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The evolving landscape of COVID-19 and post-COVID condition in patients with chronic lymphocytic leukemia: A study by ERIC, the European research initiative on CLL

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Abstract

In this retrospective international multicenter study, we describe the clinical characteristics and outcomes of patients with chronic lymphocytic leukemia (CLL) and related disorders (small lymphocytic lymphoma and high-count monoclonal B lymphocytosis) infected by SARS-CoV-2, including the development of post-COVID condition. Data from 1540 patients with CLL infected by SARS-CoV-2 from January 2020 to May 2022 were included in the analysis and assigned to four phases based on cases disposition and SARS-CoV-2 variants emergence. Post-COVID condition was defined according to the WHO criteria. Patients infected during the most recent phases of the pandemic, though carrying a higher comorbidity burden, were less often hospitalized, rarely needed intensive care unit admission, or died compared to patients infected during the initial phases. The 4-month overall survival (OS) improved through the phases, from 68% to 83%, $p = .0015$. Age, comorbidity, CLL-directed treatment, but not vaccination status, emerged as risk factors for mortality. Among survivors, 6.65% patients had a reinfection, usually milder than the initial one, and 16.5% developed post-COVID condition. The latter was characterized by fatigue, dyspnea, lasting cough, and impaired concentration. Infection severity was the only risk factor for developing post-COVID. The median time to resolution of the post-COVID condition was 4.7 months. OS in patients with CLL improved during the different phases of the pandemic, likely due to the improvement of prophylactic and therapeutic measures against SARS-CoV-2 as well as the emergence of milder variants. However, mortality remained relevant and a significant number of patients developed post-COVID conditions, warranting further investigations.

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ERIC Cooperative Group members are listed in Appendix A.

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1 | INTRODUCTION

In late 2019, a new Coronavirus (SARS-CoV-2) started causing a severe respiratory infection termed COVID-19, characterized by a heterogeneous clinical course, ranging from an asymptomatic disease to an acute multisystem illness.[1,2] During the past 2 years, different SARS-CoV-2 variants emerged and alternated during the pandemic. It soon became clear that patients suffering from cancer and COVID-19, in particular those with hematological malignancies, experienced a dismal outcome.[3,4] Studies conducted early in the pandemic showed that patients with chronic lymphocytic leukemia (CLL) had a high risk of severe COVID-19 and death.[5–7] In particular, older age, comorbidities, and CLL-directed treatment were associated with inferior overall survival (OS) among patients with CLL.[5,6] The emergence of the milder Omicron variant, the advent of vaccines against SARS-COV-2, along with the improved care of COVID-19 patients led to a decrease of the overall mortality rates, including in patients with CLL.[8–12]

Almost 10% of all patients with COVID-19 can develop persistent and often relapsing/remitting symptoms after acute infection,[13] termed as post-COVID condition.[14] Although SARS-CoV-2 infection remains a worldwide health problem and post-COVID condition is becoming a concern for survivors,[15–17] only a few studies have analyzed their long-term impact in patients with hematological malignancies.[15] Furthermore, the risk factors contributing to the development of post-COVID in these patients remain elusive.

In this study, we expanded our retrospective international multicenter cohort to reassess the risk factors for COVID-19-related fatality and investigate the outcomes of COVID-19 during the different pandemic waves, as well as the features of post-COVID complications in patients with CLL/small lymphocytic lymphoma (SLL) and high-count monoclonal B-cell lymphocytosis (MBL) infected by SARS-CoV-2.

2 | MATERIALS AND METHODS

2.1 | Study design and data collection

This is a retrospective international multicenter study by ERIC, the European Research Initiative on CLL. We expanded our previous cohort of patients with COVID-19 and CLL/SLL or high-count CLL-like MBL, a pre-CLL condition also characterized by an increased risk of COVID-19.[18] Diagnosis, treatment decisions, review of medical history, molecular and cytogenetic analysis, and assessment of patient status were performed by the local teams following international guidelines.[19–24]

This study was approved by the local institutional ethics committees and data were processed and treated lawfully and fairly in a transparent manner that ensured the appropriate security of the personal data, abiding by the General Data Protection Regulation. Informed consent was obtained from all patients who survived the infection from the beginning of the pandemic until May 2022. This study is the continuation of previous works conducted during the first two waves of the pandemic.[5–7]

2.2 | COVID-19 infection and post-COVID

In keeping with international practice, patients were deemed to have COVID-19 if a qRT-PCR assay test from a throat and/or nose swab was positive for SARS-CoV-2 RNA. Patients with antigenic test positivity were confirmed by qRT-PCR. Date of COVID-19 resolution, that is, negative swab, and of discharge were also collected. Severe COVID-19 was defined as infection requiring hospitalization with need of oxygen or admission into an intensive care unit (ICU); non-severe/mild COVID-19 was defined when confinement at home or hospitalization without need of oxygen were adequate. Based on the disposition of cases in our cohort and SARS-CoV-2 variant emergence,[25] we identified four phases: January 1, 2020–June 2020, July 2, 2020–February 2021, March 3, 2021–December 2021, and January 4, 2022–May 2022 (Figure 1A).

Post-COVID was defined according to the WHO definition as a condition occurring in individuals with a history of SARS-CoV-2 infection, usually 3 months from the onset of COVID-19, with symptoms not explained by an alternative diagnosis.[14,26] All recorded symptoms and their median resolution time are listed in the Supporting Information (Table S1).

