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Research Paper

Determinants of outcome in Covid-19 hospitalized patients with lymphoma: A retrospective multicentric cohort study

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ABSTRACT

Background: Patients with lymphoma are immunocompromised because of the disease *per se* and its treatments. We aimed to describe the characteristics of patients with lymphoma hospitalized for Coronavirus Disease 2019 (Covid-19) and to analyze pre-Covid-19 determinants of mortality.

Methods: This retrospective multicentric cohort study used the *Programme de Médicalisation des Systèmes d'Information* database to identify all adult patients with lymphoma, hospitalized for Covid-19 in March and April 2020, in 12 hospitals of three French regions with pandemic outbreaks. The characteristics of lymphoma and Covid-19 were collected from medical charts.

Findings: Eighty-nine patients were included. The median age was 67 years (range, 19–92), 66% were male and 72% had a comorbidity. Most patients had B-cell non-Hodgkin lymphoma (86%) and had received a lymphoma treatment within one year (70%). With a median follow-up of 33 days from admission, 30-day overall survival was 71%, (95% confidence interval, 62–81%). In multivariable analysis, having an age $\geq$ 70 years (hazard ratio 2·87, 1·20–6·85, p = 0·02) and relapsed/refractory lymphoma (hazard ratio 2·54, 1·14–5·66, p = 0·02) were associated with mortality. Recent bendamustine treatment (n = 9) was also pejorative (hazard ratio 3·20, 1·33–7·72, p = 0·01), but was strongly associated with relapsed/refractory lymphoma. Remarkably, 30-day overall survival for patients $<$ 70 years of age without relapsed/refractory lymphoma was 88% (78% - 99%).

Interpretation: Thirty-day mortality was associated with being older and relapsed/refractory lymphoma. Survival of patients younger than 70 years without relapsed/refractory lymphoma was comparable to that of the general population.

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Research in context

Evidence before this study

There is a lack of data describing in detail the natural history of patients with lymphoma who have Covid-19. As of June 26, 2020, literature concerning patients with cancer in general or hematological malignancies and Covid-19 is growing. Data describing cancer patients demonstrate a worse outcome for older patients, patents with progressive disease and patients with hematological malignancies within 5 years. However, no analyses were performed on the specific population of patients with lymphoma.

Added value of this study

We report a large series of consecutive patients with lymphoma and hospitalized for Covid-19, including 89 patients from French regions with an outbreak of the pandemic. The population is homogeneous, lymphoma sub-types are representative of the known epidemiology: most of them had B-cell non-Hodgkin lymphoma, and had been treated for lymphoma within 1 year. We found significant associations between 30-day mortality and increasing age and relapsed/refractory lymphoma. Remarkably, in absence of those factors, mortality was comparable to the French Covid-19 population. There was no significant impact of active lymphoma treatment within one year, except for bendamustine which was associated with mortality.

Implications of all the available evidence

We identified factors that are associated with increased 30-day mortality in patients with lymphoma hospitalized for Covid-19. In absence of those factors, mortality appears comparable to the general population, encouraging health-care providers to treat them with the standard of care.

1. Introduction

The first cases of coronavirus disease 2019 (Covid-19) were reported to the World Health Organization (WHO) in December 2019 in China with an unprecedented impact on the entire worldwide oncology community reducing healthcare activities for a duration that cannot yet be accurately estimated. The incubation period of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is two to 14 days [1]. During this period, SARS-CoV-2 invades epithelial cells using angiotensin conversion enzyme (ACE) receptor 2 [2]. Then, most patients develop upper respiratory symptoms and fever. Innate and adaptive immune responses lead to recovery for 80–85% of patients, but symptoms worsen for the remaining 1520%. Hospitalization is required in 14 to 39% of symptomatic cases due to hypoxemia, evolution toward acute respiratory distress syndrome, and/or cytokine release syndrome, which occurs in 5–13% of cases, leading to death in approximately 2–9% of cases [3,4]. Risk of death is higher in patients aged above $\geq$ 60 years and/or with existing comorbidities, including obesity, hypertension, diabetes, or a past history of cancer [5]. Among patients with hematological malignancies, an over-risk of death has been reported with hazard ratios (HRs) ranging from $1 \cdot 9$ to $3 \cdot 5$, depending on the time since diagnosis of the malignancy [5].

The one-year incidence of lymphoma in France is estimated to be approximately 30,000 [6]. Several factors contribute to immunosuppression in patients with lymphoma: hypogammaglobulinemia, neutropenia and lymphopenia are frequent biological features of lymphoma *per se,* lymphoma treatment, chemotherapy and/or immunotherapy also contributes to immune deficiency leading to an over incidence of infections [7,8]. Among chemotherapy regimen, bendamustine is a strong inducer of T-cell immune deficiency [9]. Anti-CD20 monoclonal antibodies, such as rituximab or obinutuzumab, induce rapid depletion of more than 95% of CD20-positive mature B-cells. This alters the generation of antibody responses, including memory responses to new pathogens, increasing the incidence of infections [10,11]. However, data on the impact of Covid-19 in lymphoma patients are scarce. In a study from the Covid-19 and Cancer Consortium (CCC19) on 1035 patients with Covid-19 and various cancers, no analysis was conducted specifically on the 81 patients with lymphoma [12]. In other studies on Covid-19, few patients with lymphoma were described [13–15].

