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Journal:	*Leukemia and Lymphoma*
Manuscript ID	Draft
Manuscript Type:	Letter to the Editor
Date Submitted by the Author:	n/a
Complete List of Authors:	Kohn, Milena; Centre Hospitalier de Versailles, Hématologie-oncologie Alsuliman, Tamim Lamure, Sylvain Cheminant, Morgane Delage, Jeremy Tudesq, Jean-Jacques Merle De Boever, Corinne Marjanovic, zora; Hopital Saint-Antoine, hématologie et thérapie cellulaire Van de Wyngaert, Zoé ; Hopital Saint-Antoine, Department of Hematology and Cellular Therapy Malard, Florent Brissot, Eolia; Hopital Saint-Antoine, Service d'Hématologie Clinique et Thérapie Cellulaire; Sorbonne Universite Faculte de Medecine Rigaudeau, Sophie; Centre Hospitalier de Versailles, Hematology and Oncology Therby, Audrey Marque-Juillet, Stephanie Cartron, Guillaume; CHU Montpellier, Rousselot, Philippe; Centre Hospitalier de Versailles, ; Universite Versailles Saint-Quentin-en-Yvelines, UMR1173 Hermine, Olivier Duléry, Rémy; Hôpital Saint Antoine, APHP, Sorbonne Université, INSERM UMRs 938, Paris, France, Hématologie clinique et thérapie cellulaire Besson, Caroline; Centre Hospitalier de Versailles, Hématologie-oncologie
Keywords:	sars-cov2, lymphoma, omicron, cll

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Milena Kohn[a]*, Tamim Alsuliman[b]*, Sylvain Lamure[c]*, Morgane Cheminant[d], Jéremy Delage[e], Jean Jacques Tudesq[c], fi, Zora Marjanovic[b], Zoé Van de Wyngaert[b], Florent Malard[b], Eolia Brissot[b], Sophie Rigaudeau[a], Stéphanie Marque-Juillet[g], Audrey Therby[h], Guillaume Cartron[c], Philippe Rousselot[a], Olivier Hermine[d], Rémy Duléry[b]§, Caroline Besson[a,i]§

a. Service d'Hématologie, Centre Hospitalier de Versailles, Le Chesnay, France

b. Sorbonne Université, INSERM UMRs938, Service d'Hématologie Clinique et de Thérapie Cellulaire, Hôpital Saint Antoine, AP-HP, Paris, France

c. Department of Clinical Hematology, Montpellier University Hospital, IGMM UMR5535 CNRS, University of Montpellier, Montpellier, France

d. Service d'Hématologie, Hôpital Necker, Paris

e. Service d'Hématologie, Clinique du Parc, Castelneau-Le-Lez

f. Département des maladies infectieuses et tropicales, Montpellier University Hospital, Montpellier, Clinique du Parc, Castelneau-Le-Lez

g. Laboratoire de virologie, Centre Hospitalier de Versailles, Le Chesnay, France

h. Service de médecine interne, Centre Hospitalier de Versailles, Le Chesnay, France

i. Université Paris-Saclay, UVSQ, Inserm, Équipe "Exposome et Hérédité", CESP, Villejuif, France

** and §: Equivalent contribution*

Correspondance: Pr Caroline Besson, cbesson@ch-versailles.fr; 177, rue de Versailles - 78150 LE CHESNAY, France.

Word count: 1 200

Abstract word count 149

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Abstract

Patients with lymphoid malignancies are at high risk for severe COVID-19. Nevertheless, since December 2021, Omicron variant became dominant and was associated with lower severity in the general population.

We investigated the outcomes of SARS-CoV-2 infection during Omicron epidemic phase in patients with lymphoid malignancies in five French hospitals.

