoms, computed tomography (CT) manifestations, treatment processes, and laboratory tests, including complete blood counts, T cell subpopulation counts, C-reactive protein level, D-Dimer, total immunoglobulin levels, prealbumin levels, liver and kidney function levels, and the duration of viral shedding time. All laboratory test results are from the first day of patient admission. According to the World Health Organization guideline for clinical management of COVID-19, we divided the patients into mild/moderate and severe/critical groups [14].

Data on lymphoma subtype, disease status, prior lines of therapy, timing of rituximab or other anti-CD20 therapy, chemotherapy intensity, vaccination history, and prior COVID-19 episodes were collected. However, because of the retrospective design and small sample size, these variables could not be included in multivariable models.

Statistical analysis

We used descriptive statistics to summarize the data. Results are presented as means and standard deviations or medians and ranges. For comparing categorical variables, a chi-square test and Fisher's exact two-sided tests were used and for continuous variables, the Wilcoxon, Rank sum, or *t* test was used. Categorical variables were described as counts and percentages. For numeric risk factors of COVID-19 disease severity, logistic regression was used for univariate analyses. Using the Cox proportional hazard mode, the impact of these selected variables on prolonged viral detection was analyzed by univariate and multivariable analyses. The risk factors that p-value$\leq$0.05 in univariate analyses were selected to do the multivariate analyses. Given the small sample size, the primary analysis was descriptive. Univariate analyses were performed only for hypothesis generation. Multivariable Cox regression was exploratory and should be interpreted with caution because of the limited number of events and the risk of model instability. The statistical test employed a two-tailed test, with a p-value$<$0.05 considered statistically significant.

Results

Patient characteristics

A total of 24 lymphoma individuals with a COVID-19 diagnosis were identified. All of them were confirmed with positive PCR tests or positive mNGS/tNGS tests. Demographic and clinical characteristics were summarized in Table 1. The median age of patients was 63 years old, and 54% of them were male. The types of lymphoma were Hodgkin lymphoma, diffuse large B-cell lymphoma, marginal zone lymphoma, and mantle cell lymphoma. Among all of the patients, 18 were mild/moderate COVID-19 infections and 6 were severe/critical types. The median duration of positive viral detection was 40 days (range, 7–97 days). 18 of 24 patients presented with lymphopenia (average 0.64×10^9/L), and 23 of 24 patients had B-cell depletion (average 25/uL). Among the 24 patients, 4 patients were tested for COVID-19 antibodies. Among the 4 patients, 3 patients' immunoglobulin G (IgG) were positive, but the titers were all very low, with the highest being 22 S/CO, and all 4 patients' immunoglobulin M (IgM) were negative. For outcomes, 18 patients were discharged from the hospital, 3 died, and 3 were later re-hospitalized for Covid-19 recurrence.

Table 1 Baseline characteristics of patients with lymphoma and COVID-19

Age, years	Total ($n=24$)	Mild/moderate ($n=18$)	Severe/critical ($n=6$)	p-value
	63(35–88)	61(35–88)	68(47–82)	0.318
Sex				0.813
Female	11	8	3	
Male	13	10	3	
Lymphoma subtypes				
Hodgkin lymphoma	4	4	0	
Diffuse large B-cell lymphoma	4	4	0	
Follicular lymphoma	8	5	3	
Marginal zone lymphoma	2	1	1	
Mantle cell lymphoma	1	0	1	
Other B-cell lymphoma	5	4	1	
Chemotherapy or immunosuppressor				
Yes	22	21	1	
No	2	1	1	
Duration of viral positive (days)	40(7–97)	11(7–74)	71(39–97)	**0.013**
Laboratory finding				
WBC ($\times10^9$/L)	4.75±2.05	4.62±1.57	5.14±3.28	**0.037**
Lymphocyte count ($\times10^9$/L)	0.64±0.35	0.70±0.36	0.45±0.25	0.334
CD3+ (/uL)	449±253	478±262	290±128	0.247
CD3+CD4+ (/uL)	188±122	203±115	101±151	0.533
CD3+CD8+ (/uL)	223±152	238±160	140±42	0.057
CD56+ (/uL)	48±46	54±48	13±8	0.097
CD19+ (/uL)	25±89	29±95	1±0	0.337
Hemoglobin (g/L)	107±23	108.56±20.38	102.33±31.40	0.44
PLT ($\times10^9$/L)	179±74	192.44±66.01	137.00±86.63	0.26
ALB (g/L)	36.82±4.86	37.29±5.06	35.38±4.27	0.46
PAB (g/L)	0.14±0.07	0.16±0.06	0.08±0.02	**0.006**
AST (U/L)	28.79±13.12	29.28±11.43	27.33±18.57	0.261
ALT (U/L)	32.17±22.39	31.06±21.43	35.50±26.98	0.523
CREA (umol/L)	55.00±14.83	57.48±15.06	47.57±12.33	0.837
CRP (mg/L)	6.47±4.78	6.64±4.66	5.96±5.65	0.738
D-dimer (ng/mL)	923.77±493.88	865.23±431.09	1157.91±724.05	0.207

