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B-cell malignancies treated with targeted drugs and SARS-CoV-2 infection: A European Hematology Association Survey (EPICOVIDEHA)

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Patients with lymphoproliferative diseases (LPD) are vulnerable to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Here, we describe and analyze the outcome of 366 adult patients with chronic lymphocytic leukemia (CLL) or non-Hodgkin Lymphoma (NHL) treated with targeted drugs and laboratory-confirmed COVID-19 diagnosed between February 2020 and January 2022. Median follow-up was 70.5 days (IQR 0-609). Most used targeted drugs were Bruton-kinase inhibitors (BKIs) (N= 201, 55%), anti-

CD20 other than rituximab (N=61, 16%), BCL2 inhibitors (N=33, 9%) and lenalidomide (N=28, 8%). Only 16.2% of the patients were vaccinated with 2 or more doses of vaccine at the onset of COVID-19. Mortality was 24% (89/366) on day 30 and 36% (134/366) on the last day of follow-up. Age >75 years ($p < 0.001$, HR 1.036), active malignancy ($p < 0.001$, HR 2.215), severe COVID-19 ($p = 0.017$, HR 2.270) and admission to ICU ($p < 0.001$, HR 5.751) were risk factors for mortality at last day of follow up. There was no difference in OS rates in NHL vs CLL patients ($p = 0.306$), nor in patients treated with or without BKIs ($p = 0.151$). Mortality in ICU was 66% (CLL 61%, NHL 76%). Overall mortality rate decreased according to vaccination status, being 39% in unvaccinated patients, 32% and 26% in those having received one or two doses, respectively, and 20% in patients with a booster dose ($p = 0.245$). Overall mortality rate dropped from 41% during the first semester of 2020 to 25% at the last semester of 2021. These results show increased severity and mortality from COVID-19 in LPDs patients treated with targeted drugs.

KEYWORDS

SARS-CoV-2, targeted drugs, infection risk, immune system COVID19, lymphoproliferative diseases (LPD), chronic lymphocytic leukemia (CLL), non-Hodgkin lymphoma (NHL)

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has challenged particularly vulnerable individuals such as those with cancer (1–4). Even among patients with cancer, the overall outcome, degree of immunodeficiency, and effect of cancer therapy on immunocompetence vary widely, leading to very different outcomes, depending on the underlying malignancy and its treatment.

Lymphoproliferative diseases (LPD) are a group of malignancy associated with a marked immunodeficiency, characterized by hypogammaglobulinemia, qualitative and quantitative B- and T-cell defects (5), CD4+ lymphopenia, as well as innate immune dysfunction and neutropenia (6). These immunodeficiencies are a result of the disease itself and its treatment, and lead to impaired immune response to common pathogens and poor response to vaccination (7, 8)

The introduction of targeted agents in the treatment of B-cell malignancies has changed their management. These therapies

attempt to harness power from the patient's immune system to eradicate lymphoma. In chronic lymphoid leukemia (CLL), oral Bruton tyrosine-kinase inhibitors (BKIs) such as ibrutinib and acalabrutinib, and the BCL2 inhibitor (venetoclax) have been increasingly used, replacing conventional chemotherapy in frontline treatment because of their improved progression-free survival (9–13). In indolent lymphomas, several phosphoinositide 3-kinase (PIK3) inhibitors have been approved in patients with relapse disease (14–16), but the use of these agents has been limited due to toxicities, including infection. A combination of lenalidomide and rituximab is a safe and effective therapy for patients with refractory indolent lymphoma (17). Anti-CD30 and anti-PD1 have improved the prognosis of naïve (18) and relapsed (19) Hodgkin lymphomas, and the new antibody conjugate polatuzumab vedotin has been introduced in the treatment of diffuse large B-cell lymphoma (20).

Targeted drugs differ from conventional chemotherapy regarding the risk for infection. Opportunistic infections have been reported in patients receiving ibrutinib (21). Therapy with idelalisib has been associated with an overall risk of infection, especially fungal (16, 22, 23), and in combination with rituximab-bendamustine (RB), high rates of cytomegalovirus (CMV) reactivation have been reported (24). By contrast, venetoclax does not seem to be associated with additional risks of infection (23). The risk of infection in patients with LPD treated with brentuximab (25, 26) are variable while neutropenia is a common side effect.

Abbreviations: BKIs, Bruton tyrosine-kinase inhibitors; CLL, chronic lymphocytic leukemia; COVID19 Coronavirus disease 2019; CMV, cytomegalovirus; HR, hazard ratio; IMiDs, immunomodulatory drugs; ICU, intensive care unit; IQR, Interquartile Range; LPD, lymphoproliferative diseases; NHL, non-Hodgkin lymphoma; OS, overall survival; PIK3, phosphoinositide 3-kinase; RT-PCR, reverse transcriptase-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RB, rituximab-bendamustine.

Focusing on COVID-19 infection, several studies have reported impaired serologic response after COVID-19 vaccination in CLL patients, especially those treated with anti-CD20 antibodies in the 12 months prior to infection, followed by BKIs and venetoclax-treated patients (27–29).

Several small series of CLL patients with COVID-19, mostly treated with ibrutinib, have been published to date, reporting a high rate of mortality and severity of infection (30, 31). Ibrutinib was initially thought to improve the outcome of COVID-19, based on retrospective studies (32, 33), but several subsequent clinical trials failed to confirm such benefit (34).

To date, only limited data are available on the clinical course of COVID-19 in patients with different underlying LPD treated with targeted drugs. We undertook a retrospective international multicenter study to evaluate the outcome of COVID-19 in patients with LPD treated with targeted drugs and in order to identify potential predictors of outcome.

