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Clinical Features and Prognosis of Patients with COVID-19 and B-Cell Non-Hodgkin Lymphoma

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Purpose: There is a lack of real-world data on the epidemiology, clinical manifestations, treatment effects, and prognosis of coronavirus disease 2019 (COVID-19) in patients with B-cell non-Hodgkin lymphoma (B-NHL). This study aimed to investigate the clinical features and prognostic factors of COVID-19 in patients with B-NHL.

Patients and Methods: This study included individuals diagnosed with B-NHL who were also diagnosed with COVID-19 and hospitalized. A retrospective analysis was conducted, and univariate and multivariate logistic regression were used to identify independent factors affecting the duration of the positive-to-negative transition of COVID-19 nucleic acid test results and prognoses. Receiver operating characteristic curves were used to assess diagnostic accuracy and determine the optimal threshold.

Results: Among 80 patients with COVID-19 and B-NHL, relapsed or refractory lymphoma and diffuse large B-cell lymphoma (DLBCL) accounted for 13.8% and 65% of cases, respectively. The mean age was 60.4 ± 13.0 years, and 50% of patients were women. The median duration of the positive-to-negative transition was 14 days (interquartile range [IQR], 17.2), and the median hospitalization duration was 12 days (IQR, 13). The rate of severe disease was 26.25%, and the 28-day mortality rate was 10.00%. Univariate and multivariate logistic regression analyses revealed that pathological classification of B-NHL, infection with COVID-19 within 3 months after the last dose of anti-CD20 monoclonal antibodies, and corticosteroid use were independent factors associated with a prolonged duration of the positive-to-negative transition. Compared with patients with DLBCL or FL and COVID-19, patients with B-NHL had longer nucleic acid test transition durations and higher rates of severe disease and mortality.

Conclusion: In patients with B-NHL, infection with COVID-19 within 3 months after treatment with anti-CD20 monoclonal antibodies prolonged the positive-to-negative transition of nucleic acid test results and increased the risks of severe disease and 28-day mortality. Treatment with corticosteroids further prolonged this transition.

Keywords: COVID-19 infection, B-cell non-Hodgkin lymphoma, clinical features, prognosis

Introduction

Although vaccination and public health measures have helped control the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus is constantly mutating, requiring vigilance against a potential epidemic rebound. For patients with compromised immune systems, coronavirus disease (COVID-19) infection can lead to adverse outcomes,[1,2] and current treatment strategies for these populations are insufficient.

B-cell non-Hodgkin lymphoma (B-NHL), a blood system tumor, heightens the risk of infection due to a compromised immune system resulting from the disease or treatments such as targeted immunotherapy. Additionally, patients with

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chronic lymphocytic leukemia exhibit a diminished response to COVID-19 vaccines, leading to increased rates of COVID-19 infection, severe disease, and mortality.[3–6] This can be attributed to an impaired humoral immune response caused by anti-CD20 monoclonal antibodies and other targeted therapeutics, which increase susceptibility to infection.[7] Research has demonstrated that the average hospitalization duration for patients with COVID-19 and B-NHL is 88 days.[8] Marcacci et al[9] documented a case of mantle cell lymphoma in which, after nine rituximab treatments, a subsequent COVID-19 infection rapidly progressed from asymptomatic to severe.

Considerable variability exists in the persistence of novel coronavirus nucleic acids in the human body.[10–14] Typically, they persist for approximately 20 days but can last up to 300 days in patients with B-NHL, leading to lower survival rates.[15,16] A comprehensive multicenter study in Italy involving 856 adult patients with lymphoma found that a shorter interval between the last anti-CD20 monoclonal antibody treatment and COVID-19 diagnosis was associated with higher mortality rates.[17] Additionally, one report suggests that anti-CD20 monoclonal antibody therapy may alleviate COVID-19 symptoms in patients with lymphoma.[18] A study in China reported that a patient with follicular lymphoma (FL) developed pulmonary ground-glass opacities due to COVID-19 infection within 2 months of receiving anti-CD20 monoclonal antibody treatment, with the condition persisting for 3 months.[2] This may be attributed to impaired humoral immune responses, consistent with previous findings from China showing that patients with lymphoma have impaired humoral immune responses to SARS-CoV-2 infection and that anti-CD20 monoclonal antibody treatment is an independent risk factor for these patients.[19] Clinical management of lymphoma has been challenging since the COVID-19 pandemic,[20] but Omicron variants, which emerged in South Africa in November 2021, are less aggressive than other variants in previous epidemics and are less likely to cause severe and critical cases.[21]