Data are presented as n, median (range), or mean±SD. *WBC* white blood cell, *PLT* platelet,*ALB* albumin, *PAB* prealbumin, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *CREA* creatinine, *CRP* C-reactive protein

Clinical evolution of patients with severe/critical Covid-19 infection

Most patients with lymphoma did not experience severe or critical COVID-19 infection (75%). The 6 patients who had severe/critical COVID-19 outcomes differed from patients with mild/moderate COVID-19 infection in terms of white blood cells ($p=0.037$) and prealbumin ($p=0.006$). However, the mean white blood cell level is within the normal range in both groups and has no clinical impact. The occurrence of statistical difference may be due to bias caused by the relatively small sample size. Therefore, this difference should be interpreted cautiously and may not reflect a clinically meaningful difference. In our analysis, patients with severe/critical disease took longer duration of positive viral detection. For mild/moderate patients, the average viral positive time was 11 days, and for severe/critical patients, it was 71 days. ($p=0.013$). There is no difference between the mild/moderate and severe/critical patients for other projects like lymphocyte count, hemoglobin, platelet, T lymphocyte subsets, liver function, and kidney function. (Table 1)

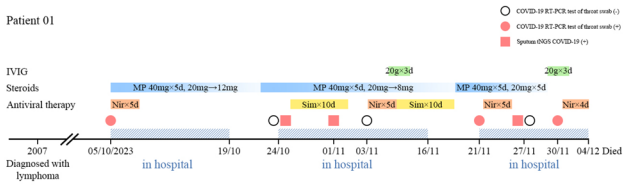


Fig. 1 History and COVID-19 related disease course of Patient 01. IVIG: intravenous immunoglobulin; MP: methylprednisolone; Nir: Nirmatrel/Ritonavir; Sim: Simnotrelvir/Ritonavir

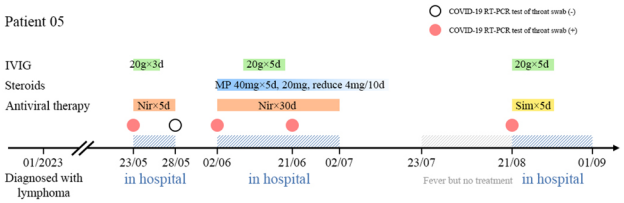


Fig. 2 History and COVID-19 related disease course of. Patient 05. IVIG: intravenous immunoglobulin; MP: methylprednisolone; Nir: Nirmatrel/Ritonavir; Sim: Simnotrelvir/Ritonavir

Persistent positive viral detection of COVID-19 in lymphoma patients

After summarizing the clinical data of all 24 lymphoma patients, we observed a prolonged average COVID-19 viral detected positive time of 40 days. Ten patients had a viral detected positive time of more than 20 days, and 5 patients were discharged with COVID-19 still positive. To better describe the disease courses of these persistent viral detection patients, two typical cases were reported below.

Patient 01 is a 70-year-old man with a past medical history of marginal zone lymphoma who received four cycles of treatment of Rituximab and Bendamustine. The time of last treatment was one month before the COVID-19 infection. The symptoms of the COVID-19 infection of the patient were repeated fever and fatigue. In 3 times of hospitalizations, he was treated with several rounds of Simnotrelvir/Ritonavir or Nirmatrel/Ritonavir, steroids, and intravenous immunoglobin (IVIG). The COVID-19 nucleic acid failed to turn negative constantly. He developed a coinfection of Rhizopus microspores in the latter half of the disease course and died 2 months later. The clinical course is shown in Fig. 1.