Methods

In this retrospective observational, multicenter study, we collected data on adult patients with LPD who received targeted therapy and were diagnosed with COVID-19 between February 2020 and January 2022 across 25 countries that participated in the survey promoted by the European Hematology Association (EHA) – Scientific Working Group Infection in Hematology EPICOVIDEHA survey (35, 36). Targeted drugs included: BKIs (acalabrutinib, ibrutinib, zanabrutinib), BCL2 inhibitors (venetoclax), anti-CD20 antibodies (obinutuzumab, ofatumumab) anti-CD30 (brentuximab), anti-CD79 (polatuzumab), anti-PD1 (pembrolizumab, nivolumab), immunomodulatory drugs (IMiDs) (lenalidomide) and PI3K inhibitors (idelalisib). Patients treated with rituximab were not specifically included in this study as another analysis has been performed by the EPICOVIDEHA survey (35, 36). Confirmed cases of COVID-19 were defined by a positive reverse transcriptase-polymerase chain reaction (RT-PCR) assay of a specimen collected by a nasopharyngeal swab. Pandemic waves were defined in time as follows: January–June 2020 (n=108), July–December 2020 (n=144), January–June 2021 (n=62), July–January 2022 (n=52). Each institutional review board independently approved the study. The study was conducted following the Declaration of Helsinki. Researchers at each center collected data using an online questionnaire hosted at www.clinicalsurveys.net (EFS Fall 2018, Questback, Cologne, Germany). EPICOVIDEHA is registered at <http://www.clinicaltrials.gov>, with the identifier NCT 04733729. Only de-identified data were entered and analyzed. We obtained

demographic data, comorbidities, and underlying hematological disease including clinically significant outcomes (hospital admission and intensive care unit [ICU] admission, vital status) and COVID-19 management strategies. The severity of COVID-19 at admission was graded according to the China Centers for Disease Control and Prevention definitions: mild (non-pneumonia and mild pneumonia), severe (dyspnea, respiratory frequency ≥ 30 breaths per min, SpO₂ $\leq 93\%$, PaO₂/FiO₂ 50%), and critical (respiratory failure, septic shock, or multiple organ dysfunction or failure).

SPSSv25.0 was used for statistical analyses (SPSS, IBM Corp., Chicago, IL, United States). Categorical variables were presented as frequencies and percentages, while continuous variables by the median, interquartile range (IQR), and absolute range. Additionally, overall mortality was evaluated by a Cox proportional hazard model. A Univariable Cox regression model was performed including variables that potentially played a role in the mortality of patients. Variables with a p-value ≤ 0.1 were considered for the multivariable analysis. The Multivariable Cox regression model was calculated by the Wald backward method, and only statistically significant variables were reported. A p-value ≤ 0.05 was considered statistically significant.

Results

In the study period, we identified 366 patients with LPD receiving targeted drugs at diagnosis of COVID-19. The median age at COVID-19 diagnosis was 68 years (IQR 58–77, range 25–96).

Characteristics of the cohort

Baseline characteristics for the entire cohort are described in Table 1. Of the 366 patients, 204 (55.7%) were CLL and 162 (44.3%) NHL. The population had a male predominance (n=222, 60.7%). Contributing countries are listed in Figure 1. Around 33.1% (n=132) of the patients had two or more comorbidities: chronic cardiopathy (n=125, 34.2%), chronic pulmonary disease (n=80, 21.9%) and diabetes (n=64, 17.5%) were the most common ones.

Thirty-five percent (n=128) of the patients were receiving the targeted drug as first-line therapy, 29.8% (n=109) as 2nd line, 18.9% (n=69) as 3rd line, and 16.4% (n=60) had been heavily pretreated with 4 or more prior lines of therapy.

The most commonly used targeted drugs were BKIs (n=201, 54.9%), anti-CD20 other than rituximab (n=60, 16.4%), BCL2 inhibitors (n=33, 9%) and lenalidomide (n=28, 7.7%)

TABLE 1 Patients' characteristics.

Sex		
Female	144	39.3%
Male	222	60.7%
Age, (IQR), [range]		
18-25 years old	2	0.5%
26-50 years old	36	9.8%
51-69 years old	154	42.1%
≥ 70 years old	174	47.5%
Comorbidities before COVID-19		
No comorbidities	121	33.1%
1 comorbidity	113	30.9%
2 comorbidities	90	24.6%
3 or more comorbidities	42	11.5%
<i>Chronic cardiopathy</i>	125	34.2%
<i>Chronic pulmonary disease</i>	80	21.9%
<i>Diabetes</i>	64	17.5%
<i>Liver disease</i>	16	4.4%
<i>Renal impairment</i>	26	7.1%
<i>Obesity</i>	23	6.3%
<i>Smoking history</i>	43	11.7%
<i>No risk factor identified</i>	116	31.7%
Malignancy		
Chronic lymphoid leukemia	204	55.7%
Non-Hodgkin lymphoma	162	44.3%
Malignancy status at COVID-19 diagnosis		
Controlled malignancy	213	58.2%
<i>Complete remission</i>	92	25.1%
<i>Partial remission</i>	121	33.1%
Stable malignancy	59	16.1%
Active malignancy	84	23.0%
<i>Onset</i>	15	4.1%
<i>Refractory/Resistant</i>	69	18.9%
Unknown	10	2.7%
Time last chemotherapy before COVID-19		
In the last month	255	69.7%
In the last 3 months	52	14.2%
Chemotherapy ended > 3 months before COVID-19	57	15.6%
# lines until COVID-19 onset		
1 line	128	35.0%
2 lines	109	29.8%
3 lines	69	18.9%
4 lines	30	8.2%
>4 lines	30	8.2%
Neutrophils at COVID-19 onset		
≤ 500	15	4.1%
501 - 999	17	4.6%
≥ 1000	285	77.9%
Lymphocytes at COVID-19 onset		
≤ 200	22	6.0%

(Continued)

