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COVID-19 (SARS-CoV-2 infection) in lymphoma patients: A review

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection now has a global resonance and represents a major threat for several patient populations. Observations from initial case series suggested that cancer patients in general might have an unfavorable outcome following coronavirus disease 2019 (COVID-19), due to their underlying conditions and cytotoxic treatments. More recently, data regarding the incidence and clinical evolution of COVID-19 in lymphomas have been reported with the aim to identify those more frequently associated with severe complications and death. Patients with lymphoma appear particularly vulnerable to SARS-CoV-2 infection, only partly because of the detrimental effects of the anti-neoplastic regimens (chemotherapy, pathway inhibitors, monoclonal antibodies) on the immune system. Here, we systematically reviewed the current literature on COVID-19 in adult patients with lymphoma, with particular emphasis on disease course and prognostic factors. We also highlighted the potential differences in COVID-19 clinical picture according to lymphoma subtype, delivered treatment for the hematological disease and its relationship on how these patients have been managed thus far.

Key Words: Lymphoma; SARS-CoV-2 infection; Hematological malignancies; COVID-19; Rituximab; Bendamustine

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Core Tip: Recently, the scientific literature has been widely occupied by reports on severe acute respiratory syndrome coronavirus 2 infection. However, patients with cancer have been under-represented, and patients with lymphoma have rarely been described. The real impact of this tremendous pandemic on the life expectancy of patients with different subtypes of lymphoma is still unknown, especially in relation to chemo-, chemo-immunotherapy and/or biologic treatments. Furthermore, the

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relationship between lymphoma patients' characteristics and the infection behavior is undescribed. With this review we pointed out what literature clarifies in the prognosis and management of patients with lymphoma during the coronavirus disease 2019 pandemic.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic is a worldwide medical emergency impacting virtually all aspects of medical care. The clinical spectrum of individuals who are infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is remarkably heterogeneous, ranging from mild flu-like symptoms to life-threatening respiratory failure[1]. Mortality due to the infection is largely dependent on patients age, and the infection fatality ratio is lowest among 5-9-year-old children, with a log-linear increase by age among individuals older than 30 years. Estimated age-specific infection fatality ratios range from 0.001% in those aged 5-9-years-old to 8.29% in those aged 80+. Population age structures, heterogeneous inclusion criteria in terms of comorbidities and burdens in nursing explain some of the heterogeneity between countries in infection fatality ratio[2]. The leading cause of mortality is the acute respiratory distress syndrome. Indeed, after infecting the pneumocytes, SARS-CoV-2 triggers intracellular signaling pathways that promote the release of several proinflammatory mediators, leading to the recruitment of neutrophil and monocyte-macrophages[3-5].

Subgroups of patients with COVID-19 have been identified to be at increased risk of morbidity and mortality, including patients of older age, male sex (*vs* female) and those with comorbidities, such as hypertension, chronic lung disease, diabetes, immunodeficiency and cancer[6]. In particular, cancer patients often follow a more severe and rapid disease course, with requirement of high-level intensive care and an increased risk of COVID-19-related death[7-10]. In the first published report from the COVID-19 and Cancer Consortium, mortality among 928 analyzed adult patients with any malignancy was 13%, with 23% mortality for any admission to the hospital and 38% mortality for admission to the intensive care unit (ICU)[11]. Among 800 patients with cancer included in the United Kingdom Coronavirus Cancer Monitoring Project, reported mortality in the overall cohort was 28%[12]. A multicenter study in China of 205 patients with cancer reported mortality of 20%[13]. In the latter series, 22 patients with hematologic malignancies (HM) were included and had a mortality rate of 41%. In cancer series, hematologic patients account for 20%-25% of the total including a variable distribution of pathologies. Heterogeneous series addressing SARS-CoV-2 infection in patients with HM have been published, reflecting mortality rates ranging from 30% to 40%; however, these reports offer limited information on the characteristics of the various hematological diseases and their relationship with anticancer treatments. Patients with HM are immunocompromised, which makes them highly susceptible to severe infections. On the other hand, some authors have suggested that some patients with HM might be "protected" from severe COVID-19 morbidity due to an attenuated inflammatory response. In this review, we synthesized the current literature to illustrate the demographic, immunological and clinical features of COVID-19 infection in the specific setting of patients affected by lymphoma, a heterogeneous group of cancers arising from B or T lymphocytes and often associated with various degrees of immune dysfunction.