Therefore, the clinical management of COVID-19 in patients with B-NHL necessitates tailored treatment decisions, such as determining the timing and dosing of antitumor therapy or deciding whether to suspend or delay it. Currently, there is a global shortage of real-world research data on this topic. This study aimed to address these gaps and offer insights for clinical diagnosis and treatment.

Materials and Methods

Study Design and Inclusion Criteria

We collected and analyzed data from patients with B-NHL diagnosed with COVID-19 who were hospitalized at Shulan (Hangzhou) Hospital (Hangzhou, China) and the First Affiliated Hospital of Zhejiang University School of Medicine (Zhejiang, China) between December 7, 2022, and March 7, 2023. The inclusion criteria were: (1) diagnosis of COVID-19 following the Guidelines for Prevention and Control of Coronavirus Disease 2019 (10th Edition);[22] (2) age ≥18 years; and (3) diagnosis of B-NHL based on the Classification of Hematopoietic and Lymphoid Tissue Tumors (5th Edition). The exclusion criteria were: (1) respiratory infections or pneumonia caused by other known pathogens (eg, respiratory viruses); (2) respiratory inflammation caused by non-infectious causes (eg, vasculitis, dermatomyositis, organizing pneumonia); (3) severe immunodeficiency such as human immunodeficiency virus infection; and (4) incomplete patient information. This study adhered to the principles of the Declaration of Helsinki and was reviewed and approved by the ethics committee of Shulan (Hangzhou) Hospital. Written informed consent was waived for this retrospective study, and strict measures were taken to protect the privacy of the patients involved.

Data Collection

Clinical data were retrieved from the electronic medical records system, encompassing demographic information (age, sex, height, weight), B-NHL disease status, history of anti-CD20 monoclonal antibody immunotherapy (dates of first and last doses, cumulative dose), comorbid conditions such as hypertension and diabetes, tobacco use history, and COVID-19-specific data. COVID-19-specific data included results from nasal/pharyngeal swabs for COVID-19 antigen or PCR tests, laboratory findings (lymphocyte count, platelet count, troponin, procalcitonin), lung computed tomography (CT) scans, antiviral treatments, and outcomes, such as duration of the positive-to-negative transition of COVID-19 nucleic acid test results, hospitalization duration, and 28-day survival status.

Definitions

COVID-19 Clinical Classifications

The diagnosis and clinical categorization of COVID-19 were conducted in accordance with the Guidelines for Prevention and Control of Coronavirus Disease 2019 (10th Edition). The diagnostic criteria for COVID-19 in this study were related clinical manifestations of COVID-19 infection and positive nucleic acid or antigen tests. COVID-19 cases were classified by severity into mild, moderate, severe, and critical, as follows. (1) Mild: manifestations of upper respiratory tract infection, such as dry throat, sore throat, cough, and fever. (2) Moderate: persistent high fever for more than 3 days and/or cough, shortness of breath, etc, with a respiratory rate (RR) < 30 breaths/min, oxygen saturation at rest > 93%, and imaging showing characteristic neoplasia with pneumonia. (3) Severe: patients meeting any of the following criteria with COVID-19, including shortness of breath, RR ≥ 30 breaths/min, oxygen saturation at rest ≤ 93%, arterial partial oxygen pressure (PaO2)/oxygen absorption concentration (FiO2) ≤ 300 mmHg (corrected for high altitude as: $PaO_2/FiO_2 \times$[760/atmospheric pressure (mmHg)]). (4) Critical: progressive exacerbation of clinical symptoms with lung imaging showing lesion progression > 50% within 24–48 hours.