TABLE 1 Continued

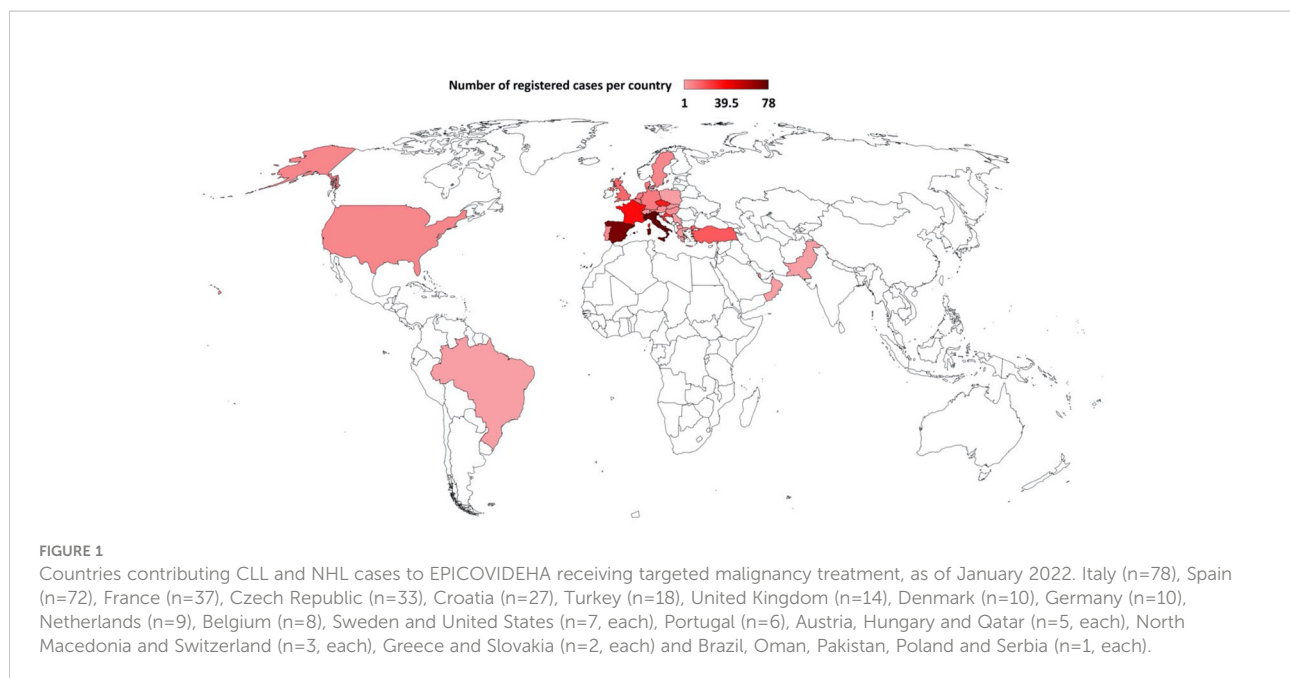
Sex		
201 - 499	43	11.7%
≥ 500	249	68.0%
Last vaccination before COVID-19		
Not vaccinated	288	78.7%
One dose	19	5.2%
Two doses	54	14.8%
Three doses	5	1.4%
Last type of vaccination before COVID-19		
mRNA	65	17.8%
<i>BioNTech/Pfizer</i>	53	14.5%
<i>Moderna COVE</i>	12	3.3%
Vector-based	11	3.0%
<i>AstraZeneca Oxford</i>	9	2.5%
<i>Sputnik</i>	1	0.3%
<i>J&J - Janssen</i>	1	0.3%
Inactivated	2	0.5%
<i>CoronaVac Sinovac</i>	2	0.5%
COVID-19 severity		
Asymptomatic	59	16.1%
Mild infection	53	14.5%
Severe infection	174	47.5%
Critical infection	80	21.9%
COVID-19 symptoms at onset		
Pulmonary	135	36.9%
Pulmonary + Extrapulmonary	107	29.2%
Extrapulmonary	62	16.9%
Screening	62	16.9%
Stay during COVID-19 episode		
Home	106	29.0%
Hospital	277	75.7%
ICU	80	21.9%
Invasive mechanical ventilation	55	15.0%
Non-invasive mechanical ventilation	29	7.9%
Outcome		
Mortality	134	36.6%
COVID-19	92	25.1%
COVID-19 + Hematological malignancies	28	7.7%
Hematological malignancies ± other reason(s)	14	3.8%

(Table 2). Of note, only 21.0% of the patients had received two or more doses of SARS-CoV-2 vaccine at the onset of COVID-19: mRNA vaccines were administered in 83% patients. Respiratory symptoms were present in 66.1% of patients (n= 242) while 16.9% (n= 62) presented with extrapulmonary symptoms. Of note, our series includes 16.9% (n=62) asymptomatic COVID-19 patients detected upon screening.

The majority of patients (n=277, 75.7%) were hospitalized, with a median stay of 16 days (IQR 8-26, range, 1-137).

Factors associated with severe COVID-19

Severe COVID-19 was observed in 47.5% (n=174) of patients, including 21.9% (n=80) who were admitted to intensive care unit (ICU). Among the latter, 55 (68.8%) were CLL patients, and 25 (31.3%) were non-Hodgkin lymphoma (NHL) patients. Fifty-five (44%) of the ICU-admitted patients underwent invasive mechanical ventilation. The median ICU stay in the entire cohort was 9 days (IQR 2-50, range, 6-14).



The presence of comorbidities was significantly associated with severe COVID-19 infection in the entire cohort ($p=0.002$) as well as in the CLL and NHL subsets and BKIs cohort. Severe infection was more frequent in the first COVID-19 pandemic wave comparing to more recent waves ($p=0.001$). Another factor associated with severe infection was male sex ($p=0.001$). Age (both >65 or >75), type of targeted drug therapy and time from the last treatment of the hematologic malignancy to COVID-19 infection were not associated with severe infection in any subgroup analysis. No significant risk factor for severe COVID-19 was found in patients receiving BLC-2 inhibitors plus anti-CD20 monoclonal antibodies.