Lymphoma patients are at high risk of infections: patients with HM (and lymphomas) tend to carry more comorbidities than age and sex matched population, have more frequent contacts with medical systems and are often treated with immunosuppressive medications potentially blunting the antiviral immune responses. Hematologic malignancies affect the production and function of blood cells in fighting off infections[14]. Affected patients often have multiple immune dysfunctions of the innate and adaptive immune system including low immunoglobulin G serum levels (

i.e. chronic lymphocytic leukemia or other B cell neoplasms) or functionally impaired granulocytes (*i.e.* myeloid neoplasms)[15,16]. Crippled cellular and humoral immunity places these patients at risk of a diverse array of infections including COVID-19[17].

Lymphomas are a heterogeneous group of cancers broadly divided into two main histological subtypes: Hodgkin lymphoma (HL) and non-HL (NHL). HL tends to spread in a fairly orderly way from one group of lymph nodes to the next group and it affects young adults aged 20–40 years more frequently, while NHL can spread to extra nodal organs, bone marrow and spleen. The World Health Organization has recognized several forms of NHL, with diffuse large B-cell lymphoma being the most common subtype in adults[18].

Chemotherapy treatment combined with rituximab (widely available immunotherapy against B-lymphocytes) is the current standard upfront treatment for most histologies[19]. Together with lymphodepleting therapies, several intrinsic factors contribute to the typical immunosuppressive status of patients with lymphoma. Among them hypogammaglobulinemia, neutropenia and lymphopenia (both B- and T-cell related) are frequently observed features at disease presentation[20,21]. Furthermore, lymphomas are more likely to develop in patients with underlying immunosuppressive conditions, such as the human immunodeficiency virus infection, rheumatological chronic disorders, autoimmune disease or inherited congenital immune-deficiency states[22]. Lymphoma therapy has historically been based on chemotherapy variably associated with immunotherapy and radiotherapy. Moreover, in recent years, the approval of new molecules with different mechanisms of action (monoclonal antibody, small molecules, biologic agents, cell therapy) has allowed us to expand the therapeutic arsenal available for the treatment of these diseases. Among chemotherapy regimens, bendamustine is a strong inducer of T-cell immune deficiency[23]. Anti-CD20 monoclonal antibodies, such as rituximab or obinutuzumab, induce rapid depletion of more than 95% of CD20-positive mature B-cells, impairing cellular and humoral response towards new pathogens[24-26].

LITERATURE REVIEW

A review of the literature reporting on SARS-CoV-2 infection in lymphoma patients was conducted. In particular, we focused on the relationship with lymphoma characteristics and the clinical course of COVID-19 infection. An electronic search was performed to identify all studies reporting on the management of lymphoma patients during the SARS-CoV-2 pandemic. The PubMed/MEDLINE database was searched on February 6th, 2021. The search strategy was “SARS-CoV-2” OR “COVID-19” AND “lymphoma.” Potential case duplicates were ruled out by analysis of demographic characteristics of the included patients and institution of origin of the reports.

PREVALENCE OF CANCER AND HM AMONG SARS-COV-2 INFECTED PEOPLE

Human infections with SARS-CoV-2 were first reported in late 2019. At the end of February 2021, the global cumulative numbers were 110.7 million cases and over 2.4 million deaths since the start of the pandemic[27]. The prevalence of cancer in patients with COVID-19 is uncertain. Studies from China reported that 1% to 2% of COVID-19 patients had cancer, and a study from the United States reported that 6% of hospitalized patients with COVID-19 had cancer. In Lombardy, Italy, they observed that 8% of the patients admitted to the ICU for COVID-19 had cancer. In a meta-analysis, the prevalence of cancer was 2% among COVID-19 patients[28].