Patient 05 is a 66-year-old woman with a past medical history of follicular lymphoma who received two cycles of treatment of Rituximab. Two weeks after the last treatments, the patient got a fever and was diagnosed with the COVID-19 infection. 5 days of Nirmatrel/Ritonavir Tablet and 3 days of IVIG were used before discharge. 3 days later, the patient's body temperature raised again compared with persistent viral detection. After 30 days of Nirmatrel/Ritonavir Tablet, 5 days of IVIG, and 40 days of steroids, the patient was relieved and discharged. 1 month later, her symptoms returned. But this time, the patient was quickly cured after 5 days of Nirmatrel/Ritonavir Tablet and 5 days of IVIG. So far, it has not been repeated. The clinical course is shown in Fig. 2.

From the above cases, it can be seen that lymphoma patients with persistent viral detection have experienced recurrent fever, resulting in repeated hospitalization. Their COVID-19 nucleic acid results were repeatedly positive and even failed to turn negative for a long time. When COVID-19 PCR tests of throat swabs turned negative, the sputum mNGS/tNGS results were positive. The treatment process for these patients is both difficult and lengthy, especially with the application of steroids and antiviral drugs. Because of the lymphopenia and B-cell depletion, these patients often required additional treatment, such as IVIG.

We also found some characteristics in the chest CT examination of these persistent viral detection patients. The cardinal hallmark of bilateral distribution of ground glass opacities (GGO) was observed in all 24 lymphoma individuals. For most patients, GGO was quickly absorbed with the clearance of the virus. However, for some patients with persistent viral detection, the evolution of imaging manifested as organizing pneumonia, pulmonary fibrosis, or the recurrence of GGO (Fig. 3). Organizing pneumonia was observed in 2 patients, pulmonary fibrosis was observed in 2 patients and the recurrence of GGO was observed in 1 patient.

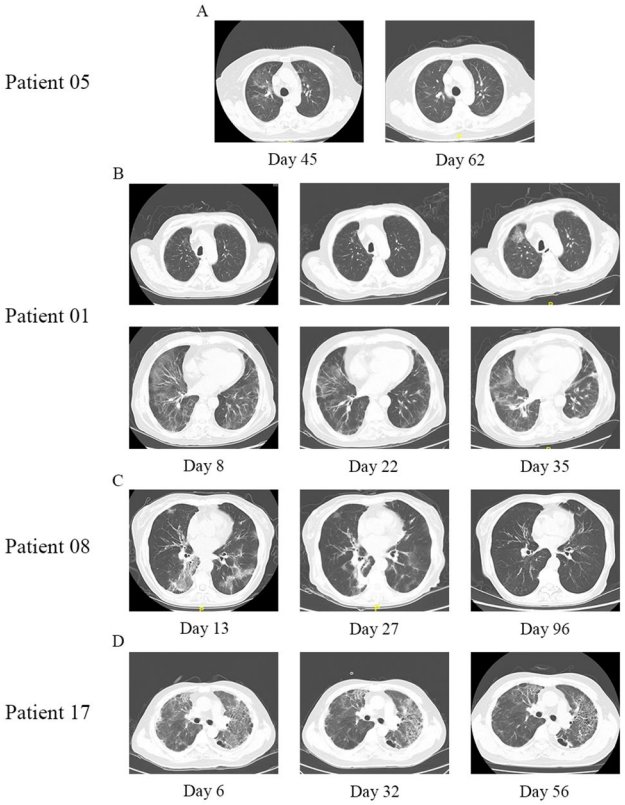


Fig. 3 The CT examination of 4 patients with persistent positive COVID-19 viral detection. The images of (**A**) belong to patient 05, GGO in her images was absorbed with the clearance of the virus. The images of (**B**) belong to patient 01. GGO in his images became organized and some new GGO appeared. The images of (**C**) belong to patient 08 and it is a process of GGO, organizing and absorbing. The images of (**D**) belong to patient 17 and his outcome turned into pulmonary fibrosis

We conducted univariate and multivariate analyses to evaluate the risk factors associated with persistent viral detection (Table 2). Lymphocyte count, $CD3^+CD4^+$T cell count, prealbumin, and creatinine were associated with persistent viral detection in univariate analysis. In the multivariable analysis, lymphocyte count reduction (hazard ratio [HR] 62.241, 95% confidence interval [CI] 0.931-4431.791, $p=0.048$) and prealbumin decrease (HR 0, 95% CI 0-0.804, $p=0.047$) were associated with persistent viral detection. Because of the small number of patients and events, the multivariable model was unstable, as reflected by very wide confidence intervals and implausible estimates. These results are therefore presented for descriptive purposes only and should not be interpreted as independent risk factors. All 24 patients have accepted the antiviral therapy.