Overall, 63 patients with lymphoid malignancies were identified. Seventy-six percent of patients had received 3 or 4 doses of vaccine and 14% had received pre-exposition antibody prophylaxis. Most patients had no or mild symptoms but 21 (33%) were hospitalized, including 4 (6%) in an intensive care unit. All four patients with R/R disease were hospitalized. During a median follow-up of 28 days, four patients died, all aged above 70 years. R/R malignancy and older age were associated with an inferior 30-day overall survival.

In conclusion, our results show a low severity of Omicron variant among vaccinated patients with lymphoid malignancies.

Key words: COVID-19; Omicron variant; Lymphoma; Chronic Lymphocytic Leukemia

Introduction

Since the outbreak of SARS-CoV-2, patients with a history of cancer[1], especially those with hematological malignancies[2] were shown to be at high risk of severe COVID-19. Considering lymphoma patients, COVID-19 mortality was associated with older age, recent treatment with anti-CD20 monoclonal antibodies, and relapsed/refractory disease.[3] Furthermore, immunocompromised patients have an altered humoral response to COVID-19 vaccines, especially after treatment with anti-CD20 monoclonal antibodies,[4] even after a booster dose.[5] In this population with absence or weak vaccine response, neutralizing monoclonal antibody cocktails such as casirivimab/imdevimab and tixagevimab/cilgavimab[6,7] have been developed for COVID-19 pre- and/or post-exposure prophylaxis and/or for curative treatment.

The Omicron variant emerged in South Africa at the end of November 2021, and was described as partially resistant to vaccination induced neutralizing antibodies and to some monoclonal antibodies including casirivimab/imdevimab.[8] In contrast, it induces a lower rate of severe and critical COVID-19.[9] In the setting of a rapidly increasing epidemic wave of the Omicron variant, becoming predominant in France since December 20, 2021, we aimed to describe its impact on patients with lymphoma and chronic lymphocytic leukemia (CLL) in the real-life setting through a multicenter study.

Patients and methods

This retrospective multicenter study was conducted in five French hospitals. Adult patients with a past or current diagnosis of lymphoma/CLL and presenting with SARS-CoV-2 infection between December 20, 2021, and January 20, 2022, were identified from local registries and medical files in each hospital. Data were collected on demographics, SARS-CoV-2 infection and lymphoma/CLL characteristics, prophylactic and curative treatments and

outcomes (Supplementary methods 1). Refractory/relapsed lymphoma was defined as progressive disease after more than two lines of treatment or palliative care due to comorbidities. Patients with Delta variant infection were excluded from the study. Outcomes were censored on February 9, 2022. Patients who had been hospitalized due to COVID-19 (hospitalized patients) were compared to other patients according to their initial characteristics (Supplementary methods 2). The probability of overall survival (OS) was estimated using the Kaplan-Meier method. Statistical tests were two-tailed and P values < 0.05 were considered to denote statistical significance. Analyses were performed using SPSS 20 (IBM SPSS Statistics for Windows, Version 20.0. IBM Corp, Armonk, NY). This study was conducted in accordance with the Declaration of Helsinki and was approved by the local research ethics committee on February 21, 2022.

Results

Characteristics of the study population:

Out of the 68 patients with SARS-CoV-2 infection during the inclusion period, five had a confirmed Delta variant infection and were excluded from the present study. Among the 63 patients with Omicron variant infection (n=34) or undetermined variant (n=29), 27 patients (43%) were 70 years old or more and 38 (60%) were male (Table 1). Predominant malignancies were diffuse large B-cell lymphoma (13 patients, 21%), CLL (11 patients, 17%) and follicular lymphoma (10 patients, 16%). Of note, only six patients (10%) were treatment-naïve, and 35 patients (56%) had received an anti-CD20 monoclonal antibody in the year before SARS-CoV-2 infection. Regarding vaccination status, 76% of patients had received three or four injections, and only one patient was COVID-19 vaccine naïve. Remarkably, nine patients (14%) had received a pre-exposition antibody prophylaxis because of negative or

weak vaccinal response (casirivimab/imdevimab in eight patients, tixagevimab/cilgavimab in one).