Reports about the prevalence of HM among COVID-19 patients are very limited. In a study from Turkey[29], 0.39% of the laboratory-confirmed COVID-19 patients had underlying blood cancer. Patients with HM were reported to be at increased risk for developing COVID-19 as compared to general population, after adjusting for age, gender, race and known COVID-19 risk factors. It has been reported that patients with cancer with different tumor types have differing susceptibility to SARS-CoV-2 infection and COVID-19 phenotypes[30]. Individualized risk tables have been generated for patients with cancer, considering age, sex and tumor subtype, reporting an increased susceptibility to SARS-CoV-2 in patients with HM.

CLINICAL MANAGEMENT AND FATALITY RATES OF PATIENTS WITH COVID-19 AND HM (INCLUDING LYMPHOMAS)

Among papers investigating the characteristics of COVID-19 infection in cancer patients, only some stratified the population by type of malignancy (reported in Table 1). He *et al*[31] conducted a cohort study at two centers in Wuhan, China, involving 128 hospitalized subjects with HM, 13 (10%) of whom developed COVID-19. There were no significant differences in baseline covariates between subjects with HM developing COVID-19 or not. Case rates for COVID-19 were similar between the two groups, but hospitalized subjects with HM were reported to suffer from more severe disease and higher case fatality rate (CFR). In a study conducted by Mehta *et al*[32] the CFR in COVID-19 patients with HM was 37%. A study from Spain[33] reported a CFR of 32% among 34 hospitalized COVID-19 patients with HM. Authors concluded that the status of underlying malignancy at the time of COVID-19 correlated with mortality, with disease activity that was directly associated with worse outcomes. Aries *et al*[34] reported a CFR as high as 40% in a small cohort including 35 patients with HM. In a study conducted by Yang *et al*[13] among 52 COVID-19 patients with solid tumors or HM, the rate of severe/critical disease was 36.5% and CFR of severe/critical patients was 57.8%. Wood *et al*[35] described 250 cases of patients with HM and COVID-19 that were enrolled into the ASH Research Collaborative COVID-19 Registry. Consistent with previous reports, patients with HM had poor outcomes, with an overall mortality rate of 28%, which increased to 42% for those patients requiring hospital-level care.

In Rüttrich *et al*[36] retrospective analysis of LEOSS study a total of 435 cancer patients with SARS-CoV-2 were included. The majority of patients were hospitalized (98%). Lymphoma and leukemia were documented for 76 (17.5%) and 48 (11%) patients, respectively. The commonest HM was NHL (16.5%). In solid tumors and HM, mortality appeared somewhat comparable, but HM were overrepresented compared to a non-COVID-19 cancer cohort from the United Kingdom, reporting a prevalence of 9.5%[30].

In the study by Passamonti *et al*[37], 536 HM patients were described. A high frequency of severe infections was reported: dyspnea occurred in 51% of patients and fever in 75% of patients. This was also evidenced by the high proportion (18%) of patients admitted to the ICU and the high number of deaths (198, 37%). Mortality of patients with HM and COVID-19 was nearly four times higher than that of the general population with COVID-19.

Similar conclusions have been reached by the Turkish study conducted by Yigenoglu *et al*[29] where COVID-19 patients with HM ($n = 740$) and an age, sex and comorbidity-matched cohort of COVID-19 patients without cancer ($n = 740$) were enrolled. NHL (30.1%), myelodysplastic syndrome (19.7%) and myeloproliferative neoplasm (15.7%) were the most common HM. The rates of severe and critical disease, hospital and ICU admission and mechanical ventilation support were significantly higher in patients with HM compared with patients without cancer. The length of hospital stay and ICU stay was similar between groups. The CFR was 13.8% in patients with HM and 6.8% in the control group. The lower CFR in this study compared with the other studies may be attributed to a high number of myeloproliferative neoplasm patients who were thought to be less immunocompromised compared with leukemia, multiple myeloma or lymphoma patients. Interestingly, they described higher use of antiviral drugs such as lopinavir/ritonavir in patients with HM.