For therapeutic factors, the disparities in antiviral drug and glucocorticoid treatment were the starting time of therapy and lasting time of therapy. Univariate and multivariable analyses of the factor associated with persistent viral detection are shown in Table 2. Unfortunately, we have not been able to draw the conclusion that earlier antiviral therapy and long-term antiviral therapy affect the clearance of COVID-19. For the treatment of glucocorticoid treatment, expect for the standardized treatment in the first five days, the dosage and duration of subsequent glucocorticoid use are inconsistent and vary from person to person, so statistical analysis were not conducted. The heterogeneity in antiviral and glucocorticoid regimens reflects real-world clinical practice but limits our ability to compare treatment efficacy. Prospective studies with standardized protocols are urgently needed.

Co-infection in lymphoma patients infected with COVID-19

In this study, 11 patients were carried out mNGS/tNGS tests. We summarized all the positive microbes that were evaluated for co-infected pathogens (Table 3). Bacterial included *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Acinetobacterbaumannii*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Enterococcus faecium*, and *Mycobacterium abscessus*. Fungus included *Candidia albicans*, *Aspergillu*, and *Rhizopus microspores*. Viruses included *Metapneumovirus*, *Herpesvirus*, *Cytomegalovirus*, *Coronavirus*, and

Table 2 Univariate and multivariable analyses for persistent viral detection

Model covariate	Univariate analysis			Multivariable analysis		
	HR	95% CI	*p*	HR	95% CI	*p*
age	0.992	0.946–1.040	0.744			
gender	1.122	0.283–4.448	0.87			
Laboratory finding						
WBC	0.788	0.546–1.138	0.203			
Lymphocyte count	16.697	1.239-225.039	**0.034**	62.241	0.931-4431.791	**0.048**
CD3+	1.002	0.999–1.004	0.142			
CD3+CD4+	1.002	0.998–1.007	0.343			
CD3+CD8+	1.005	1.000-1.010	**0.037**	1.002	0.997–1.007	0.481
CD56+	1.003	0.984–1.022	0.778			
CD19+	1.011	0.980–1.042	0.504			
Hemoglobin	0.99	0.967–1.013	0.402			
PLT	1.004	0.995–1.013	0.385			
ALB	1.077	0.910–1.273	0.39			
PAB	0.006	0-53.069	**0.035**	0	0-0.804	**0.047**
AST	1.007	0.965–1.052	0.74			
ALT	0.986	0.957–1.016	0.345			
CREA	1.034	1.001–1.068	**0.045**	1.05	0.973–1.134	0.212
CRP	0.956	0.838–1.090	0.499			
D-dimer	1	0.998–1.001	0.637			
Starting time of antiviral therapy	0.917	0.787–1.068	0.237			
Lasting time of antiviral therapy	0.941	0.872–1.016	0.079			

WBC white blood cell, *PLT* platelet, *ALB* albumin, *PAB* prealbumin, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *CREA* creatinine, *CRP* C-reactive protein

Table 3 mNGS tested co-infections of lymphoma patient with COVID-19

Co-infections	Total ($n=11$)
Bacteria	
Streptococcus pneumoniae	2
Haemophilus influenzae	2
Staphylococcus aureus	1
Acinetobacter baumannii	1
Pseudomonas aeruginosa	1
Klebsiella pneumoniae	1
Enterococcus faecium	1
Mycobacterium abscessus	1
Fungus	
Candidia albicans	5
Aspergillus	2
Rhizopus microsporus	1
Virus	
Metapneumovirus	4
Herpesvirus	2
Cytomegalovirus	2
Coronavirus	1
Influenza A virus	1