Comparison of the hospitalized patients with the other patients (Table)

Overall, 42 patients did not require hospitalization and were either asymptomatic (n=9, 14%), or suffered from mild symptoms (n=33, 52%), except one patient who received ambulatory oxygenation supply. Twenty-one patients (33%) were hospitalized due to COVID-19, all required oxygenation supply, 14 were treated with corticosteroids (22%), four (6%) with curative monoclonal antibodies (tixagevimab/cilgavimab) and one (2%) with convalescent plasma. Four (6%) patients were transferred to an intensive care unit (ICU) (two of these were intubated). The median in-hospital stay was 14 days (range 1-35), and median ICU stay was 5 days (1-19). In contrast with other patients, all four patients with relapsed/refractory disease were hospitalized. No significant associations were found between hospitalization status and type of lymphoid malignancy, lymphoma treatment, vaccine dose number, pre-exposition monoclonal antibodies, anti-spike serology, lymphopenia and hypogammaglobulinemia, as shown in table 1.

COVID-19 related mortality

During a median follow-up of 28 days (5-44), four patients died, representing 6% of the total cohort, and 19% of the hospitalized patients. Their age ranged from 78 to 83 years, three had at least one comorbidity and two had a relapsed/refractory disease. Omicron was identified in three cases and variant determination was missing for one case. All four patients were treated in the year before COVID-19 infection with anti-CD20 antibodies and two with targeted therapy. One of these patients had received only two doses of COVID-19 vaccine. Two patients received anti-SARS-CoV-2 monoclonal curative antibodies

(tixagevimab/cilgavimab). Due to a palliative malignancy situation, none of them were transferred to an ICU. This is reflected by an inferior OS for patients with refractory disease (30-day OS: 50% vs 96%, respectively) or age ≥ 70 years (30-day OS: 82% vs 100%, respectively) when compared with others (Figure 1).

Discussion

We report the first cohort of patients with lymphoma or CLL with SARS-CoV-2 infection diagnosed during the Omicron epidemic wave. The percentage of hospitalized patients remains significant (33%), but the mortality rate has largely decreased to 6%. It was largely limited to patients with a relapsed/refractory disease and/or aged 70 years and older.

In the international EPICOVIDEHA survey run during 2020 when wild-type SARS-CoV-2 was dominant, 29 % of CLL patients and 56% of non-Hodgkin lymphoma patients had severe or critical infection and 28% and 30% died, respectively[2]. Other cohort studies from different countries reported comparable severity.[10] Our results show that the Omicron variant is associated with a lower severity. A refractory malignancy seems to remain heavily associated with both higher hospitalization and mortality rates, as reported previously for patients with wild type COVID-19.[3] This can be explained by the deep immunodepression[11] due to the malignancy and the former treatments and by do-not-resuscitate orders taken in a palliative context. In line with our previous studies,[3,12] the OS appeared lower in patients aged ≥ 70 years. Remarkably, none of the patients aged < 70 years died. Of note, comorbidities did not appear to be a risk factor for hospitalization or death in this study while most previous studies have shown a negative impact of cardiovascular or respiratory diseases on outcome.[3,12,13] This may be explained by differences in vaccination coverage as well as by the intrinsic characteristics of the Omicron variant.[14] Although almost all the population was vaccinated, 21 patients were hospitalized and four

died which is consistent with the frequent lack of seroconversion described in this population. Beyond vaccination, two out of nine patients were hospitalized despite pre-exposition prophylaxis, which may be explained by the lack of activity of casirivimab/imdevimab on the Omicron variant.

A limitation of this study is that, due to the national policy on SARS-CoV-2 sequencing, variant type was not documented in some patients, mainly those with asymptomatic or mild COVID-19. The comparison of patients with documented Omicron variant with those with no documentation showed similar characteristics and OS (Supplementary figure 2). Although management of patients with lymphoid malignancies during the COVID-19 pandemic is still a challenge,[15] these results show that the Omicron variant is less aggressive than previously reported with other variants.