Duration of Positive-to-Negative Transition of COVID-19 Nucleic Acid Test Results

The duration from the first positive COVID-19 nucleic acid test result to the second of two consecutive negative test results was defined as the positive-to-negative transition duration. According to a concurrent study of COVID-19 in China,[23] the average positive-to-negative transition durations for two patient groups discharged from the hospital using different CT value criteria were 14.5 ± 4.6 days and 11.8 ± 4.0 days. Accordingly, using a 14-day threshold for the positive-to-negative transition, this study defined durations ≥14 days as prolonged.

Duration of Hospitalization

The median hospitalization duration in general wards of Chinese hospitals is 14 days (interquartile range [IQR], 10–19 days); in other countries, it is 3 days (IQR, 3–9 days). For intensive care units (ICUs), the median hospitalization duration in China is 8 days (IQR, 5–13 days), compared to 7 days (IQR, 4–11 days) in other countries. Consequently, this study adopted a 15-day threshold for hospitalization durations, with those ≥15 days defined as prolonged.

Statistical Analysis

Statistical analysis was conducted using SPSS 26.0 software (IBM Corp., Armonk, NY, USA). Data not following a normal distribution are expressed as the median and IQR. Differences between the two groups were assessed using the Wilcoxon signed-rank test. Count data are presented as numbers of cases and percentages, with comparisons between groups made using either the chi-squared test or Fisher's exact test. The chi-squared test was also employed to evaluate differences between groups of categorical and ordinal data. Factors influencing outcomes were analyzed using both univariate and multivariate logistic regression. Receiver operating characteristic (ROC) curves were used as diagnostic evaluation metrics. For statistical testing, a two-tailed approach was adopted, and results with $P < 0.05$ were considered statistically significant.

Results

Study Design and Flow Chart

We initially collected data from 122 patients with B-NHL and COVID-19. After excluding 42 cases due to incomplete data or the presence of other pulmonary infections, 80 patients were included. Figure 1 shows a flowchart of the patient selection process.

Clinical Features of Patients with COVID-19 and B-NHL

The mean age of the 80 included patients with COVID-19 and B-NHL was 60.4 ± 13 years, with men constituting 50% of the patients. The mean body mass index (BMI) was 22.7 ± 2.9 kg/m²; 13.8% (11/80) of the patients experienced relapsed or refractory lymphomas, and 65% (52/80) were diagnosed with diffuse large B-cell lymphoma (DLBCL). The median duration of the positive-to-negative transition of nucleic acid test results was 14 days (IQR, 17.2 days), with