We conducted a retrospective multicentric cohort study in French regions with an outbreak of the pandemic to characterize the clinical presentation and outcomes of patients with lymphoma hospitalized for Covid-19. The analysis of the determinants of survival focused on pre-Covid-19 demographics, comorbidity, and lymphoma characteristics.

2. Methods

2.1. Setting

This retrospective multicenter study was conducted in 12 hospitals in three French regions: Île-de-France, Grand-Est and Bourgogne-Franche-Comté. Adult patients with a past or current diagnosis of lymphoma (with any known lymphoma code since September 1st, 2019) and admitted for Covid-19 between March 1st and April 30th, 2020 were identified, in each hospital, by the local *Programme de Médicalisation des Systèmes d'Information* (PMSI), which is a centralized repository of administrative and medical data of every hospital stay in France. PMSI data includes the main diagnosis leading to hospitalization, as well as the associated diseases of each patient, coded according to the 10th edition of the International Classification of Diseases [16,17]. After extraction of the list of putative patients, each local investigator confirmed the cases with a diagnosis of Covid-19 based on a positive polymerase chain reaction (PCR) test result for SARS-CoV-2 from nasopharyngeal or oropharyngeal swabs or a typical clinical history associated with chest computed tomography (CT) with Covid-19 lesions [18]. Patients with any lymphoma subtype could be enrolled in the study, except those with lymphoblastic and lymphocytic lymphomas, which are being investigated in other specific ongoing studies.

Patients or their relatives (for those who were sedated) were informed according to French law on biomedical research. The ethics committee for research of the Université Paris-Saclay approved this study (CER-Paris-Saclay-2020–045) and it was conducted in accordance with the Declaration of Helsinki. Information on the study is available at clinicaltrials.gov (NCT 04386512).

2.2. Data sources and assessment of variables

Data were extracted from the medical charts in each hospital by the local investigator. The following data were obtained for each

patient: age, sex, body mass index (BMI), patient-reported smoking status, past and current comorbidities and medications; the physical examination, recorded symptoms and vital signs, and inpatient laboratory test results at admission; the most relevant chest computed tomography (CT) scan interpretation, specific medications for Covid-19, including experimental antiviral or immunomodulatory drugs, oxygenation supply modality including ventilator use, and hospital discharge modality. The data obtained concerning lymphoma history included the date of diagnosis, pathological classification according to the WHO classification for lymphoid neoplasms [19], number of treatment lines, past autologous or allogeneic stem cell transplant, chimeric antigen receptor (CAR) T-cell therapy, detailed bendamustine and 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). Refractory/relapsed lymphoma was defined as progressive disease after more than two lines of treatment or progressive disease and palliative care due to comorbidities, regardless of the number of lines of treatment.

2.3. Statistical analysis

Continuous variables are given as their median and range and categorical variables as their frequency and percentage. Follow-up was measured from hospitalization for Covid-19 to the last follow-up or date of death. Data were censored on May 26th, 2020. Overall survival (OS) was measured from hospitalization to last follow-up or death. The probability of OS was estimated using the Kaplan-Meier method, and differences compared using the log-rank test. Cox proportional hazard regression models were used to identify predictors of OS. Covariates considered in this analysis were age ($\geq$ 70 years versus below), gender, BMI ($\geq$ 30 kg/m^2 versus below), smoking status, presence of comorbidities (overall or hypertension, diabetes, chronic lung disease, or past history of cancer) and ongoing antihypertensive treatment with an ACE inhibitor or angiotensin-receptor blocker (ARB), main lymphoma subtypes (Hodgkin lymphoma, B-cell non-Hodgkin lymphoma (NHL), or T-cell NHL), recent administration of corticosteroids (within one month), use of bendamustine (within one year), or anti-CD20 monoclonal antibody (within one year), time between diagnosis of lymphoma and hospitalization for Covid-19 ($<$ 2 years versus $\geq$ 2 years), past history of autologous stem cell transplant, and lymphoma status (refractory/relapsed versus others). Covariates with *P*-values $<$ 0·10 by univariable analysis were included in the multivariable analysis. Statistical tests were two-tailed and *P* values $<$ 0·05 and *P*-values $<$ 0·05 were considered to denote statistical significance. Analyses were performed using Epi Info V7.1.5 (CDC, Atlanta, USA) and Kaplan Meier survival curves with SPSS software V26 (IBM, New York, USA).

2.4. Role of the funding source

There have been no specific funds to run this study.

3. Results

3.1. Characteristics of patients at admission

The data of 98 patients were collected. Nine patients were excluded because they were not admitted during the time period of the study (n = 6), had lymphocytic lymphoma (n = 2) or had SARS-CoV-2 infection without overt Covid-19 disease (n = 1). Characteristics of the 89 included patients are summarized in Table 1. Their median age was 67 years (range, 19–92) and 66% were male. Sixty-four patients (72%) had at least one significant comorbidity, including 39 (44%) with hypertension, 20 (22%) with diabetes, and 12 (13%) with a history of previous cancer (including 3 with prostate, 3 with lung, and 2 with breast cancer). Moreover, four patients had an ongoing autoimmune disease (Gougerot-Sjögren, rheumatoid polyarthritis, giant cell arteritis, and hemorrhagic rectocolitis), one had a previous renal transplantation, and two were treated for human immunodeficiency virus infection.