Finally, recipients of autologous and allogeneic stem cell transplantation (HSCT) who develop COVID-19 have also been reported to have poor survival rates. The Center for International Blood and Marrow Transplant Research reported 318 HSCT recipients diagnosed with COVID-19. Disease severity was mild in 155 (49%) of 318 patients, while severe disease requiring mechanical ventilation occurred in 45 (14%), *i.e.* 28 (15%) of 184 allogeneic HSCT recipients and 17 (13%) of 134 autologous HSCT recipients. At 30 d after COVID-19 diagnosis, overall survival was 68% (95% confidence interval: 58%–77%) for recipients of allogeneic HSCT and 67% (55–78) for recipients of autologous HSCT[38]. Age 50 years or older, male sex and development of COVID-19 within 12 mo of transplantation were associated with a higher risk of mortality among allogeneic HSCT recipients.

When cancer patients are compared with control groups it appeared evident that the cancer itself constituted an independent prognostic factor in the case of COVID-19 infection. Studies investigating clinical factors associated with worse outcome in HM are summarized in Table 2.

Table 1 Characteristics of included studies

Ref.	Location	Type of malignancy included	Duration of study	Total No. of pts with HM included	Matched COVID-19 control	No. of lymphoma pts	No. of NHL pts	No. of HL pts	Mortality rate attributed to COVID-19 (Global)	Mortality rate attributed to COVID-19 (Lymphoma)	Mortality rate attributed to COVID-19 (NHL)	Mortality rate attributed to COVID-19 (HL)
Cancer studies including lymphoma pts												
Rüthrich <i>et al</i> [36], 2020	Europe	All	5 mo	435	2636	76	71	5	96/435 (22%)	20/76 (26%)	NR	NR
Lee <i>et al</i> [12], 2020	UK	All	1 mo	1044	282878	79	NR	NR	319/1044 (31%)	25/79 (31%)	NR	NR
Tian <i>et al</i> [50], 2020	China	All	9 wk	232	519	6	6	0	46/232 (20%)	2/6 (33%)	2/6 (33%)	NR
HM studies including lymphoma pts												
Aries <i>et al</i> [34], 2020	UK	HM	2 mo	35	No	8	8	0	14/35 (40%)	NR	NR	/
Biernat <i>et al</i> [51], 2020	Poland	HM	1 mo	10	No	3	3	0	7/10 (70%)	NR	NR	/
Booth <i>et al</i> [52], 2020	UK	HM	2 mo	66	No	15	15	0	34/66 (52%)	6/15 (40%)	6/15 (40%)	/
Cattaneo <i>et al</i> [42], 2021	Italy	HM	1 mo	102	101	42	40	2	40/102 (39%)	17/42 (40%)	16/40 (40%)	1/2 (50%)
Fox <i>et al</i> [53], 2020	UK	HM	1 mo	55	No	17	17	0	19/55 (35%)	7/17 (41%)	7/17 (41%)	/
Garcia-Suarez <i>et al</i> [54], 2020	Spain	HM	8 wk	697	No	220	187	33	230/697 (33%)	68/220 (31%)	59/187 (32%)	9/33 (27%)
Infante <i>et al</i> [55], 2020	Spain	HM	1 mo	41	No	15	14	1	15/41 (37%)	NR	NR	NR
Lattenist <i>et al</i> [56], 2021	Belgium	HM	2 mo	12	No	2	2	0	6/12 (50%)	2/2 (100%)	2/2 (100%)	/
Malard <i>et al</i> [57], 2020	France	HM	1 mo	25	No	7	7	0	10/25 (40%)	0/7 (0%)	0/7 (0%)	/
Martin-Moro <i>et al</i> [33], 2020	Spain	HM	5 wk	34	No	6	5	1	11/34 (32%)	0/6 (0%)	0/5 (0%)	0/1 (0%)
Mehta <i>et al</i> [32], 2020	USA	HM	3 wk	54	No	20	15	5	20/54 (37%)	8/20 (40%)	5/15 (33%)	3/5 (60%)
Passamonti <i>et al</i> [37], 2020	Italy	HM	12 wk	536	No	170	153	17	198/536 (37%)	65/170 (38%)	62/153 (40%)	3/17 (18%)
Sanchez-Pina <i>et al</i> [58], 2020	Spain	HM	1 mo	39	53	12	NR	NR	14/39 (36%)	2/12 (14%)	NR	NR
van Doesum <i>et al</i> [59], 2020	Europe	HM	9 wk	59	No	17	15	2	NR	NR	NR	NR
Yigenoglu <i>et al</i> [29], 2021	Turkey	HM	15 wk	740	188897	250	223	27	103/740 (14%)	28/250 (11%)	24/223 (11%)	4/27 (14%)
Wood <i>et al</i> [35], 2020	Worldwide	HM	3 mo	250	No	79	68	11	70/250 (28%)	20/79 (25%)	16/68 (24%)	4/11 (36%)
Lymphoma studies												
Regalado-Artamendi	Spain	Lymphoma	12 wk	177	No	177	158	9	61/177 (29%)	61/177 (29%)	NR	NR