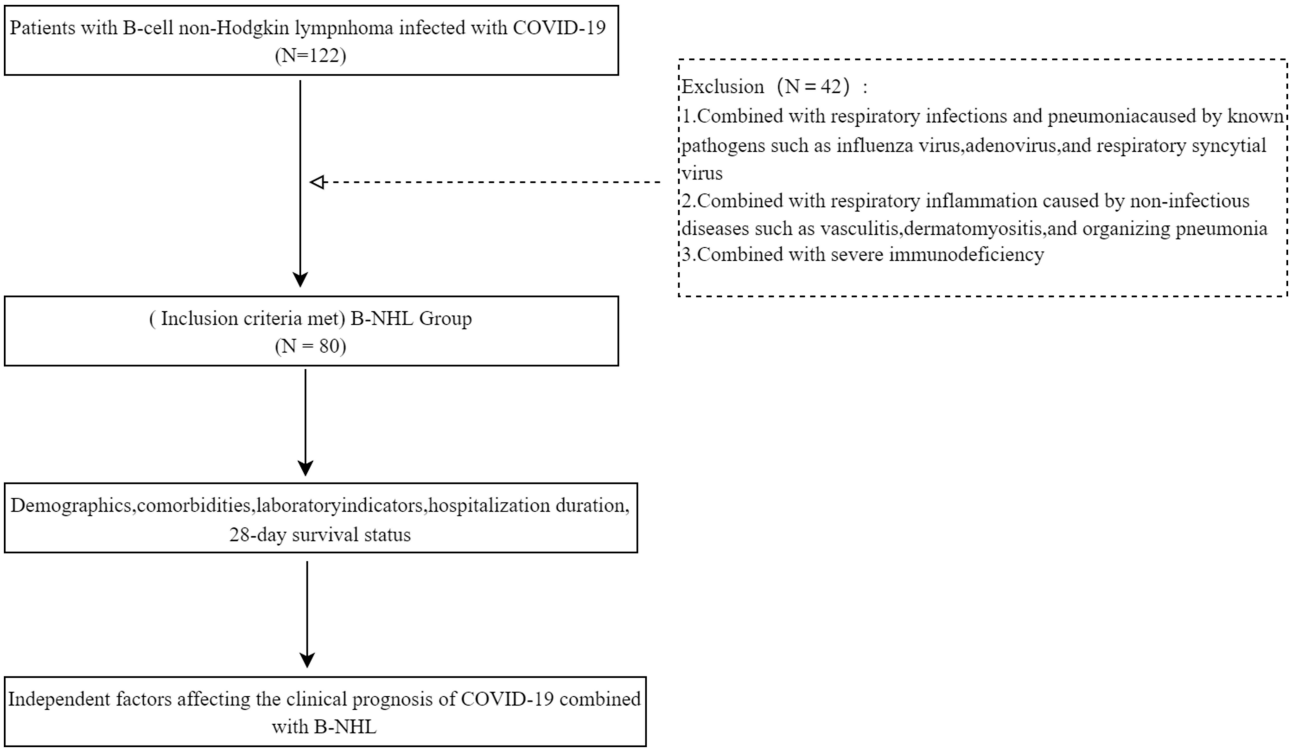

Figure 1 Patient selection flow chart. B-NHL, B-cell non-Hodgkin lymphoma; COVID-19, coronavirus disease 2019.

a median hospitalization duration of 12 days (IQR, 13 days). The rate of severe disease was 26.25% (21/80), and the 28-day mortality rate was 10.00% (8/80). When categorizing the patients into groups based on the clinical classification of COVID-19, the negative conversion time of the severe group was significantly prolonged (P = 0.015), and the 28-day fatality rate was significantly increased (P < 0.001). No statistically significant difference was observed in the hospitalization duration between the groups (Table 1).

Factors Influencing Prolonged Positive-to-Negative Transition

Variables potentially influencing the duration of the positive-to-negative transition of nucleic acid test results and prognosis were scored as follows: 0 for age <70 years and 1 for age ≥70 years; 0 for female and 1 for male; 0 for the

Table 1 Clinical Features of Patients with COVID-19 and B-NHL

Variables	Total (n = 80)	Mild + Moderate (n = 59)	Heavy + Critical (n = 21)	p
Age, mean ± SD	60.4 ± 13.0	60.0 ± 14.2	61.3 ± 9.1	0.707
Sex, n (%)				0.799
Female	40 (50.0)	30 (50.8)	10 (47.6)	
Male	40 (50.0)	29 (49.2)	11 (52.4)	
BMI, mean ± SD	22.7 ± 2.9	22.8 ± 2.7	22.3 ± 3.6	0.508
Pathologic type of B-NHL, n (%)				0.08
Diffuse large B-cell lymphoma	52 (65.0)	39 (66.1)	13 (61.9)	
Follicular cell lymphoma	13 (16.2)	12 (20.3)	1 (4.8)	
Other B-NHL	15 (18.8)	8 (13.6)	7 (33.3)	
PD, n (%)				0.467
No	69 (86.2)	52 (88.1)	17 (81)	
Yes	11 (13.8)	7 (11.9)	4 (19)	

(*Continued*)

Table 1 (Continued).