Lymphoma histological subtypes were Hodgkin lymphoma in for five patients (6%), B-cell NHL for 77 (86%), and T-cell NHL for seven (8%). The median time between diagnosis of lymphoma and admission in hospital for Covid-19 was 26 months (range, 0–25 years). Lymphoma had been diagnosed for less than one month before Covid-19 for three patients and two were diagnosed with lymphoma concomitantly with Covid-19. Within the last 12 months before hospitalization for Covid-19, 62 patients (70%) received treatment for their lymphoma, including anti-CD20 monoclonal antibody for 47 (53%) and bendamustine for nine (10%). At admission, lymphoma was in complete/partial remission for 40 patients (45%), in first- or second-line therapy for 24 (26%), in watch and wait surveillance for 12 (14%), and relapsed/refractory for 13 (15%).

The clinical, radiological and biological characteristics at admission to hospital are detailed in Supplemental Table 1. The most common symptoms were dyspnea (n = 58, 65%), cough (n = 53, 60%), fever (n = 43, 48%), and diarrhea (n = 21, 24%). The median duration of symptoms before admission was six days (range, 0–43). Lymphopenia was observed in 66% of patients, neutropenia in 18%, anemia in 66% and thrombocytopenia in 39%. The albumin level was $<$ 30 g/L for 42% evaluable patients and the gamma globulin level $<$ 6·5 g/L for 48%. Chest CT was performed on 75 patients (84%) and bilateral ground-glass opacities evocative of Covid-19 were observed for 67 (75%). Eight patients had negative PCR tests, although they all had evocative clinical symptoms: the diagnosis of SARS-CoV-2 pneumonia was confirmed by chest CT and infectiology expertise in all eight cases.

3.2. Clinical evolution after admission

As of May 26, 2020, 48 patients (54%) had been discharged from hospital, 30 had died (34%), and 11 (13%) were still hospitalized (including six patients in an intensive care unit (ICU)). During hospitalization, 18 patients (20%) did not require supplemental oxygen, 44 (49%) received low-dose supplemental oxygen, six (7%) non-invasive ventilation or high-flow oxygen, and 21 (24%) invasive mechanical ventilation. Including these last patients, 25 patients (28%) were admitted to the ICU during the study time period (Table 1): 17 (68%) were male and their median age was 61 years (range 52–77), four patients being older than 70 (16%). Overall, 20 patients (22%) were hospitalized for more than 30 days and three (3%) for more than 60.

Twenty-one patients were prescribed a treatment against SARS-CoV-2: chloroquine and hydroxychloroquine were given to 11 patients, either alone (n = 5) or associated with azithromycin (n = 3), nicotine (n = 1), lopinavir + ritonavir (n = 1), or remdesivir (n = 1). Of note, one patient was already receiving chronic hydroxychloroquine treatment for Gougerot-Sjögren's syndrome before Covid-19 and it was not interrupted during the infection. Five other patients received lopinavir + ritonavir, associated with interferon beta for one, and five had remdesivir. Six patients received treatment for cytokine shock (tocilizumab, anakinra, and eculizumab for two patients each). Seventeen patients (19%) developed a documented co-infection and three an (3%) acute pulmonary embolism.

3.3. Overall survival and its determinants

With a median follow-up of 33 days from admission (range, 3–72), the Kaplan-Meier estimate of 30-day OS was 71% (95% confidence interval (CI), 62%–81%) (Fig. 1A). According to histological type of the lymphoma, 30-day OS were 80% (45%–100%) for Hodgkin

Table 1
Baseline characteristics of patients with lymphoma and Covid-19.