Acknowledgement: We thank Pr Mohamad Mohty for his careful review of the manuscript.

Bibliography :

[1] Han S, Zhuang Q, Chiang J, et al. Impact of cancer diagnoses on the outcomes of patients with COVID-19: a systematic review and meta-analysis. BMJ Open. 2022;12:e044661.

[2] Pagano L, Salmanton-García J, Marchesi F, et al. COVID-19 infection in adult patients with hematological malignancies: a European Hematology Association Survey (EPICOVIDEHA). J Hematol Oncol. 2021;14:168.

[3] Duléry R, Lamure S, Delord M, et al. Prolonged in-hospital stay and higher mortality after Covid-19 among patients with non-Hodgkin lymphoma treated with B-cell depleting immunotherapy. Am J Hematol. 2021;96:934–944.

[4] Fendler A, Shepherd STC, Au L, et al. Adaptive immunity and neutralizing antibodies against SARS-CoV-2 variants of concern following vaccination in patients with cancer: the CAPTURE study. Nature Cancer. 2021;2:1305–1320.

[5] Kohn M, Delord M, Chbat M, et al. A third anti-SARS-Cov2 mRNA dose does not overcome the pejorative impact of anti-CD20 therapy and/or low immunoglobulin levels in patients with lymphoma or chronic lymphocytic leukemia. Haematologica. 2021;

[6] O'Brien MP, Forleo-Neto E, Musser BJ, et al. Subcutaneous REGEN-COV Antibody Combination to Prevent Covid-19. New England Journal of Medicine. 2021;385:1184–1195.

[7] Loo Y-M, McTamney PM, Arends RH, et al. The SARS-CoV-2 monoclonal antibody combination, AZD7442, is protective in non-human primates and has an extended half-life in humans. Science Translational Medicine. 0:eabl8124.

[8] Dejnirattisai W, Huo J, Zhou D, et al. SARS-CoV-2 Omicron-B.1.1.529 leads to widespread escape from neutralizing antibody responses. Cell. 2022;185:467-484.e15.

[9] Wolter N, Jassat W, Walaza S, et al. Early assessment of the clinical severity of the SARS-CoV-2 omicron variant in South Africa: a data linkage study. The Lancet. 2022;399:437–446.

[10] Borah P, Mirgh S, Sharma SK, et al. Effect of age, comorbidity and remission status on outcome of COVID-19 in patients with hematological malignancies. Blood Cells Mol Dis. 2021;87:102525.

[11] Passamonti F, Romano A, Salvini M, et al. COVID-19 elicits an impaired antibody response against SARS-CoV-2 in patients with haematological malignancies. Br J Haematol. 2021;195:371–377.

[12] Lamure S, Duléry R, Di Blasi R, et al. Determinants of outcome in Covid-19 hospitalized patients with lymphoma: A retrospective multicentric cohort study. EClinicalMedicine. 2020;27:100549.

[13] Visco C, Marcheselli L, Mina R, et al. A prognostic model for patients with lymphoma and COVID-19: a multicentre cohort study. Blood Advances. 2022;6:327–338.

[14] Lewnard JA, Hong VX, Patel MM, et al. Clinical outcomes among patients infected with Omicron (B.1.1.529) SARS-CoV-2 variant in southern California [Internet]. Epidemiology; 2022 [cited 2022 Feb 17]. Available from: http://medrxiv.org/lookup/doi/10.1101/2022.01.11.22269045.

[15] de la Cruz-Benito B, Lázaro-Del Campo P, Ramírez-López A, et al. Managing the front-line treatment for diffuse large B cell lymphoma and high-grade B cell lymphoma during the COVID-19 outbreak. Br J Haematol. 2020;191:386–389.