Variables	Total (n = 80)	Mild + Moderate (n = 59)	Heavy + Critical (n = 21)	p
Smoking history, n (%)				1
No	72 (91.1)	53 (91.4)	19 (90.5)	
Yes	7 (8.9)	5 (8.6)	2 (9.5)	
Combined with diabetes, n (%)				0.341
No	64 (80.0)	49 (83.1)	15 (71.4)	
Yes	16 (20.0)	10 (16.9)	6 (28.6)	
Combined with hypertension, n (%)				0.768
No	62 (77.5)	45 (76.3)	17 (81)	
Yes	18 (22.5)	14 (23.7)	4 (19)	
28-day survival status, n (%)				< 0.001
Survive	72 (90.0)	58 (98.3)	14 (66.7)	
Death	8 (10.0)	1 (1.7)	7 (33.3)	
Antiviral therapy, n (%)				0.081
No	23 (29.1)	20 (34.5)	3 (14.3)	
Yes	56 (70.9)	38 (65.5)	18 (85.7)	
LOS, median (IQR)	12.0 (13.0)	11.0 (12.5)	17.0 (15.0)	0.262
NCT, median (IQR)	14.0 (17.2)	12.0 (16.0)	24.0 (25.0)	0.015

Abbreviations: COVID-19, coronavirus disease; BMI, body mass index; B-NHL, B-cell non-Hodgkin lymphoma; IQR, interquartile range; LOS, length of stay; NCT, negative conversion time; PD, Parkinson's disease; SD, standard deviation.

absence of comorbidities and 1 for the presence; 1 when the last dose of anti-CD20 monoclonal antibodies was administered within 3 months of COVID-19 onset and 0 for doses administered more than 3 months before onset; 0 for cumulative doses of anti-CD20 monoclonal antibodies ≤1000 mg, 1 for >1000 mg and ≤2000 mg, 2 for >2000 mg and ≤ 3000 mg, 3 for >3000 mg and ≤8000 mg, and 4 for >8000 mg; 0 for clinical symptoms classified as mild or moderate and 1 for severe or critical; 0 for a positive-to-negative transition duration of nucleic acid test results ≤14 days, and 1 for >14 days. Laboratory indices were scored based on normative ranges, with 1 indicating elevated troponin and procalcitonin levels or decreased lymphocyte and platelet counts. Univariate and multivariate logistic regression identified three independent factors associated with a prolonged positive-to-negative transition: pathological type of B-NHL (odds ratio [OR], 6.43; 95% confidence interval [CI], 1.37–30.04; P = 0.018), infection with COVID-19 within 3 months after the last anti-CD20 monoclonal antibody dose (OR, 6.35; 95% CI, 2.04–19.76; *P*=0.001), and treatment with glucocorticoids (OR, 4.54; 95% CI, 1.19–17.30; P = 0.027; Table 2).

Table 2 Factors Influencing the Positive-to-Negative Transition of Nucleic Acid Test Results

Variables	Univariate		Multivariate	
	P	OR (95% CI)	*P*	OR (95% CI)
Age ≥ 70 years	0.897	1.07 (0.39–2.96)		
Male sex	0.502	1.35 (0.56–3.27)		
BMI ≥ 24 kg/m^2	0.500	0.72 (0.27–1.89)		
Pathologic classification of B-NHLs, n (%)				
Diffuse large B-cell lymphoma		1.00 (Reference)		1.00 (Reference)
Follicular cell lymphoma	0.901	0.93 (0.27–3.13)	0.647	0.74 (0.20–2.72)
Other B-NHL[a]	0.037	4.32 (1.09–17.12)	0.018	6.43 (1.37–30.04)
Lymphoma progress	0.955	1.04 (0.29–3.72)		

(*Continued*)

Table 2 (Continued).