Characteristics	Entire population (n = 89)	Admitted to an ICU (n = 25)	Fatal events (n = 30)
Demographic characteristics			
Age, years			
Median (range)	67 (19–92)	61 (52–77)	75 (63–92)
≥ 70, n (%)	38 (43)	4 (16)	21 (70)
Male gender, n (%)	59 (66)	17 (68)	21 (70)
Body mass index (kg/m^2)			
Median (range)	23 · 9 (15 · 9–41 · 6)	25 (19 · 4–41 · 6)	24 · 4 (16 · 7–38 · 6)
≥ 30, n (%)	13 (15)	5 (20)	4 (13)
Data missing, n (%)	4 (4)	1 (4)	3 (10)
Smoking status, n (%)			
Never smoked	43 (48)	15 (60)	12 (41)
Former smoker	29 (33)	5 (20)	13 (43)
Current smoker	5 (6)	1 (4)	1 (3)
Unknown	12 (13)	4 (16)	4 (13)
Comorbidities			
Comorbidity ≥ 1, n (%)	64 (72)	12 (48)	25 (83)
Past diagnoses, n (%)			
Hypertension	39 (44)	6 (24)	18 (60)
Diabetes	20 (22)	3 (12)	9 (30)
Chronic lung disease†	8 (9)	2 (8)	3 (10)
Cancer	12 (13)	1 (4)	7 (23)
HIV infection	2 (2)	0 (0)	0 (0)
Medication at baseline, n (%)			
ACE inhibitor or ARB	22 (25)	5 (20)	10 (33)
Systemic glucocorticoid	11 (12)	2 (8)	4 (13)
Lymphoma characteristics			
Histologic subtypes, n (%)			
Hodgkin lymphoma	5 (6)	2 (8)	1 (3)
Diffuse large B-cell lymphoma	34 (38)	9 (36)	15 (50)
Follicular lymphoma	16 (18)	7 (28)	2 (7)
Marginal zone lymphoma	14 (16)	1 (4)	5 (17)
Mantle cell lymphoma	10 (11)	4 (16)	4 (13)
Hairy cell leukemia	2 (2)	0 (0)	0 (0)
Lymphoplasmacytic lymphoma	1 (1)	1 (4)	1 (3)
T-cell lymphoma	7 (8)	1 (4)	2 (7)
Lymphoma treatment, n (%)			
Anti-CD20 monoclonal antibody#	47 (53)	16 (64)	19 (63)
Bendamustine#	9 (10)	1 (4)	7 (23)
Any chemotherapy#	62 (70)	19 (76)	22 (73)
Autologous stem cell transplant	17 (19)	8 (32)	8 (27)
Allogeneic stem cell transplant	3 (3)	1 (4)	1 (3)
CAR T-cell	4 (4)	2 (8)	1 (3)
Lymphoma status, n (%)			
Complete remission	39 (44)	16 (64)	10 (33)
Partial remission	1 (1)	0 (0)	0 (0)
Ongoing therapy < 3 lines	24 (26)	4 (16)	9 (30)
Watch and wait	12 (14)	3 (12)	2 (7)
Relapsed/refractory	13 (15)	2 (8)	9 (30)
Time between diagnosis of lymphoma and hospitalization for Covid-19 (months), median (range)	26 (0–300)	25 (0–289)	26 (1–289)

HIV: human immunodeficiency virus, ACE: angiotensin-converting enzyme, ARB: angiotensin-receptor blocker, CAR: chimeric antigen receptor.
† Chronic lung disease was defined as chronic obstructive pulmonary disease, asthma, or chronic bronchitis.
# Treatment administrated within the last 12 months before hospitalization for Covid-19.

lymphoma, 71% (95% CI, 61%–82%) for B-cell NHL and 71% (95% CI, 38%–100%) for T-cell NHL (Fig. 1B). Among the 30 patients who died during the study period, 22 died in standard care units after do-not-resuscitate orders for all of them. Their median age was 77 (range, 53–92) years, 14 were male, and they all had at least one significant comorbidity. Lymphoma status distribution was refractory/relapsed (n = 7), under ongoing therapy (n = 7), in complete remission (n = 6) and on a 'watch and wait' policy (n = 2). Eight other patients died in the ICU (Table 2). Six deaths were directly related to Covid-19: All were men, aged 55 to 77 years, four were in complete remission after first (n = 3) or second line therapy (n = 1) while two patients were under ongoing first line chemotherapy with R-CHOP for a DLBCL or autologous transplant for a relapsed follicular lymphoma. Two deaths were directly related to refractory lymphomas. The case fatality rate was 13% in the 55 patients without do-not-resuscitate orders.

In univariable analysis, there was no significant impact of the patients' gender, BMI, diabetes status, smoking status, medications at baseline, use of any treatment, including anti-CD20 monoclonal antibody within 12 months, or history of autologous stem cell transplant on OS (Table 3). The main factors associated with mortality were age ≥ 70 years (HR 3 · 78, 95% CI 1 · 73–8 · 25, p = 0 · 0009), hypertension (HR 2 · 20, 95% CI 1 · 06–4 · 59, p = 0 · 03), previous cancer (HR 2 · 11, 95% CI 0 · 90–4 · 92, p = 0 · 08), use of bendamustine within 12 months before admission to hospital (HR 3 · 05, 95% CI 1 · 31–7 · 11, p = 0 · 01), and refractory/relapsed lymphoma (HR 2 · 62, 95% CI 1 · 20–5 · 72, p = 0 · 02). Since there was a strong interaction between recent bendamustine administration and refractory/relapsed lymphoma (Odds-ratio: 20 · 0, p < 0 · 001), we performed two multivariable analyses to account for these factors. In the first multivariable analysis, combining age subgroup, hypertension, previous cancer, and recent bendamustine use, age ≥ 70 years (HR 2 · 94, 95% CI 1 · 26–6 · 83, p = 0 · 01) and recent bendamustine use (HR 3 · 20, 95% CI 1 · 33–7 · 72, p = 0 · 01) were both associated with mortality. In the second multivariable model, combining age subgroup, hypertension, previous