Table 1. Baseline characteristics of patients with lymphoid malignancies and SARS-Cov-2 infection

	All population n=63	Hospitalized n=21	Others n=42	p-value
Demographic characteristics				
Median age (range)	66 (21-97)	65.5 (21-97)	64.5 (21-87)	
Age ≥ 70 years, n (%)	27 (43)	10 (48)	17 (41)	0.60
Male gender, n (%)	38 (60)	11 (52)	27 (64%)	0.42
Comorbidities[¥], n (%)				
Comorbidity ≥1	25 (40)	8 (38)	17 (41)	0.86
Obesity	10 (16)	4 (19)	6 (14)	
Hypertension	21 (33)	5 (24)	16 (38)	
Diabetes	3 (5)	1 (5)	2 (5)	
Chronic lung disease	4 (6)	1 (5)	3 (7)	
Lymphoma characteristics				
Malignancy, n (%)				0.52[&]
Hodgkin lymphoma	9 (14)	2 (10)	7 (17)	
DLBCL	13 (21)	6 (29)	7 (17)	
Follicular lymphoma	10 (16)	4 (19)	6 (14)	
Other lymphomas°	20 (31)	7 (32)	13 (31)	
CLL	11 (18)	2 (10)	9 (21)	
Lymphoma/CLL treatments, n (%)				
Any therapy#	46 (73)	14 (67)	32 (76)	0.42
Anti-CD20 Mab#	35 (56)	13 (62)	22 (52)	0.47
Targeted therapy#*	8 (13)	2 (10)	6 (14)	
Autologous HCT	5 (8)	1 (5)	4 (10)	
Allogeneic HCT	1 (2)	0 (0)	1 (2)	
CAR T-cell therapy	1 (2)	0 (0)	1 (2)	
Lymphoma/CLL status at infection, n (%)				
At diagnosis/Watch and wait	6 (10)	4 (19)	2 (5)	
Remission (complete or partial)	44 (70)	10 (48)	34 (81)	<0.01
Ongoing therapy < 3 lines	9 (14)	3 (14)	6 (14)	
Relapsed/refractory[ϕ]	4 (6)	4 (19)	0 (0)	
Immunological characteristics				
SARS-CoV-2 Vaccine				0.32°°
0 dose	1 (2)	1 (5)	0 (0)	
1 dose	1 (2)	0 (0)	1 (2)	
2 doses	11 (17)	5 (24)	6 (14)	
3 or more doses	48 (76)	15 (71)	33 (79)	
Missing	2 (3)	0 (0)	2 (5)	
Negative/low SARS-CoV-2 serology**, n (%)	28 (44)	11 (52)	17 (41)	0.37
Missing	28 (44)	7 (33)	21 (50)	
Past COVID-19 history	8 (13)	4 (19)	4 (10)	
Pre-exposition anti-SARS-CoV-2 Mab[£]	9 (14)	2 (10)	7 (17)	
Curative anti-SARS-CoV-2 antibodies***	7 (11)	5 (24)	2 (5)	
SARS-CoV-2 variant				
Omicron	34 (54)	16 (76)	18 (43)	0.02[µ]
Missing	29 (46)	5 (24)	24 (57)	

Abbreviations CLL: chronic lymphocytic leukemia, HCT, hematopoietic cell transplantation, CAR: chimeric antigen receptor, Mab: monoclonal antibodies.

[¥] Hypertension, diabetes, pulmonary disease and/or obesity

° 7 marginal zone lymphoma, 7 mantle cell lymphoma, 4 T-cell lymphoma, 1 Burkitt lymphoma and 1 hairy cell leukemia

[&]: Comparison of Hodgkin lymphoma, NHL or CLL

Treatment administered within the last 12 months before hospitalization for COVID-19.