Factors associated with mortality

Overall, 134 patients (36.6%) died (Table 3). The primary cause of death was COVID-19 in 92 patients (68.7%), LPD in 14 patients (10.4%), and a combination of both in 28 patients (20.9%). The mortality rate was 24.3% (89/366) on day 30 of COVID-19 diagnosis and 36.6% (134/366) on the last day of follow-up. The median follow-up at the time of this analysis was 70.5 days (IQR 19-159, range 0-609 days). Distribution of registered cases along time is shown in Figure 2.

Survival in patients admitted to ICU was 33.7% (CLL 38.1%, NHL 24%). The overall mortality rate decreased with vaccination, being 34.2% in unvaccinated patients, 15.9-18% with one or two doses, and 9.7% in patients with a booster dose ($p<0.001$) (Figure 3). Additionally, the mortality rate dropped from the first semester of 2020 (41.3%) to the last semester of 2021 (25%).

Table 4A summarizes the univariable and multivariable analyses of baseline characteristics as predictors of OS in the entire cohort and in the subsets of CLL and NHL patients (Tables 4B, C in supplementary materials). In univariable analysis, age >75 years, active hematological disease, severe and critical COVID-19 infection, heart disease, and renal impairment were associated with an increased mortality rate.

By multivariable analysis, age >75 years (hazard ratio [HR] 1.036, 95% confidence interval [CI] 1.019-1.052, $p<0.001$), active hematological malignancy (HR 2.215, 95% CI 1.501-3.267, $p<0.001$), severe COVID-19 disease (HR 2.270, 95% CI 1.156-4.460 $p=0.017$) and critical COVID-19 disease (HR 5.751, 95% CI 2.875-11.506, $p<0.001$) remained as risk factors for mortality in the entire cohort. All factors remained significant for NHL, while in CLL patients all but active malignancy was significant.

There was no difference in OS in NHL vs CLL patients ($p=0.344$), in BKIs vs no BKIs-treated patients ($p=0.137$), nor when comparing patients treated with different targeted drugs ($p=0.343$) (Figure 4). We did not observe a clear protective or detrimental effect of BKIs on the outcome when compared with other targeted drugs.

Discussion

To the best of our knowledge, we describe a large international series of LPD patients receiving targeted drug treatment at the time of COVID-19 infection. The rates of severe infection and overall mortality were 47.5% and 36.6%, respectively. The presence of comorbidities and lack of vaccination were associated with higher mortality rate. Prior

TABLE 2 LPD directed therapy at time of COVID-19 diagnosis.

Anti-CD20 ± combination	60	16.4%
Obinutuzumab	58	15.8%
Ofatumumab	1	0.3%
Obinutuzumab + Lenalidomide	1	0.3%
Anti-CD30 ± combination	16	4.4%
Brentuximab	15	4.1%
Brentuximab + Nivolumab	1	0.3%
Anti-CD79	5	1.4%
Polatuzumab	5	1.4%
Anti-PD1	3	0.8%
Nivolumab	1	0.3%
Pembrolizumab	2	0.5%
BCL2 ± combination	33	9.0%
Venetoclax	27	7.4%
Obinutuzumab + Venetoclax	6	1.6%
IMiDs	28	7.7%
Lenalidomide	28	7.7%
BTKs ± combination	201	54.9%
Ibrutinib	172	47.0%
Acalabrutinib	6	1.6%
Zanabrutinib	8	2.2%
Ibrutinib + Obinutuzumab	1	0.3%
Ibrutinib + Venetoclax	9	2.5%
Ibrutinib + Acalabrutinib	1	0.3%
Idelalisib + Acalabrutinib	1	0.3%
Obinutuzumab + Zanabrutinib	1	0.3%
Venetoclax + Acalabrutinib	2	0.5%
PI3K inhibitor	17	4.6%
Idelalisib	17	4.6%
Other treatment combinations	3	0.8%
Ibrutinib + Obinutuzumab + Venetoclax	1	0.3%
Ibrutinib + Idelalisib + Venetoclax	1	0.3%
Obinutuzumab + Venetoclax + Acalabrutinib	1	0.3%

vaccination was a protective factor. There were no significant differences in mortality across different targeted drugs. Patients treated with targeted chemotherapy were matched to controls treated with any other strategy for hematological malignancy before COVID-19. Cases and controls were matched in age, sex, hematological malignancy, malignancy status at COVID-19 and time of last chemotherapy strategy before COVID-19 (<3 months or >3 months). No statistically significant differences were observed in mortality probability between groups (p=0.056).

Patients with hematological malignancy have been heavily hit by the COVID-19 pandemic, and several reports confirm high rates of severe disease and mortality (2–4). Patients with B-malignancies have been particularly affected due to their intrinsic immune dysregulation (30, 31, 37–39). Moreover, the potential impact of LPD targeted therapies on the course of COVID-19 still needs to be fully understood.

The high mortality rates in our series appear similar to that of other series of hematological patients with COVID-19 infection (30, 31, 40–42). Surprisingly, despite the number of asymptomatic patients included in our study (diagnosed through screening for COVID-19) the rates of hospital admission and ICU admission were high. This data suggests that our cohort is at high risk of severe/critical COVID-19 when admitted to the hospital for symptomatic COVID-19.

Vaccination reduced mortality in our series, even after only 2 doses. Doubts have been raised about the efficacy of vaccination in patients with altered B cell immunity. Specifically in patients treated with anti-CD20, BKIs, or venetoclax, data demonstrating seroconversion failure after COVID-19 vaccination have been published (43, 44). Despite the lack of seroprevalence data in our series, we do consider that the COVID vaccines were a protective prognostic factor against mortality in these patients as mortality rates decreased as their vaccination status was increasing.