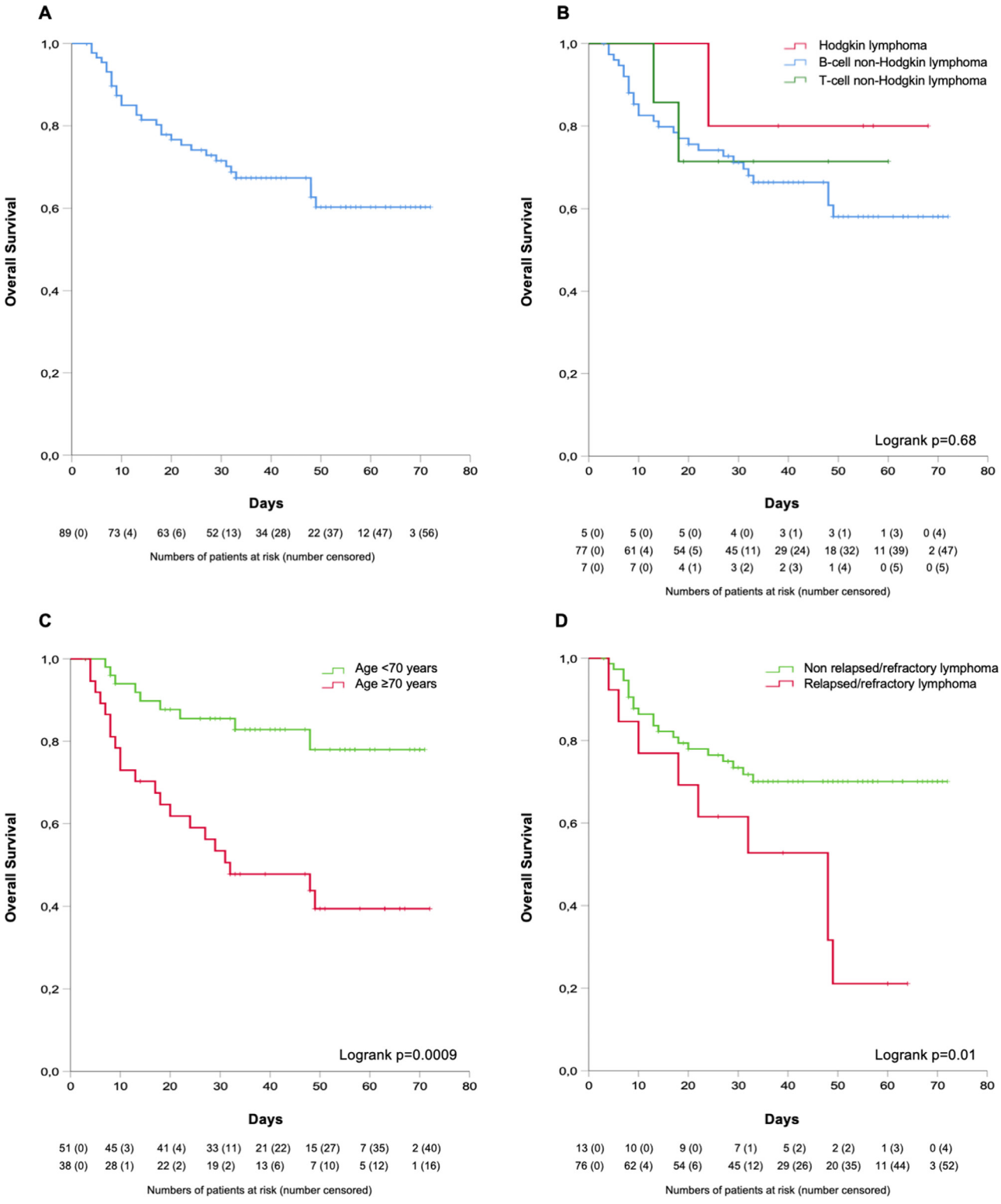

Fig. 1. Overall survival of patients with Covid-19 and lymphoma in (A) the whole population (N = 89), (B) according to lymphoma subtype, (C) to age group, and (D) lymphoma status.

A) 30-day OS, 71% (95% CI, 62–81%).

B) 30-day OS of five patients with Hodgkin lymphoma, 80% (95% CI, 45–100%); of 77 patients with B-cell non-Hodgkin lymphoma, 71% (95% CI, 61–82%); and of seven patients with T-cell non-Hodgkin lymphoma, 71% (95% CI, 38–100%).

C) 30-day OS of 51 patients aged < 70 years, 85% (95% CI, 76–95%); and of 38 patients aged ≥ 70 years, 53% (95% CI, 37–70%).

D) 30-day OS of 76 patients with non-refractory/relapsed lymphoma 73% (95% CI, 63–84%); and of 13 patients with relapsed/refractory lymphoma 61% (95% CI, 35–88%).

Median follow-up from admission for Covid-19, 33 days (range, 3–72). CI: confidence interval, OS: overall survival.

Table 2
Description of Covid-19 patients with lymphoma who died while in intensive care.