<i>et al</i> [40], 2021												
Lamure <i>et al</i> [39], 2020	France	Lymphoma	8 wk	89	No	89	84	5	30/85 (34%)	30/85 (35%)	29/84 (34%)	1/5 (20%)
Laurence <i>et al</i> [60], 2021	France	PCNSL	2 mo	13	No	13	13	/	3/13 (23%)	3/13 (23%)	3/13 (23%)	

COVID-19: Coronavirus disease 2019; HM: Hematologic malignancy; HL: Hodgkin lymphoma; NHL: Non-Hodgkin lymphoma; NR: Not reported; PCNSL: Primary central nervous system lymphoma; pts: Patients; UK: United Kingdom; USA: United States of America.

Table 2 Prognostic factors associated with survival in lymphoma series

Ref.	Details on study cohort	Univariate analysis for predictors of death	Multivariate analysis for predictors of death
Regalado-Artamendi <i>et al</i> [40], 2021	Lymphoma patients	Age \geq 70 yr Comorbidities CURB65 \geq 3 Low platelet count Low hemoglobin level High D-dimer C-reactive protein >10 mg/dL LDH $>$ 300 U/L Active disease ¹ (reference to CR) DLBCL histology (reference to FL) High-risk lymphoma ² (reference to low risk)	Age \geq 70 yr Comorbidities CURB \geq 2 Active disease
Lamure <i>et al</i> [39], 2020	Hospitalized lymphoma patients	Age \geq 70 yr Hypertension Previous cancer Bendamustine treatment Active disease	Age \geq 70 yr Active disease

¹Partial response or progression.

²High risk according to prognostic index at diagnosis. CR: Complete response; CURB65: Confusion, urea concentration, respiratory rate, blood pressure and age $>$ 65; DLBCL: Diffuse large B cell lymphoma; FL: Follicular lymphoma; LDH: Lactate dehydrogenase.

LYMPHOMA SERIES AND CASE REPORTS, CLINICAL FEATURES AND FATALITY RATES

Lymphoma patients represented a small proportion of the entire cancer series, also reflecting the relative prevalence of this disease compared to solid tumors. Figure 1 resumed the number of lymphoma patients described all over the world in the largest HM studies. However, subset data from and disease-specific cohorts are emerging. Two recently published series focused specifically on patients with lymphoma. The first report was from France where Lamure *et al*[39] described clinical characteristics and outcomes of 89 adult patients with lymphoma hospitalized for COVID-19 in 12 hospitals during the first pandemic wave. Overall, reported 1 mo overall survival was 71%. The most common symptoms at presentation were dyspnea (65%), cough (60%), fever (48%) and diarrhea (24%). The median duration of symptoms before admission was 6 d. Lymphopenia was observed in 66% of patients. During hospitalization, 25 patients (28%) were admitted to the ICU. This CFR was documented despite a significant fraction of patients had received the best available cures against SARS-CoV-