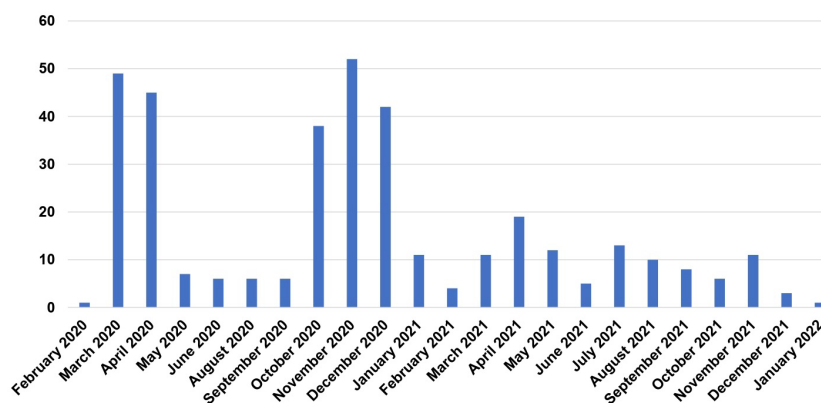
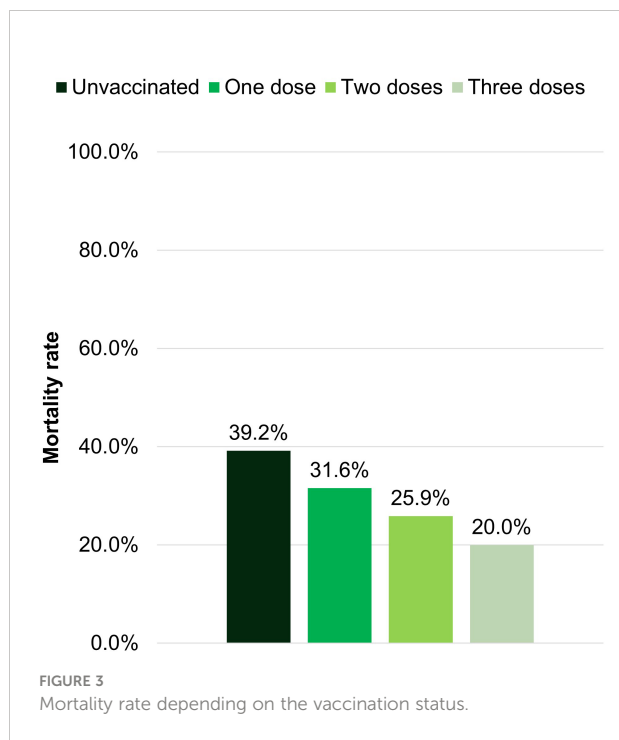


FIGURE 2 Distribution of registered cases along time.

TABLE 3 Patient's disposition based on mortality.

	Alive		Dead		p value
	n	%	n	%	
Sex					0.294
Female	96	66.7%	48	33.3%	
Male	136	61.3%	86	38.7%	
Age					0.001
<65 years old	111	73.0%	41	27.0%	
≥65 years old	121	56.5%	93	43.5%	
Comorbidities before COVID-19					
Chronic cardiopathy	71	56.8%	54	43.2%	0.06
Chronic pulmonary disease	47	58.8%	33	41.3%	0.33
Diabetes	38	59.4%	26	40.6%	0.463
Liver disease	10	62.5%	6	37.5%	0.94
Renal impairment	7	26.9%	16	61.5%	<0.001
Obesity	18	78.3%	8	34.8%	0.521
Smoking history	24	55.8%	19	44.2%	0.272
No risk factor identified	79	68.1%	37	31.9%	0.202
Time last chemotherapy before COVID-19					0.658
In the last month	158	62.0%	97	38.0%	
In the last 3 months	33	63.5%	19	36.5%	
Chemotherapy ended > 3 months before COVID-19	39	68.4%	18	31.6%	
Malignancy status at COVID-19 diagnosis					0.003
Controlled disease	146	68.5%	67	31.5%	
Stable disease	40	67.8%	19	32.2%	
Active disease	40	47.6%	44	52.4%	



The mortality rate has decreased across the different COVID-19 waves, possibly reflecting improvements in patients care and the development of COVID-19 treatments: while we did not specifically examine COVID-19 treatment in our cohort, we can speculate that the early initiation of corticosteroids, heparin and the introduction of tocilizumab in the management of these patients might have improved the outcome. At the beginning of the pandemic, there was some reluctance about the use of corticosteroids and tocilizumab in hematological patients, due to the fear of stressing their immunodepression. Over time, the early initiation of those therapies was beneficial in those patients as well as the general population.

In our study, we did not find any association between specific targeted drugs and mortality. The majority of patients in our cohort were treated with BKIs. In the initial phase of the pandemic, some data suggested that BKIs could modulate the immune response to COVID-19 infection through blockade of inflammatory cytokines in the lungs, with a reduction of hyperinflammatory response (45, 46). The widespread use of early dexamethasone treatment in patients with severe COVID-19, based on the RECOVERY trial (47), achieved a more effective suppression of the host humoral response through the downregulation of proinflammatory cytokine production. We

TABLE 4A Univariable and multivariable analysis of predictors of mortality in the entire cohort.