Age (year)	Gender	Comorbidity	Lymphoma subtype	Last treatment	Interval between last treatment and Covid-19	Lymphoma Status	Lymphocyte count (/μL)	CRP (mg/L)	Ferritin (ng/L)	Intubation	Complication	Interval from ICU admission and death (days)
Patients who died from Covid-19 in complete remission												
57	M	No	Mantle cell lymphoma	Obinutuzumab	2 months	Complete remission	80	72	5565	Yes	Ventilator associated pneumonia	7
59	M	Pulmonary embolism	Follicular lymphoma	BEAM	9 months	Complete remission	170	238	3	Yes	Catheter thrombosis	30
61	M	Atrial fibrillation	DLBCL	R-CHOP	5 months	Complete remission	400	352	2566	Yes	NA	9
77	M	Diabetes Hypertension Cardiopathy	DLBCL	R-CHOP	12 months	Complete remission	500	96	1388	No	NA	11
Patients who died from Covid-19 while being treated for lymphoma												
55	M	Lung cancer Emphysema	Follicular lymphoma	BEAM	6 days	Ongoing consolidation treatment	NA	NA	NA	Yes	Aspergillosis	29
71	M	No	DLBCL	R-CHOP	13 days	Ongoing induction	840	62	2053	Yes	NA	25
Patients who died from lymphoma progression while having Covid-19												
60	F	No	T-cell lymphoma	BEAM	5 months	Relapse	730	45	NA	No	NA	13
72	M	No	Lympho plasmacytic lymphoma	R-Bendamustine	7 days	Refractory	630	39	2271	No	Pulmonary embolism	15

CRP:C-reactive protein, DLBCL: diffuse large B-cell lymphoma, BEAM: autologous stem cell transplantation with carmustine - etoposide - cytarabine and melphalan conditioning regimen, ICU: intensive care unit, NA not available.

Table 3
Cox univariable and multivariable analyses of overall survival among patients with lymphoma and Covid-19.

Characteristics	Study population		Univariate analysis			Multivariable analysis (model 1)			Multivariable analysis (model 2)		
	N	Fatal events, *n*	HR	95% CI	*P* value*	HR	95% CI	*P* value*	HR	95% CI	*P* value*
Age ≥ 70 years	38	21	3·78	1·73–8·25	9·10e-4	2·94	1·26–6·83	0·01	2·87	1·20–6·85	0·02
Gender					0·68						
Female	30	9	1								
Male	59	21	1·18	0·54–2·57							
Body mass index (kg/m^2)					0·61						
< 30	72	23	1								
≥ 30	13	4	1·25	0·53–2·91							
Data missing	4	3									
Smoking status											
Never smoked	43	12	1·51	0·20–11·61	0·69						
Former smoker	29	13	2·84	0·37–21·75	0·31						
Current smoker	5	1	1								
Unknown	12	4	1·90	0·21–17	0·57						
Comorbidities (1 or more)	64	25	2·17	0·83–5·67	0·11						
Past diagnoses											
Hypertension	39	18	2·20	1·06–4·59	0·03	1·45	0·66–3·20	0·36	1·45	0·64–3·29	0·38
Diabetes	20	9	1·73	0·79–3·78	0·17						
Chronic lung disease†	8	3	1·02	0·31–3·36	0·98						
Cancer	12	7	2·11	0·90–4·92	0·08	2·06	0·84–5·08	0·12	1·97	0·81–4·80	0·13
Medication at baseline											
ACE inhibitor or ARB	22	10	1·66	0·77–3·54	0·19						
Systemic glucocorticoids	11	4	0·82	0·29–2·35	0·71						
Histologic subtypes											
Hodgkin lymphoma	5	1	0·43	0·06–3·19	0·41						
B-cell NHL	77	27	1								
T-cell NHL	7	2	0·81	0·19–3·42	0·78						
Lymphoma treatment											
Anti-CD20 antibody#	47	19	1·41	0·67–2·97	0·36						
Bendamustine#	9	7	3·05	1·31–7·11	0·01	3·20	1·33–7·72	0·01			
Any therapy#	62	22	1·08	0·48–2·42	0·86						
Autologous SCT	17	8	1·64	0·73–3·69	0·23						
Lymphoma status					0·02						0·02
Relapsed/refractory	13	9	2·62	1·20–5·72					2·54	1·14–5·66	
Others	76	21	1						1		
Time between diagnosis of lymphoma and hospitalization for Covid-19 < 2 years	76	21	1·18	0·57–2·43	0·64						

ACE: angiotensin converting enzyme inhibitors, ARB: angiotensin receptor blockers, CI: confidence interval, HR: hazard ratio, NHL: non-Hodgkin lymphoma, SCT: stem cell transplantation.
† Chronic lung disease was defined as chronic obstructive pulmonary disease, asthma, or chronic bronchitis.
# Treatment administrated within the last 12 months before hospitalization for Covid-19.
* Logrank test.

cancer, and refractory/relapsed lymphoma, age ≥ 70 years (HR 2·87, 95% CI 1·20–6·85, $p = 0·02$) and having refractory/relapsed lymphoma (HR 2·54, 95% CI 1·14–5·66, $p = 0·02$) were significantly associated with the risk of death (Table 3). Overall, the Kaplan-Meier estimate of 30-day OS was 61% (95% CI, 35%–88%) for patients with refractory/relapsed lymphoma, 52% (95% CI, 34%–70%) in patients ≥ 70 years of age with non-refractory/relapsed lymphoma, and 88% (95% CI, 78%–99%) for patients < 70 years old with non-refractory/relapsed lymphoma (Fig. 2).