Table 4 The patients' co-infections, treatment, and prognosis

Patient	Co-infection	Co-infection treatment	Outcome
1	Aspergillus and Rhizopus microsporus	Isavuconazole for 6 days	Death
2	Coronavirus	No specific treatment	Discharged after improvement
3	Staphylococcus aureus, Metapneumovirus and Candida albicans	Vancomycin for 5 days, Fluconazole for 13 days and Ribavirin for 5 days	Discharged after improvement
4	Candida albicans and Herpesvirus	No specific treatment	Discharged after improvement
5	Cytomegalovirus	No specific treatment	Discharged after improvement
6	Streptococcus pneumoniae, Pseudomonas aeruginosa, Candida albicans and Herpesvirus	Piperacillin/tazobactam for 17 days and Fluconazole for 22 days	Discharged after improvement
7	Mycobacterium abscessus and Aspergillus fumigatus	The patient refused treatment	Discharged after improvement
8	Klebsiella pneumoniae, Candida albicans, Acinetobacter baumannii and Cytomegalovirus	Sulbactam sodium/Cefoperazone sodium for 12 days, Moxifloxacin for 12 days, Fluconazole for 12 days and Ganciclovir for 11 days	Discharged after improvement
9	Haemophilus influenzae and Metapneumovirus	Moxifloxacin for 5 days and Ribavirin for 7 days	Discharged after improvement
10	Haemophilus influenzae, Streptococcus pneumoniae, Metapneumovirus and Candida albicans	Sulbactam sodium/Cefoperazone sodium for 10 days, Moxifloxacin for 10 days and Fluconazole for 3 days	Discharged after improvement
11	Enterococcus faecium, Influenza A virus and Metapneumovirus	Ganciclovir for 14 days, Oseltamivir for 5 days and Linezolid for 14 days	Discharged after improvement

Influenza A virus. All patients' co-infection, treatment for co-infections, and prognosis were listed in Table 4. Only patient 1 co-infected with Aspergillus and Rhizopus microspores were dead, other patients were discharged after improvement. Patient 7 were co-infected with low sequence quantity of Mycobacterium abscessus and Aspergillus fumigatus. She refused to receive relevant treatment, but the lung patchy shadows resolved on re-examination after 3 months. Her co-infection detected by mNGS may have been caused by contamination.

Discussion

Prolonged COVID-19 symptoms are an important emerging concern that bothered individuals who have survived a COVID-19 infection [15–17]. Several reports have described the persistence of COVID-19 replication with severe symptoms for immunocompromised patients, including those with lymphoma [18–26]. Previous studies have shown that in the general population, the median duration of viral shedding was 20 days [27]. In our study, the average duration of persistent viral detection was 40 days, and even longer in severe/critical patients. Many studies have reported the COVID-19 viral persistence in lymphoma patients, and the longest report was more than 200 days [28–34]. The definition of "prolong" is still vague and needs to be distinguished from secondary infections. It should be emphasized that PCR and NGS detect viral RNA and cannot distinguish viable virus from non-viable RNA remnants. Therefore, our outcome should be interpreted as persistent viral detection rather than true infectious prolonged viral shedding. And if conditions permit, the types of COVID-19 virus strains infected at different times during the course of disease need to be studied.

The prolonged viral shedding time resulted in recurring symptoms, and the treatment process for these patients is both difficult and lengthy. We all know that the general therapeutic regime of COVID-19 has been settled so far, but due to immune deficiency, there is no standard scheme for the treatment of lymphoma patients with COVID-19.[35] Based on our observation, the antiviral treatment course for these patients seems to need to be extended, but

personalized long-term antiviral plans still need to be developed. In some cases, more than 30 days of antiviral therapy have not achieved virus clearance. It has been reported that combination therapy including two antiviral drugs (mainly remdesivir and nirmatrelvir/ritonavir) was associated with higher rates of virological and clinical response in immunocompromised patients with prolonged COVID-19.[36] For hospitalized patients with severe COVID-19 infection, corticosteroids are the mainstay of treatment [37]. But these drugs should not be used for long periods, as long-term immunosuppression can promote chronic infections and potentially increase the risk of secondary infections [38].