	Univariable				Multivariable			
	p value	HR	95% CI		p value	HR	95% CI	
			Lower	Upper			Lower	Upper
Sex								
Female	-	-	-	-				
Male	0.336	1.191	0.835	1.698				
Age	<0.001	1.029	1.014	1.045	<0.001	1.036	1.019	1.052
Status malignancy at COVID-19 diagnosis								
Controlled malignancy	-	-	-	-	-	-	-	-
Stable malignancy	0.893	1.036	0.622	1.724	0.830	0.945	0.561	1.590
Active malignancy	0.003	1.798	1.222	2.646	<0.001	2.215	1.501	3.267
Malignancy								
Chronic lymphoid leukemia	-	-	-	-				
Non-Hodgkin lymphoma	0.330	1.185	0.842	1.669				
COVID-19 infection								
Asymptomatic	-	-	-	-	-	-	-	-
Mild	0.899	1.056	0.458	2.435	0.718	1.176	0.488	2.834
Severe	0.043	1.948	1.021	3.714	0.017	2.270	1.156	4.460
Critical	<0.001	4.563	2.376	8.764	<0.001	5.751	2.875	11.506
Chronic cardiopathy	0.025	1.491	1.052	2.113	0.775	1.056	0.726	1.536
Chronic pulmonary disease	0.393	1.188	0.800	1.763				
Diabetes mellitus	0.615	1.116	0.727	1.715				
Liver disease	0.837	1.090	0.480	2.474				
Obesity	0.820	0.920	0.450	1.882				
Renal impairment	<0.001	2.705	1.577	4.638	0.086	1.667	0.929	2.992
Smoking history	0.482	1.190	0.732	1.936				
Neutrophils								
≤ 500	-	-	-	-				
501 - 999	0.987	1.008	0.398	2.555				
≥ 1000	0.107	0.553	0.269	1.137				
Lymphocytes								
≤ 200	-	-	-	-				
201 - 499	0.874	1.067	0.479	2.375				
≥ 500	0.918	0.965	0.487	1.913				
Time last chemotherapy								
In the last month	-	-	-	-				
In the last 3 months	0.975	1.008	0.616	1.649				
>3 months before COVID-19	0.313	0.767	0.458	1.284				
Chemotherapy lines before COVID-19								
1	-	-	-	-				
2	0.062	1.516	0.979	2.347				
3	0.158	1.441	0.868	2.395				
4	0.043	1.886	1.020	3.489				
>4	0.061	1.867	0.972	3.584				
SARS-CoV-2								
α mutation (Alpha)	-	-	-	-				
β mutation (Beta)	0.837	1.121	0.376	3.343				
Wild type	0.953	1.032	0.367	2.902				

(Continued)

TABLE 4A Continued

	Univariable				Multivariable			
	p value	HR	95% CI		p value	HR	95% CI	
			Lower	Upper			Lower	Upper
Not tested/Unknown	0.880	1.065	0.468	2.426				
Vaccine doses before COVID-19								
No vaccination	-	-	-	-				
One dose	0.972	1.015	0.445	2.312				
Two doses	0.829	0.940	0.537	1.646				
Three doses	0.867	0.845	0.118	6.068				
Time last vaccination to COVID-19								
≤14 days before COVID-19	-	-	-	-				
>14 days before COVID-19	0.732	1.190	0.439	3.222				
COVID-19 treatment								
No treatment	-	-	-	-				
Antivirals +/- corticosteroids +/- plasma	0.292	1.752	0.617	4.974				
Monoclonal antibodies +/- corticosteroids +/- plasma	0.659	1.623	0.189	13.925				
Antivirals + monoclonal antibodies +/- corticosteroids +/- plasma	0.544	1.444	0.440	4.740				
Corticosteroids	0.022	3.119	1.180	8.246				
Plasma +/- corticosteroids	0.632	0.591	0.069	5.063				
Unknown	0.198	1.810	0.734	4.460				

TABLE 4B Univariable and multivariable analysis of predictors of mortality in the CLL patients.

	CLL							
	Univariable				Multivariable			
	p value	HR	95% CI		p value	HR	95% CI	
Lower			Upper	Lower			Upper	
Sex								
Female	-	-	-	-				
Male	0.381	1.262	0.750	2.124				
Age	0.010	1.031	1.008	1.056	0.002	1.040	1.015	1.066
Status malignancy at COVID-19 diagnosis								
Controlled malignancy	-	-	-	-				
Stable malignancy	0.977	1.009	0.548	1.859				
Active malignancy	0.146	1.594	0.850	2.989				
Malignancy								
Chronic lymphoid leukemia								
Non-Hodgkin lymphoma								
COVID-19 infection								
Asymptomatic	-	-	-	-	-	-	-	-
Mild	0.911	0.913	0.184	4.523	0.988	0.988	0.199	4.897
Severe	0.057	3.162	0.964	10.366	0.053	3.227	0.984	10.582
Critical	0.001	7.090	2.170	23.162	<0.001	8.251	2.516	27.062
Chronic cardiopathy	0.081	1.532	0.949	2.472	0.480	1.200	0.723	1.991
Chronic pulmonary disease	0.435	1.235	0.728	2.095				

(Continued)

TABLE 4B Continued

	CLL							
	Univariable				Multivariable			
	p value	HR	95% CI		p value	HR	95% CI	
			Lower	Upper			Lower	Upper
Diabetes mellitus	0.704	0.890	0.486	1.627				
Liver disease	0.294	1.629	0.655	4.049				
Obesity	0.804	1.112	0.481	2.571				
Renal impairment	<0.001	3.310	1.690	6.486	0.123	1.770	0.857	3.653
Smoking history	0.885	1.049	0.550	1.999				
Neutrophils								
≤ 500	-	-	-	-				
501 - 999	0.563	0.655	0.156	2.747				
≥ 1000	0.133	0.409	0.127	1.313				
Lymphocytes								
≤ 200	-	-	-	-				
201 - 499	0.127	5.009	0.634	39.609				
≥ 500	0.333	2.660	0.367	19.271				
Time last chemotherapy								
In the last month	-	-	-	-				
In the last 3 months	0.512	0.736	0.295	1.839				
>3 months before COVID-19	0.608	0.832	0.411	1.683				
Chemotherapy lines before COVID-19								
1	-	-	-	-				
2	0.063	1.739	0.971	3.114				
3	0.618	1.202	0.583	2.476				
4	0.082	2.398	0.894	6.432				
>4	0.221	1.851	0.691	4.962				
SARS-CoV-2								
α mutation (Alpha)	-	-	-	-				
β mutation (Beta)	0.853	1.140	0.285	4.563				
Wild type	0.684	0.750	0.187	3.000				
Not tested/Unknown	0.523	0.718	0.260	1.982				
Vaccine doses before COVID-19								
No vaccination	-	-	-	-				
One dose	0.759	1.172	0.425	3.237				
Two doses	0.946	1.026	0.488	2.159				
Three doses	0.815	1.267	0.175	9.173				
Time last vaccination to COVID-19								
≤14 days before COVID-19	-	-	-	-				
>14 days before COVID-19	0.847	0.892	0.280	2.841				
COVID-19 treatment								
No treatment	-	-	-	-				
Antivirals +/- corticosteroids +/- plasma	0.510	1.736	0.337	8.950				
Monoclonal antibodies +/- corticosteroids +/- plasma	0.974	0.000	0.000	.				
Antivirals + monoclonal antibodies +/- corticosteroids +/- plasma	0.185	3.158	0.577	17.278				
Corticosteroids	0.033	4.983	1.139	21.810				
Plasma +/- corticosteroids	0.690	1.629	0.148	17.978				
Unknown	0.226	2.402	0.581	9.923				