Variables	Univariate		Multivariate	
	P	OR (95% CI)	*P*	OR (95% CI)
Cumulative dose of anti-CD20 monoclonal antibodies, n (%)				
≤1000 mg		1.00 (Reference)		
1000–2000 mg	0.306	2.33 (0.46–11.81)		
2000–3000 mg	0.814	0.78 (0.10–6.32)		
3000–8000 mg	0.422	1.68 (0.47–5.93)		
>8000 mg	0.629	0.67 (0.13–3.45)		
Time from the last dose of anti-CD20 monoclonal antibodies[b], n (%)				
>3 months		1.00 (Reference)		1.00 (Reference)
≤3 months	0.003	4.62 (1.69–12.59)	0.001	6.35 (2.04–19.76)
Treated with glucocorticoids	0.052	3.00 (0.99–9.08)	0.027	4.54 (1.19–17.30)
Combined with diabetes	0.823	1.13 (0.38–3.42)		
Combined with hypertension	0.371	0.62 (0.21–1.78)		
Smoking history	0.322	2.36 (0.43–12.99)		
Decreased lymphocyte count	0.757	1.20 (0.38–3.81)		
Decreased platelet count	0.084	2.26 (0.90–5.69)		

Notes: [a]Other B-NHL:B-NHL other than diffuse large B-cell lymphoma and follicular cell lymphoma such as chronic lymphocytic leukemia, lymphoplasmic cell lymphoma, marginal zone lymphoma, mantle cell lymphoma, et al; [b]time between the last dose of anti-CD20 monoclonal antibodies and the diagnosis of COVID-19.
Abbreviations: BMI, body mass index; B-NHL, B-cell non-Hodgkin lymphoma; CI, confidence interval; OR, odds ratio; S.E., standard error.

ROC Curve Analysis of Prognostic Factors in Patients with COVID-19 and B-NHL

In the ROC curve analysis, the joint diagnostic performance of the three independent risk factors was evaluated as good, with an area under the curve of 0.750 and a 95% CI of 0.644–0.856. The optimal threshold was determined to be 0.374, yielding a specificity of 54.1% and a sensitivity of 90.7% (Figure 2).

Discussion

By late 2021, the Omicron SARS-CoV-2 variant had emerged as the fifth variant of concern globally, characterized by high transmissibility and reduced pathogenicity; most cases were either asymptomatic or presented with mild symptoms. Cellular and humoral immune responses collectively mitigate the viral harm to the body.[24]

The clinical data analyzed in this study were collected during a brief pandemic surge following China's complete relaxation of COVID-19 infection control measures. The mean patient age was 60.4 ± 13.0 years, with a severe disease rate of 26.25% (21/80) and a 28-day mortality rate of 10.00%. The severe disease rate was considerably lower than that in the early stages of the pandemic, which can be primarily attributed to infections predominantly caused by the Omicron strain. Studies from the United Kingdom[25] and Chile[26] suggest that the Omicron variant typically results in milder patient conditions, with significantly reduced virulence and pathogenicity. Furthermore, the 28-day mortality rate observed in this study was significantly lower than the 61.5% reported by Yang et al[27] at the onset of the COVID-19 outbreak in 2020. This change is not solely due to the diminished pathogenicity of the Omicron strain but also the nationwide protective effects of COVID-19 vaccination measures.[28] This study identified older people as the predominantly affected group, which is consistent with previous research[29,30] demonstrating a positive correlation between age and infection rates.

B cells play a crucial role in the immune response, participating in humoral immunity and engaging in the immune response to antigens through various mechanisms such as producing immunoglobulins, acting as antigen-presenting cells, or indirectly regulating antigen-presenting cells to produce autoantibodies and secrete cytokines. Over 95% of B-cell lymphomas express the CD20 protein, and anti-CD20 monoclonal antibodies, as targeted immunotherapy agents, eliminate B cells through three mechanisms, resulting in B-cell dysfunction and decreased humoral immunity. Beyond destroying lymphoma cells, anti-CD20 monoclonal antibody therapies can inhibit the growth of normal B cells, reduce