4. Discussion

SARS-CoV-2 infection raises specific concerns in terms of morbidity and mortality for patients with lymphoma due to their immunocompromised status induced by the disease *per se* and/or its treatment. The present retrospective multicentric cohort study aimed to estimate the mortality rate and to identify preexisting risk factors for Covid-19 related death in the lymphoma population. It focused notably on recent exposition to cytotoxic chemotherapy, including bendamustine and anti-CD20 immunotherapy. Among 89 patients with Covid-19 and lymphoma, one-month OS was 71%. Factors associated with death were advanced age and relapsed/refractory lymphoma. Bendamustine also appeared to be associated with death but most of the patients treated with bendamustine had relapsed/refractory lymphoma. Anti-CD20 treatment within one year was not associated with death. Patients younger than 70 without relapsed or refractory disease had 88% 30-day OS, similar to that of the general population in France [20].

In the previously mentioned CCC19 study, the death rate for patients with hematological malignancies was 14% during one month [12]. The lower risk of death they reported may have been due to the inclusion of both ambulatory and hospitalized patients with Covid-19 in their study. However, in the UKNHS study, analyzing hospitalized patients only, patients with hematological malignancies diagnosis within five years had a high mortality rate (29%) from Covid-19[5], similar to our findings. Among well-known risk factors for Covid-19 mortality [5], we report an association with advanced age (above 70 years) (HR 2·94), but no significant association with hypertension (HR 1·46), diabetes (HR 1·73), or obesity (HR 1·25). In accordance with the CCC19 study showing that active cancer was associated with a worse outcome (HR 5·20)(12), refractory/relapsed lymphoma was associated with an increased mortality in our study (HR 2·54).

Although recent overall administration of immunochemotherapy was not associated with mortality, a history of treatment with bendamustine within one year was associated with a higher mortality rate (HR 3·20). Bendamustine treatment induces myelosuppression and T-CD4 lymphopenia, and is associated with an increased risk of viral, bacterial or fungal infections [9]. However, among the nine patients who had received this treatment, eight had been given a do-not-resuscitate order and had a refractory/relapsed lymphoma. Further