TABLE 4C Univariable and multivariable analysis of predictors of mortality in the NHL patients.

	NHL							
	Univariable				Multivariable			
	p value	HR	95% CI		p value	HR	95% CI	
			Lower	Upper			Lower	Upper
Sex								
Female	-	-	-	-				
Male	0.536	1.170	0.711	1.926				
Age	0.002	1.031	1.011	1.052	<0.001	1.045	1.023	1.067
Status malignancy at COVID-19 diagnosis								
Controlled disease	-	-	-	-	-	-	-	-
Stable disease	0.912	1.056	0.406	2.742	0.940	0.964	0.368	2.524
Active disease	0.017	1.885	1.121	3.170	0.001	2.363	1.391	4.016
Malignancy								
Chronic lymphoid leukemia								
Non-Hodgkin lymphoma								
COVID-19 infection								
Asymptomatic	-	-	-	-	-	-	-	-
Mild	0.589	1.311	0.491	3.499	0.352	1.623	0.585	4.503
Severe	0.269	1.559	0.710	3.424	0.111	1.977	0.855	4.572
Critical	0.002	3.817	1.666	8.744	<0.001	5.969	2.450	14.543
Chronic cardiopathy	0.106	1.522	0.915	2.534				
Chronic pulmonary disease	0.596	1.175	0.648	2.131				
Diabetes mellitus	0.158	1.554	0.843	2.862				
Liver disease	0.332	0.375	0.052	2.721				
Obesity	0.477	0.599	0.146	2.453				
Renal impairment	0.207	1.815	0.719	4.584				
Smoking history	0.175	1.676	0.795	3.530				
Neutrophils								
≤ 500	-	-	-	-				
501 - 999	0.374	1.761	0.505	6.135				
≥ 1000	0.560	0.760	0.301	1.916				
Lymphocytes								
≤ 200	-	-	-	-				
201 - 499	0.252	0.573	0.221	1.486				
≥ 500	0.669	0.848	0.398	1.806				
Time last chemotherapy								
In the last month	-	-	-	-				
In the last 3 months	0.662	1.145	0.623	2.104				
>3 months before COVID-19	0.357	0.700	0.328	1.495				
Chemotherapy lines before COVID-19								
1	-	-	-	-				
2	0.521	1.247	0.635	2.447				
3	0.147	1.702	0.830	3.487				
4	0.234	1.627	0.730	3.625				
>4	0.174	1.836	0.764	4.415				
SARS-CoV-2								
α mutation (Alpha)	-	-	-	-				
β mutation (Beta)	0.791	1.274	0.212	7.669				

(Continued)

TABLE 4C Continued

	NHL							
	Univariable			Multivariable				
	p value	HR	95% CI		p value	HR	95% CI	
			Lower	Upper			Lower	Upper
Wild type	0.608	1.536	0.297	7.935				
Not tested/Unknown	0.420	1.791	0.435	7.375				
Vaccine doses before COVID-19								
No vaccination	-	-	-	-				
One dose	0.766	0.807	0.196	3.323				
Two doses	0.692	0.841	0.358	1.976				
Three doses	0.968	0.000	0.000	.				
Time last vaccination to COVID-19								
≤14 days before COVID-19	-	-	-	-				
>14 days before COVID-19	0.441	2.176	0.301	15.713				
COVID-19 treatment								
No treatment	-	-	-	-				
Antivirals +/- corticosteroids +/- plasma	0.312	2.014	0.519	7.818				
Monoclonal antibodies +/- corticosteroids +/- plasma	0.282	3.494	0.357	34.211				
Antivirals + monoclonal antibodies +/- corticosteroids +/- plasma	0.665	0.672	0.111	4.060				
Corticosteroids	0.309	2.032	0.519	7.960				
Plasma +/- corticosteroids	0.969	0.000	0.000	.				
Unknown	0.466	1.549	0.477	5.027				

did not find significant differences in OS among patients treated or not with BKIs, independently from the time of the initiation of the drug, nor in the most prevalent cohorts of targeted patients after BKIs: BCL2-inhibitors and anti- CD20. In addition, due to the limited number of patients treated with other therapies, we cannot draw any conclusion about their role in this asset.

In the present series, age >75 years, severe and critical COVID-19 infection, and active hematological disease were independent predictors of mortality. This is consistent with recent data from the EPICOVIDEHA (36) survey that described, in addition to those, other risk factors for mortality such as chronic cardiac disease, liver disease, renal impairment, smoking history, and ICU stay in a cohort of patients with various hematological malignancies. Description of risk factors in hematological patients is of great importance to identify patients at high risk and implement rapidly prophylactic measures such as vaccination, masking, social distancing, and antiCOVID19 specific prevention and treatment.