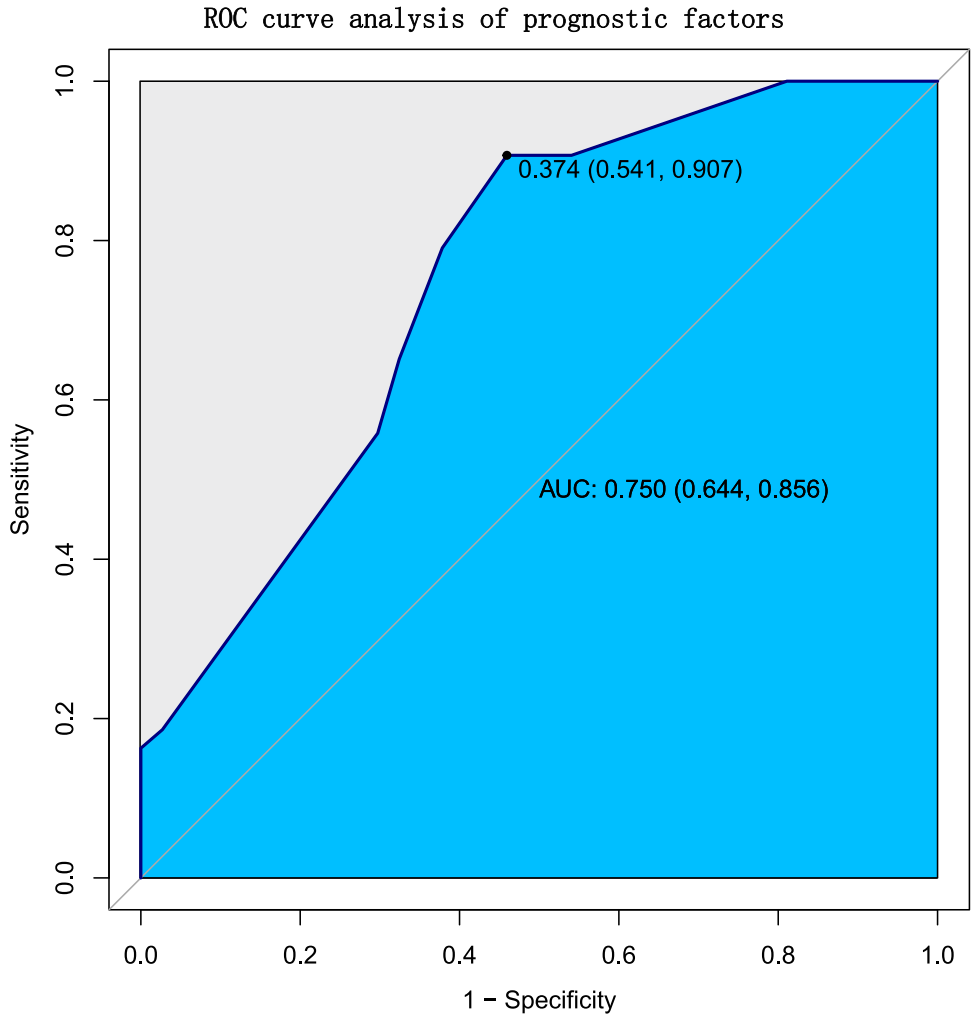

Figure 2 ROC curve for predicting the duration of positive-to-negative transition of nucleic acid test results using three independent risk factors. ROC, receiver operating characteristic; AUC, area under the curve.

lymphocyte counts, and impair humoral immune responses, thereby weakening resistance to COVID-19 and leading to a prolonged positive-to-negative transition in nucleic acid test results. The most significant impact on this transition occurs within 3 months after the last dose of anti-CD20 monoclonal antibodies, making COVID-19 infection during this period an independent factor for a prolonged transition. This finding contrasts with those from an earlier China-based study that identified age over 60 years, BMI over 24 kg/m^2, and comorbid hypertension as three independent risk factors for a prolonged positive-to-negative transition of nucleic acid test results, likely due to differences in study populations (ie, this study focused on patients with lymphoma; previous research targeted the general Chinese population). Additionally, this study showed that COVID-19 infection following anti-CD20 monoclonal antibody treatment not only prolonged the positive-to-negative transition but also increased the rate of severe disease. This aligns with findings from a study[4] showing that 156 patients with chronic lymphocytic leukemia experienced more severe COVID-19 outcomes. The present study observed a median hospitalization duration of 14 days in patients with COVID-19 and lymphoma and an increased 28-day mortality rate in patients with a prolonged positive-to-negative transition, consistent with the findings of a US-based study.[31]