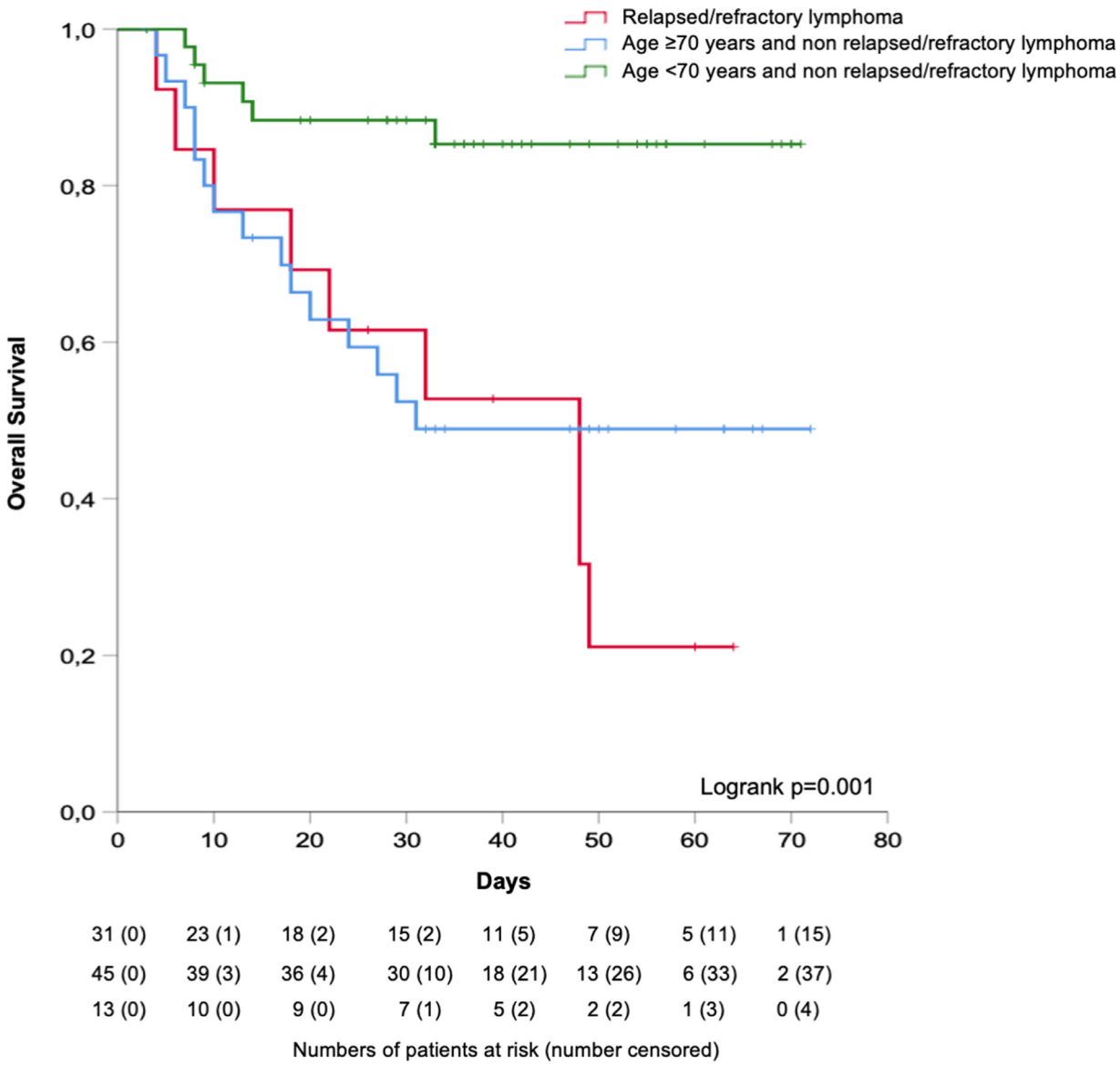

Fig. 2. Overall survival of patients with Covid-19 and lymphoma (N = 89), according to age group and refractory/relapsed lymphoma status.
- 30-day OS for 13 patients with refractory/relapsed lymphoma, 61% (95% CI, 35–88%).
- 30-day OS for 31 patients aged ≥ 70 years with non-refractory/relapsed lymphoma, 52% (95% CI, 34–70%).
- 30-day OS for 45 patients aged < 70 years with non-refractory/relapsed lymphoma, 88% (95% CI, 78–99%).
Median follow-up from admission for Covid-19: 33 days (range, 3–72); CI: confidence interval, OS: overall survival.

studies are merited to explore the impact of bendamustine on Covid-19 evolution. However, since bendamustine therapy may be associated with a higher risk of mortality, the risk of initiating this therapy in older patients in geographic areas of high prevalence of COVID-19 would warrant careful consideration. Despite the well-known importance of the adaptive immune response to clear SARS-CoV-2 [21], having received an anti-CD20 therapy up to 12 months before Covid-19 was not associated with mortality (HR 1·41). However, B-cell depletion at the time of acute infection may impair the generation of functional primary and memory anti-SARS-CoV-2 T-cell responses. Therefore, there is a concern of whether lymphoma patients on anti-CD20 who contracted SARS-CoV2 and patients who will receive SARS-CoV2 vaccines when available will be effectively protected against re-infection or infection.

Overall, patients younger than 70 without relapsed/refractory lymphoma had outcomes (30-day survival of 88%) comparable to those of the non-cancer population. According to Santé Publique France, in-hospital mortality is 18%, rising from 10% for 45- to 64-year-old patients to 18% for the 65 to 74-year-old group, and 71% for older patients [20]. This encourages the application of standard Covid-19 treatment, including intubation, for lymphoma patients with Covid-19 lymphoma diagnosis, under first- or second-line chemotherapy, or in remission. A do-not-resuscitate order was frequently given for patients undergoing advanced lines of treatment and/or with relapsed/refractory disease, limiting the interpretation of data. In patients without do-not-resuscitate order, the case fatality rate was also comparable to comparable to those of the non-cancer population.

A strength of our study was the screening of patients based on the PMSI, which limited selection bias. However, some patients may have been hospitalized for Covid-19 in hospitals other than that of their hematological unit and may have been excluded from the study. Other limitations were the retrospective nature of the study and the study design, which did not allow a direct comparison between lymphoma patients with Covid-19 and Covid-19 patients without lymphoma. Another limitation of selecting only hospitalized patients

was the exclusion of patients with mild symptoms, and old patients living in nursing homes that weren't transferred in hospital during the pandemic. Exhaustive inclusion of all patients with Covid-19 and lymphoma, including those with mild symptoms, would have been impossible due to the restricted PCR testing during the first phase of the outbreak in France, but would be recommended in the next epidemic phases, as serological and PCR testing have become largely available.

In conclusion, this cohort study reports 71% 30-day OS in patients with lymphoma and Covid-19, advanced age and having relapsed/refractory lymphoma being the main risk factors for death. However, patients younger than 70, without relapsed/refractory disease, had 88% 30-day overall survival, which is comparable to that of the general population. Longer term clinical follow-up and biological monitoring of immune responses is warranted to explore the impact of lymphoma and its treatment on the immunity and prolonged outcome of Covid-19 patients.

Declaration of Interests

The authors certify that there is no conflict of interest with any organization regarding the material presented in this manuscript.

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Authors contributions

Sylvain Lamure and Rémy Duléry designed the data collection, collected data, analyzed the data and wrote the article. Roberta Di Blasi, Adrien Chauchet, Bénédicte Deau-Fisher, Bernard Drenou, Carole Soussain, Cédric Rossi, Nicolas Noël, Sylvain Choquet, Serge Bologna, Bertrand Joly, Milena Kohn, Sandra Malak, Guillemette Fouquet, Etienne Daguindau and Sophie Bernard performed the data collection and some data interpretation. Cécile Laureana designed the PMSI analysis and collected data. Catherine Thiéblemont, Guillaume Cartron and Karine Lacombe reviewed the study design and the article. Caroline Besson designed the study, contributed to the analysis and wrote the paper.

Data sharing statement

The dataset supporting this article is available upon demand to the corresponding author and to the promoter (center Hospitalier de Versailles).

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