IVIG therapy has been suggested as a potential treatment option for hospitalized COVID-19 patients. It has been successfully used in various inflammatory and autoimmune diseases, and its mechanism of action involves multiple immune regulatory pathways: neutralizing autoantibodies, regulating the synthesis and release of cytokines/chemokines, expanding regulatory T cells, and modulating dendritic cell activity. These mechanisms are all considered potentially beneficial for patients with COVID-19.[39] However, in the meta-analysis conducted by Marcec et al.[40] a total of 13 studies were included on a total of 2313 patient outcomes. The results indicated that IVIG therapy had no significant effect on mortality or length of hospital stay. So, it is not recommended in the mainstream treatment options. For immunocompromised patients, the effectiveness of this treatment has not been determined yet, and further researches are needed.

In our analysis, imaging manifested as organizing pneumonia, pulmonary fibrosis, or the recurrence of GGO was found in some patients with persistent viral detection. Past research has demonstrated that COVID-19 pneumonia is one of the secondary causes of organizing pneumonia [41]. Pulmonary fibrosis due to COVID-19 is recognized as a sequel of ARDS, and the risk factors including advanced age, severe ARDS infection, mechanical ventilation due to ventilator-induced lung injury, smoking, and chronic alcoholism [42]. Although there is not enough data yet, based on our research, persistent viral detection may be one of the risk factors of pulmonary fibrosis. In some published cases, COVID-19 patients with B-cell lymphoma who received B-cell depleting therapy and are experiencing prolonged COVID-19 infection may demonstrate migratory airspace opacities on serial CT.[43] One of our study patients has also observed this phenomenon. It needs to be identified whether this phenomenon is due to the continuous activity of COVID-19 or combined with other infections, such as influenza, cytomegalovirus, or pneumocystis. The process of image changes is meaningful and worth studying. But not all patients underwent repeated CT scans, and the number of cases with complete CT documentation is not enough. Therefore, we did not analyze the characteristics of imaging changes between different groups. In future research, we will increase the sample size and analyze the relationship between viral shedding time and imaging changes.

In the case of patient 01, tests were done on the same day, the result of the COVID-19 PCR test from the throat swab was negative, but the sputum mNGS/tNGS COVID-19 result was positive. Of course, this phenomenon was not observed in all patients, but we have observed some patients with delayed symptoms of COVID-19 clinically, but their PCR results are negative. This phenomenon may due to the decrease in viral load after antiviral treatment, so that the sensitivity of PCR detection decreased, while NGS still has high sensitivity for pathogen detection. So, the NGS test can increase the positive rate of COVID-19 and provide better guide the use of antiviral therapy especially in the later stage of disease. On the other hand, the co-infection pathogen results obtained in our study were all from mNGS or tNGS, while the ordinary sputum smear and culture or PCR tests were prone to obtaining false negative results. Thus, when conditions permit, it is recommended to use mNGS or tNGS with samples collected from the lower respiratory tract to improve pathogen detection, and to receive earlier treatment. However, it is worth noting that due to the high sensitivity of NGS, it is essential to distinguish pathogenic bacteria from colonizing/polluting bacteria. In clinical practice, NGS results should be interpreted together with conventional microbiological tests, imaging, and clinical response, and low-sequence reads should be interpreted with caution.

In this exploratory analysis, lymphocyte count reduction and prealbumin decrease were observed in patients with persistent viral detection. These two aspects are also risk factors for severe/critical COVID-19.[44,45]It has been known that both the host's innate and adaptive immune responses play important roles in resisting the progression and prognosis of COVID-19[46] and lymphocytes are important components involved in the immune

response in the body. Thus, there is a close relationship between peripheral lymphocyte counts and the progression of COVID-19. The study of Wang showed that reduced lymphocyte count (< 0.95 × 109/L) was associated with an increased mortality risk in COVID-19 inpatients. Lymphocyte counts also had a potential predictive value for the death of COVID-19 inpatients [47]. Based on our study and previous studies, we were concerned that the severity of COVID-19 reduced the peripheral lymphocyte count level and the reduced lymphocyte counts associated with the persistent viral detection, resulting in a severe COVID-19 infection and a worse outcome. However, given the small sample size and model instability, these findings should be regarded as possible associations rather than determinants. The specific mechanism of this phenomenon in lymphoma patients was not clear. There should also be further research to determine whether these two factors still affect virus clearance in non-lymphoma patients or other kinds of immunosuppressed patients.