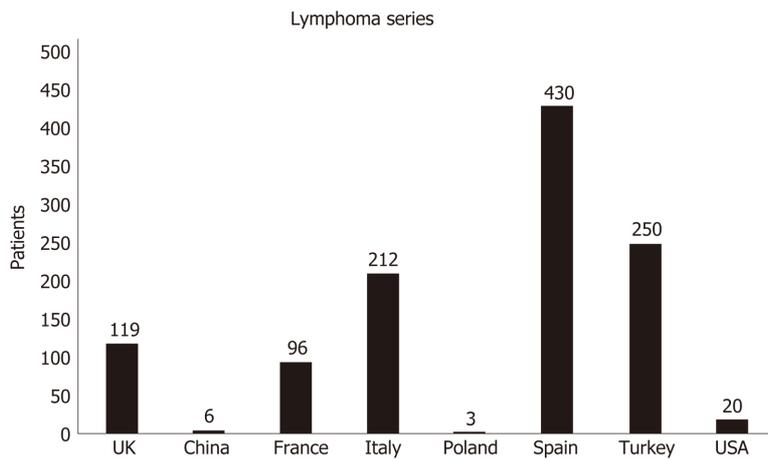


Figure 1 Number of lymphoma patients described all over the world in largest hematologic malignancy studies. UK: United Kingdom; USA: United States of America.

2: chloroquine and hydroxychloroquine (11 patients) or antiviral drugs combinations (10 patients). Six patients had received treatment for cytokine shock (tocilizumab, anakinra and eculizumab for two patients each). Seventeen patients (19%) developed a documented coinfection and three an (3%) acute pulmonary embolism.

The second series from Regalado-Artamendi *et al*[40] collected 177 cases affected by COVID-19 in Spain. The median incubation time was again 5 d, with fever and cough as the most frequent symptoms at presentation; the presence of dyspnea at presentation was related to CFR. More than 85% of patients required hospital admission, with 9% admitted to the ICU and an overall mortality rate of 34.5%.

Numerous case reports of patients affected by lymphoma and COVID-19 have been reported and summarized in Table 3. These cases have been published over the last 12 mo, witnessing the widespread interest of the scientific community and the difficulties encountered in the management of these patients. Several lymphoma histotypes are described, with disparate outcomes.

PROGNOSTIC FACTORS ASSOCIATED WITH SURVIVAL IN PATIENTS WITH LYMPHOMA

As previously mentioned, in most of the cancer series including HM, male sex, active disease and advanced age were associated with higher CFR attributed to COVID-19 [30,36,41,42]. Passamonti *et al*[37] observed that overall survival in patients affected by HM and COVID-19 was independently predicted by age, type of malignancy, disease status and the severity of COVID-19. NHL (with no mention of histological subtype), acute myeloid leukemia and plasma cell neoplasms, together with progressive disease status, were independently predictive of poor outcomes. Among patients with NHLs, 4 (31%) of 13 patients on rituximab maintenance, 27 (47%) of 57 on active treatment with rituximab-chemotherapy and 8 (44%) of 18 on chemotherapy alone died. No association between overall survival and time since HM diagnosis or last treatment was described. In Lamure *et al*[39] series from France, which specifically focused on hospital admitted lymphoma patients with a median follow-up of 33 d from admission, 30 d overall survival was 71%, (95% confidence interval: 62%-81%). Factors independently associated with death were advanced age (> 70 years) and relapsed/refractory lymphoma. Interestingly, treatment with bendamustine ($n = 9$) was associated with a higher risk of death. No significant difference in the rate of death was described for patients with different lymphoma histology.

In the Regalado-Artamendi *et al*[40] series from Spain, also specifically addressing lymphoma patients, the overall mortality rate was 34.5%. Age > 70 years, heart disease, chronic kidney disease and confusion, urea concentration, respiratory rate, blood pressure and age > 65 score ≥ 2 were statistically significant mortality predictors, resembling previous reports in cancer patients. Among the variables related to lymphoma, the presence of active disease was a strong predictor of death. However, active treatment, the number of previous lines or type of treatment did not modify mortality risk. Quite surprisingly but confirming previous reports, the use of

Table 3 Case reports and case series of coronavirus disease 2019 infection in lymphoma patients