* Bruton's tyrosine kinase inhibitor or B-cell lymphoma 2 (BCL2) inhibitor

[ϕ] Relapsed/refractory disease was defined as progressive disease after more than two lines of treatment or progressive disease in palliative care due to comorbidities, regardless of the number of lines of treatment.

°°: 0-2 doses compared to 3 or more doses

** Binding antibody units < 260 IU/mL

[£]: 8 patients received casirivimab/imdevimab and 1 tixagevimab/cilgavimab

*** 6 patients received SARS-CoV-2 monoclonal antibodies and 1 COVID-19 convalescent plasma therapy
µ: according to the national policy on SARS-CoV-2 sequencing, variant type was not documented in some patients, mainly those with asymptomatic or mild infection.

Figure 1. Overall survival of patients with lymphoid malignancies and SARS-Cov-2 infection: (A) all patients, (B) according to malignancy status, (C) according to age.

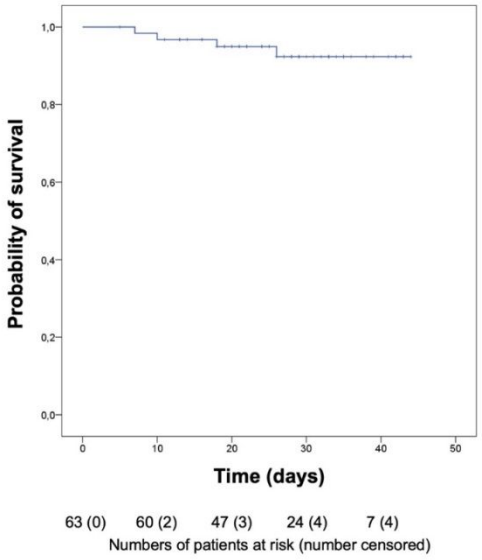
(A) 30-day OS, 92% (95% CI, 85-100%).

(B) 30-day OS of 59 patients with non-refractory/relapsed lymphoma, 96% (95% CI, 89-100%); and of 4 patients with relapsed/refractory lymphoma, 50% (95% CI, 10-99%).

(C) 30-day OS of 36 patients aged < 70 years, 100% (95% CI, 100-100%); and of 27 patients aged ≥ 70 years, 82% (95% CI, 65-98%).

Median follow-up from SARS-Cov-2 infection, 28 days (range, 5-44). CI: confidence interval, OS: overall survival.

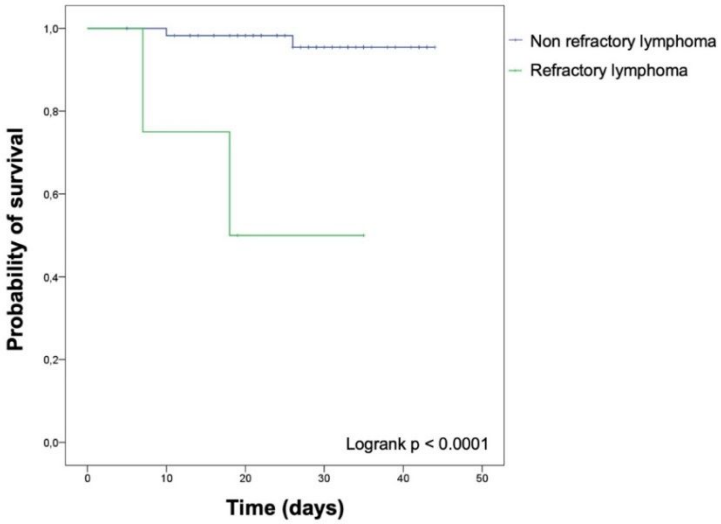
A



63 (0) 60 (2) 47 (3) 24 (4) 7 (4)

Numbers of patients at risk (number censored)