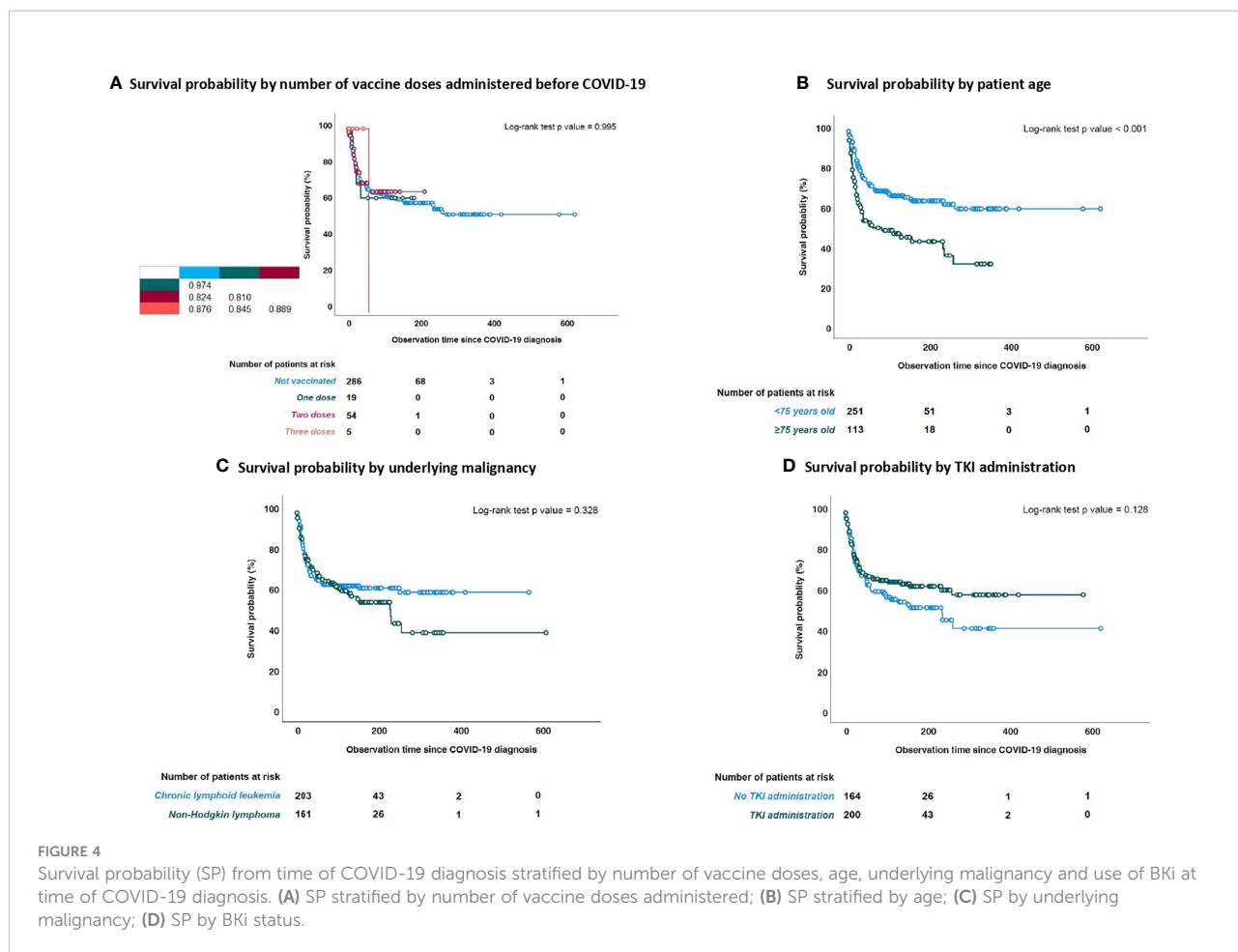
Limitations of our study include its retrospective design, which implies dependence on the accuracy of medical records, and possible selection bias. The heterogeneity of underlying diseases and drug exposure could be another limitation, as a confounding factor for infection risk in this series. We could not perform a direct comparison between targeted drug-treated

patients and chemotherapy patients as those groups would be too heterogeneous to compare.

Another limitation is the lack of patients from the latest waves infected with the delta and omicron variants and an analysis to determine if the new vaccine boosters can continue to reduce mortality in those patients. Specifically, patients treated with anti-CD20, BTKi, and BCL2-inhibitors were seroconversion failure after COVID-19 vaccination have been described, could be considered to receive early treatment with antivirals and monoclonal antibodies (48–50) or pre-exposure prophylaxis (51).

We acknowledge the potential underscoring of the real incidence of COVID-19 in this population, as we included asymptomatic patients with positive screening for COVID-19 while we must account for several asymptomatic patients not tested and therefore not diagnosed.

Our contribution is the largest international multicentric series of LPD patients under targeted drug treatment with COVID-19 infection, with a long follow-up, providing real-world evidence for increased severe disease and mortality from COVID-19 in patients with LPD treated with targeted drugs. Targeted drugs do not seem to have an impact on the survival of these patients. Efforts to prevent and aggressively manage COVID-19 should be focused on patients at a high risk of developing COVID-19 complications such as those older than 75 years, with comorbidities, especially heart disease, and active malignancy at COVID-19 onset. The importance of



vaccination should be stressed, even in this population with humoral immunity impairment where it was a protective factor for mortality. New insights into the management of the infection throughout the pandemic and the development of COVID-19 treatments showed benefits in this particularly vulnerable population.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The EPICOVIDEHA study has been approved by the local Institutional Review Board and Ethics Committee of the Fondazione Policlinico Universitario Agostino Gemelli—IRCCS, Università Cattolica del Sacro Cuore of Rome, Italy (Study ID: 3226). The corresponding local ethics committee of each participating institution may approve additionally the

EPICOVIDEHA study when applicable. EPICOVIDEHA is registered at <http://www.clinicaltrials.gov>, with the identifier (NCT number): NCT 04733729. The patients/participants provided their written informed consent to participate in this study.

Author contributions

MI, JS-G and AF-C contributed to the study conception and design. All authors contributed to data collection. Material preparation and analysis were performed by JS-G. The first draft of the manuscript was written by MI and JS-G and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest of this work.

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