Ref.	No. of patients described	Sex	Age	Details on lymphoma diagnosis	Details on lymphoma treatment	Outcome of COVID-19 infection	Global outcome
Li <i>et al</i> [61], 2020	1	M	26 yr	PMLBCL	R-DA-EPOCH	Recovered	Alive
Tepasse <i>et al</i> [62], 2020	2	M	65 yr	DLBCL with CNS relapse	R-DeVIC	Not recovered	Dead
		M	66 yr	MCL in CR	Rituximab maintenance	Not recovered	Dead
O'Kelly <i>et al</i> [63], 2020	1			cHL second relapse	Pembrolizumab	Recovered	Alive
Baang <i>et al</i> [64], 2021	1	M	60 yr	Relapsed/Refractory MCL	R-CHOP	Recovered	Alive
Moore <i>et al</i> [65], 2020	1	F	63 yr	NHL	Obinotuzumab maintenance	Recovered	Alive
Alsuliman <i>et al</i> [66], 2020	2	M	71 yr	MCL relapsed	Ibrutinib	Recovered	Alive
		M	NR	MCL relapsed	Ibrutinib	Recovered	Alive
Hoffmann <i>et al</i> [67], 2021	3	F	68 yr	DLBCL, FL	R-CHOP	Recovered	Alive
		M	60 yr	DLBCL, FL	R-ICE	Not recovered	Dead
		M	75 yr	DLBCL	R-CHOP	Not recovered	Dead
Yonal-hindilerden <i>et al</i> [68], 2021	1	F	55 yr	Relapsed/Refractory cHL	Brentuximab	Not recovered	Dead
Fujii <i>et al</i> [69], 2021	1	M	43 yr	cHL	A + AVD	Recovered	Alive
Kamel, 2021	1	M	58 yr	ALCL	None	Not recovered	Dead
Santana <i>et al</i> [70], 2021	1	F	47 yr	FL	Rituximab maintenance	Recovered	Alive
Velier <i>et al</i> [71], 2021	1	F	61 yr	WM	None	Recovered	Dead
Pelcovits <i>et al</i> [72], 2021	1	M	43 yr	High Grade B Cell Lymphoma, NOS	R-CODOX-M/IVAC	Recovered	Alive
Otsuka <i>et al</i> [73], 2020	1	M	56 yr	MCL	R-hyper CVAD/MA	Not recovered	Dead

A + AVD: Brentuximab vedotin, dacarbazine, doxorubicin, vinblastine; ALCL: Anaplastic large-cell lymphoma; cHL: Classic Hodgkin lymphoma; CNS: Cerebral nervous system; COVID-19: Coronavirus disease 2019; CR: Complete remission; DLBCL: Diffuse large B-cell lymphoma; F: Female; FL: Follicular lymphoma; M: Male; MCL: Mantle cell lymphoma; NHL: Non-Hodgkin lymphoma; NOS: Not otherwise specified; PMLBCL: Primary mediastinal large B-cell lymphoma; R-CHOP: Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R-CODOX-M/IVAC: Rituximab, cyclophosphamide, vincristine, doxorubicin and methotrexate alternating with ifosfamide, etoposide and cytarabine; R-DA-EPOCH: Dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab; R-DeVIC: Rituximab, dexamethasone, etoposide, ifosfamide carboplatin; R-hyper CVAD/MA: Rituximab/cyclophosphamide/vincristine sulfate/doxorubicin and hydrochloride/dexamethasone/methotrexate/cytarabine; R-ICE: Rituximab, ifosfamide, carboplatin and etoposide; WM: Waldenstrom macroglobulinemia.

monoclonal antibodies (*i.e.* rituximab) was not associated with impaired survival for lymphoma patients. The detrimental effect of therapy based on bendamustine was not independently confirmed in this study.

A subanalysis in regard to lymphoma histology observed that aggressive tumors (*i.e.* diffuse large B-cell lymphoma) were associated with significantly worse overall survival compared with indolent forms (*i.e.* follicular lymphoma; 50% *vs* 80%, $P = 0.0028$). However, the study was not able to demonstrate clear differences between the various lymphoma histologies and therapeutic schemes; these variables were grouped into categories that could have limited the statistical power of this subanalysis. Finally, the persistence of SARS-CoV-2-positive PCR after week 6 was significantly associated with mortality. In the previously cited series describing the outcome of transplanted patients, the subgroup of patients with lymphoma (among other HM) was associated with a higher risk of death compared with plasma cell disorder or myeloma in

autologous HSCT recipients[38].