In order to further investigate the humoral and cellular immune status of these patients, the antibody feature and T-cell subpopulation were analyzed. The COVID-19 antibody titers of these patients were all very low. This may be due to the deficiency of B cells in lymphoma patients. We analyzed the effect of T-cell subpopulation in persistent viral detection. In univariate analyses, CD3 + CD4+T cell count was associated with persistent viral detection.

T-dependent B cells were activated by CD4 + T cells to producing the virus-specific antibodies. In the meantime, the memory cell responses were induced, which have significant, effective, and long-lasting effects on the virus. Thus, with the CD3 + CD4+T cell deficiency, the clearance of virus become more difficult. As the number of cases increases in the future, multivariable analyses should be refined again to verify this conclusion.

Compared to albumin, prealbumin has a relatively short half-life of 2 to 3 days, whereas album has a half-life of 20 days. [48] Prealbumin is metabolized in the kidneys and is not significantly affected by protein-losing enteropathy. [49–50] Thus, serum prealbumin is not affected by systematic inflammation and is more sensitive to insufficient energy and protein intake than albumin. In the study of Sun, prealbumin was the independent risk factor for survival in lymphoma patients [51]. The meta-analysis by Zinellu and Akbar demonstrated that the decreased serum prealbumin concentration was significantly corrlated with the severity and mortality of COVID-19.[52,53] The mechanism of reduced serum prealbumin concentration in high-risk COVID-19 lymphoma patients may be related to the excess inflammation and malnutrition [54, 55].

Our study has some limitations. First, not all potentially variables were recorded or detected in all patients as our study is a retrospective study. Therefore, some factors may be underestimated in predicting the severity of the disease and the persistent viral detection. Second, the estimation of viral positive time is limited by some factors such as specimen collection method, RNA detection method, and the relatively low positive rate of COVID-19 RNA detection in throat-swabs [56]. Third, for patients who examined the NGS tests, the subtypes of COVID-19 were clear. But for PCR tested patients, the subtypes were not examined. In that case, a few readmission cases cannot distinguish whether it is a prolonged infection or a reinfection. Fourth, because mNGS/tNGS testing was performed in only 11 of 24 patients, the co-infection results are subject to selection bias. Patients who did not undergo sequencing may have undetected bacterial, fungal, or viral co-infections. The prevalence of co-infections in lymphoma patients with COVID-19 therefore remain uncertain. Last but not least, this is a single-center retrospective case series of only 24 patients, including 6 severe/critical cases. Our research results may be limited by the relatively small sample size, and the sample sizes between mild/moderate group and severe/critical are imbalanced, which may lead to insufficient statistical test power. Larger studies are warranted to validate our findings, and we will expand the sample size and update our research in the future.

Above all, a number of lymphoma patients with COVID-19 infection may experience a persistent viral positive time, which causes persistent symptoms and repeated hospitalization. Except for absorbing quickly, the GGO in CT scan may manifest as organizing pneumonia, pulmonary fibrosis, or the recurrence of GGO. Lymphopenia and low prealbumin were possibly associated with persistent viral detection and severe/critical COVID-19 pneumonia. The treatment for these patients is difficult and long-lasting, especially in the application of antiviral drugs and steroids. More studies are needed to formulate a standard treatment scheme for these patients.

Abbreviations

COVID-19	coronavirus disease 2019
mNGS	metagenomic next-generation sequencing
tNGS	target next-generation sequencing
CT	computed tomography
IgG	immunoglobulin G
IgM	immunoglobulin M
IVIG	intravenous immunoglobin
GGO	ground glass opacities
HR	hazard ratio

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Author contributions HYH designed the study. YY collected the data, conducted the analysis, produced the results figures and tables and wrote the initial draft of the manuscript. DHZ, HJW, XZ and YXY managed patients in clinic. All coauthors read and commented on the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Data availability The raw sequencing data of NGS tests from this study have been deposited in the Genome Sequence Archive in BIG Data Center (https://bigd.big.ac.cn/), Beijing Institute of Genomics (BIG), Chinese Academy of Sciences, under the accession number: CRA015983.

Declarations

Ethics approval and consent to participate The study was approved by the Ethics Committee of Beijing Chao-Yang Hospital, Beijing, China (# 2024-ke-406). Informed consent to participate was obtained from all of the participants in the study.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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