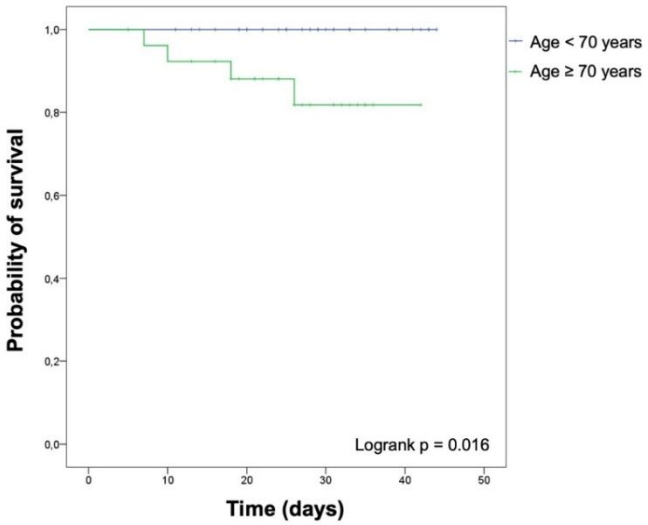
B



59 (0) 57 (1) 46 (1) 23 (2) 7 (2)
4 (0) 3 (1) 1 (2) 1 (2) 0 (2)

Numbers of patients at risk (number censored)

C



36 (0) 36 (0) 28 (0) 14 (0) 6 (0)
27 (0) 24 (2) 19 (3) 10 (4) 1 (4)

Numbers of patients at risk (number censored)

Supplementary methods 1:

Each local investigator collected the cases with SARS-CoV-2 infection confirmed by positive polymerase chain reaction (PCR) or antigenic test results for SARS-CoV-2. The following data were extracted from the medical charts by the local investigator for each patient: age, sex, body mass index (BMI), comorbidities (obesity defined as body mass index ≥ 30kg/m2, hypertension, diabetes and chronic lung disease prior to COVID-19), the recorded symptoms and inpatient laboratory test results at admission when appropriate; the most relevant chest computed tomography (CT) scan interpretation, specific medications given to prevent and/or treat COVID-19, including antiviral or immunomodulatory drugs and monoclonal antibodies, oxygenation supply modality including ventilator use, and hospital discharge modality when appropriate. The data obtained concerning lymphoma history included the date of diagnosis, pathological classification according to the WHO classification for lymphoid neoplasms, number of treatment lines, past autologous or allogeneic stem cell transplant, chimeric antigen receptor (CAR) T-cell therapy, anti-CD20 monoclonal antibody use (date of first and last administration), and lymphoma status at admission for COVID-19 (complete or partial remission, diagnosed at admission, under first or second line treatment, in watch and wait follow-up, or refractory/relapsed). Data concerning SARS-CoV-2 variant identification and anti-spike serology were also collected.

Supplementary methods 2:

Continuous variables are given as their median and range and categorical variables as their frequency and percentage. Chi-square tests were used to identify covariates associated with hospitalization. Covariates considered in this analysis were age (≥ 70 years versus below), gender, presence of comorbidities and main lymphoma subtypes (Hodgkin lymphoma, non-Hodgkin lymphoma (NHL) or CLL), recent administration of any therapy or anti-CD20 monoclonal antibody (within one year), lymphoma status (remission versus others), number of vaccine doses (0-2 versus ≥3), anti-S IgG serological status (< or ≥ 260 BAU/mL) and SARS-CoV-2 variant. Follow-up was measured from diagnosis SARS-CoV-2 infection to the last follow-up or date of death. Overall survival (OS) was measured from diagnosis to last follow-up or death. The probability of death was estimated using the Kaplan-Meier method and differences according to covariates were compared using the log-rank test.

Supplementary figure S1: Overall survival according to Omicron or undocumented variant

30-day OS of 34 patients infected with Omicron variant, 91% (95% CI, 80-100%); and of 29 patients infected with an undocumented variant, 95% (95% CI, 86-100%).

Median follow-up from COVID-19 diagnosis, 28 days (range, 5-44). CI: confidence interval, OS: overall survival.