REPORTS OF SPONTANEOUS REMISSIONS IN PATIENTS WITH LYMPHOMAS

Few cases along the literature indicate that some patients may benefit of lymphoma remission when infected by COVID-19. In one case, a dramatic transient reduction in plasmatic Epstein-Barr virus (EBV)-DNA viral copies during COVID-19 pneumonia and resolution of lymphoma relapse were reported[43]. In another report, a 61-year-old man with EBV-positive classical HL with progressive lymphadenopathy and weight loss was admitted with breathlessness and wheezing and was diagnosed with PCR-positive SARS-CoV-2 pneumonia. No corticosteroid or immunochemotherapy was administered. Four months later, palpable lymphadenopathy had reduced, and an interim positron emission tomography-computed tomography scan revealed widespread resolution of the lymphadenopathy. The EBV viral PCR had also fallen [44]. The authors hypothesized that the SARS-CoV-2 infection triggered an antitumor immune response, as it has been described with other infections in the context of high-grade NHL. It is noteworthy that in both cases EBV reactivation was present.

A 61-year-old patient affected from follicular lymphoma also noted a shrinkage of a para-aortic lymph nodal lesion compared to baseline during SARS-CoV-2 infection [45]. Finally, complete spontaneous remission of diffuse large B-cell lymphoma of the maxillary sinus after concurrent SARS-CoV-2 infection was reported, with the patient's facial swelling resolving during the hospitalization[46].

Since these reports represent anecdotal observations, further data are needed to address or confirm the relationship between the virus and lymphoma subtypes as well its behavior in parallel to anti-neoplastic response.

CONCLUSION

In our opinion, our search for lymphoma patients among other cancer in the recent COVID-19 literature may deliver some important messages for the scientific community. The analysis we performed reveals that there is an increased risk of COVID-19 related serious events (ICU admission, mechanical ventilation support or death) in patients with lymphomas as compared to COVID-19 patients without cancer and confirms the high vulnerability of such patients in the current pandemic. Overall, among the HM series, lymphoma represented the commonest malignancy. In lymphoma patients COVID-19 presentation symptoms occurred a median of 5 to 6 d before hospitalization, being represented by fever, cough and dyspnea. The mortality rate, taking into account the different characteristics of the populations studied, and different lymphoma subtypes was relatively high, attesting at approximately 30% after 1-2 mo of follow-up, at least in hospitalized patients.

In a meta-analysis of hematologic malignancies and COVID-19 that incorporated data from more than 3000 patients, pooled risk of death for lymphomas was 32% [28].

Active disease at COVID-19 infection presentation or lymphoma status as progressive disease appeared to be among the strongest predictors of early death. Among histotypes, no definitive conclusions can be drawn, while the use of bendamustine (but not anti-CD20 antibodies) has been associated with increased risk of death in at least one study. Published results indicate that the start of treatment should not be delayed given that active treatment has not been associated to increased risk of mortality. Instead, achieving disease remission could lead to better outcomes. Currently, little is known about specific phenotypic and/or functional T cell changes associated with symptomatic and asymptomatic SARS-CoV-2 infection, as in patients treated with immune checkpoint inhibitors. In cancer patients[47,48], treatment with immune checkpoint inhibitors did not increase risk of adverse events compared to standard chemotherapy and did not seem to increase COVID-19 susceptibility. However, no data are reported on patients with lymphoma.

With several vaccines available, it would be extremely important to protect frail categories as soon as possible. The humoral response of patients with lymphoma to COVID-19 vaccines has been investigated by several groups[49]. Altogether, these data suggest that the humoral response in lymphoma patients is impaired as compared to other HM, especially after treatment with anti-CD20 containing therapies. Different vaccination strategies are therefore warranted for lymphoma patients. 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 patients with COVID-19 infection.

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