Nakajima et al[32] showed that dysregulation or overactivation of the immune response is a primary cause of COVID-19 pathology. Tepasse et al[33] reported cases where SARS-CoV-2 RNA was detected in the blood of two patients who experienced cytokine storms that led to death, indicating that a dysregulated or excessive immune response can worsen the disease. Glucocorticoids can mitigate immune inflammation; however, the timing and dosage of their administration

must be carefully managed to avoid prolonging the duration of the positive-to-negative transition of nucleic acid test results.

In the present study, DLBCL represented 65% of cases, while FL comprised 16.2%. Univariate logistic regression revealed no significant effect of the pathological types of lymphoma on the duration of the positive-to-negative transition of nucleic acid test results. However, multivariate logistic regression revealed that pathological types of lymphoma other than DLBCL and FL, were positively correlated with the duration of the positive-to-negative transition. This may be attributed to rituximab, a targeted therapy agent that has been proven effective in numerous clinical studies for treating DLBCL and FL. Conversely, treatment of other B-cell lymphomas with anti-CD20 monoclonal antibodies has shown lower effectiveness and prolonged the positive-to-negative transitions of nucleic acid test results, possibly due to disease progression and reduced antiviral immunity.

According to some review articles, the median duration of the positive-to-negative transition of nucleic acid test results in patients with mild-to-moderate COVID-19 is approximately 18.4 days. In the present study, we found a 14-day median duration of the positive-to-negative transition, which is markedly shorter than that previously reported. Karataş et al noted significant variability and inconsistency in the duration of the positive-to-negative transition in a study on hematopoietic stem cell transplant recipients.

This study had certain limitations. It was a retrospective study primarily using cross-sectional surveys, and the data were not comprehensive; detailed daily monitoring data for SARS-CoV-2 RNA were lacking. Due to the insufficient development of new drugs at the onset of the pandemic, variations exist in antiviral treatments for COVID-19. The population of patients with B-NHL exhibiting mild symptoms who were not hospitalized was not included in the analysis of factors influencing the duration of the positive-to-negative transition of nucleic acid test results. Furthermore, the effect of previous lymphoma treatment on the duration of the positive-to-negative transition was not considered, which may have introduced bias into the findings. Despite these limitations, the study offers some clinical reference value.

Conclusion

This study examined the clinical features of COVID-19 in patients with B-NHL in China during the COVID-19 pandemic. The findings revealed that patients with B-NHL diagnosed with COVID-19 within 3 months of anti-CD20 monoclonal antibody treatment experienced prolonged positive-to-negative transitions of nucleic acid test results along with increased rates of severe disease and 28-day mortality. Furthermore, treatment with glucocorticoids prolonged the positive-to-negative transition. Using this information, it may be possible to achieve a balance between risk and benefit for patients with lymphoid malignancies, one of the most vulnerable populations for SARS-CoV-2 infection. When there is no indication for urgent lymphoma treatment, the clinical process is slow, and COVID-19 can be given priority during the observation and waiting period. For patients with urgent treatment indications for lymphoma, treatment should be planned with full consideration of treatment efficacy and treatment-related immunosuppressive side effects.

Abbreviations

BMI, body mass index; B-NHL, B-cell non-Hodgkin lymphoma; COVID-19, coronavirus disease; CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; IQR, Interquartile range; OR, odds ratio; PCR, polymerase chain reaction; ROC, receiver operating characteristic; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Data Sharing Statement

All data included in this study are available upon request by contact with the corresponding author.

Ethics Approval and Informed Consent

This study adhered to the principles of the Declaration of Helsinki and was reviewed and approved by the ethics committee of Shulan (Hangzhou) Hospital. Written informed consent was waived for this retrospective study, and strict measures were taken to protect the privacy of the patients involved.

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Disclosure

The authors declare that they have no competing interests in this work.

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