2.3 | Statistical analysis

Median and interquartile range (IQR) were used to describe numeric variables, while frequencies and percentages were used for categorical. Both univariate and multivariate analyses were carried out, having hospitalization, mortality, OS, or post-COVID as outcomes. For COVID-19 disease severity and mortality, χ^2 test or Fisher's exact test were used for univariate analyses with categorical risk factors, while logistic regression was used for both the univariate with numeric risk factors and the multivariate. When necessary, we performed bias reduction techniques to the logistic model estimates by adjusting Firth's logistic regression. For the comparisons of the numeric risk factors between the four waves, one-way ANOVA was conducted. The homogeneity of variance between the groups was examined through Levene's test. For the categorical risk factors, χ^2 test or Fisher's exact test were used. For the multivariate analyses, we performed a two-level variable selection approach. At first, we obtained the risk factors with p-value ≤.2 from univariate analyses and used them as risk factors for a multivariate model. We further explored the multivariate model by performing backward elimination using Akaike's Information Criterion (AIC). OS was calculated as months from COVID-19 diagnosis to death or last available follow-up. The log-rank test was used for the univariate analyses and Cox regression was conducted for the multivariate of OS. The cumulative incidence of post-COVID-19 was calculated as months from SARS-CoV-2 infection to post-COVID syndrome or last available follow-up. All statistical analyses were conducted using R 4.1.3. The used packages have been previously reported.[5] The significance level was set to 5%. In post-hoc comparisons, the Bonferroni correction was used.

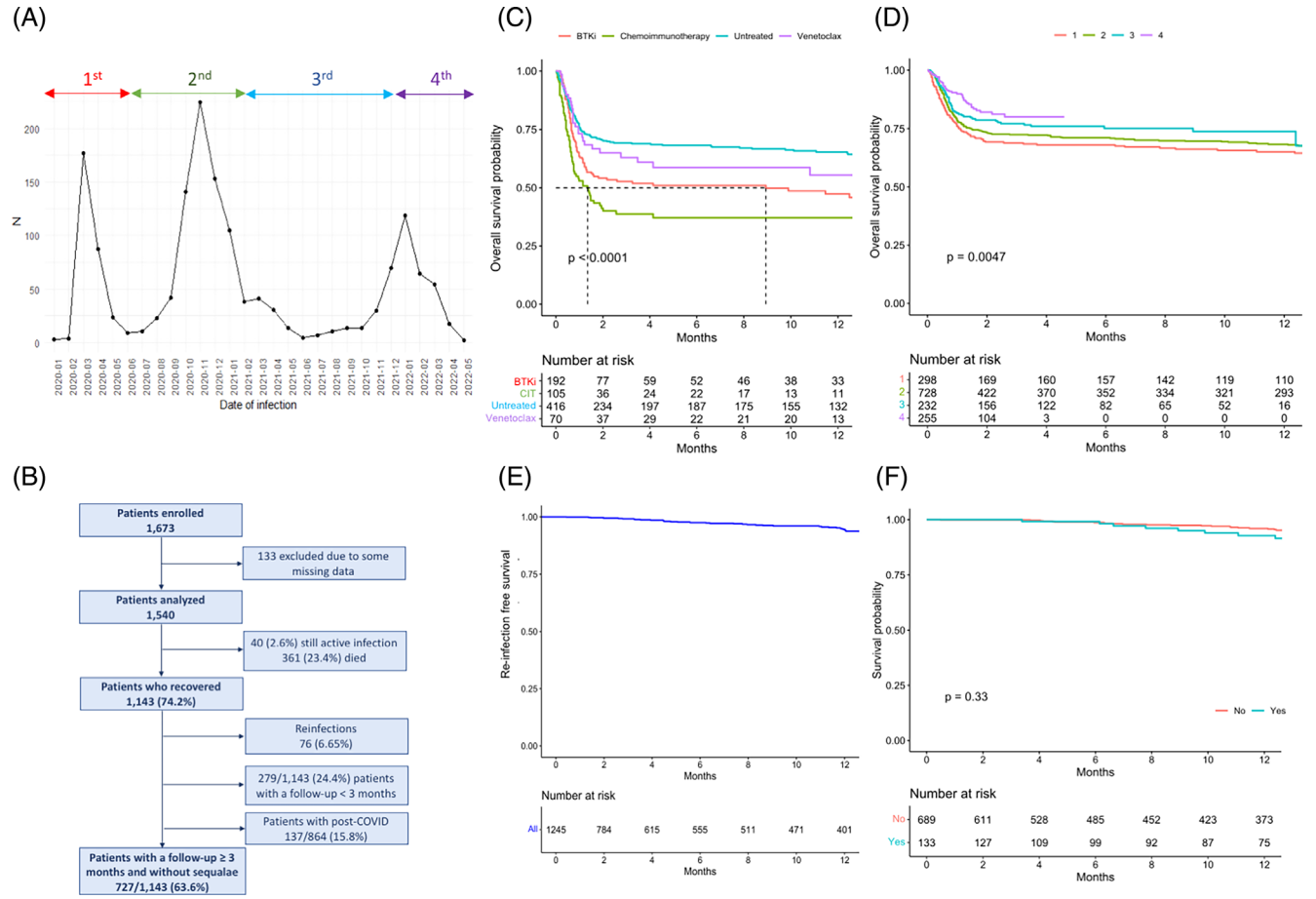

FIGURE 1 Patients disposition and survival analysis. The left upper panel (A) reports the distribution of patients from January 2020 to May 2022. Three hundred and four (19.7%) patients were infected during the first, 737 (47.9%) patients during the second, 235 (15.3%) patients during the third, and 264 (17.1%) patients during the last fourth phase of the pandemic. The left lower panel (B) shows the study chart. Upper middle and right panels: the Kaplan–Meier analysis of overall survival according to the CLL-specific treatment (C) and the COVID-19 pandemic wave (D; January 1, 2020–June 2020; July 2, 2020–February 2021; March 3, 2021–December 2021; January 4, 2022–May 2022). Among treated patients, those who received chemoimmunotherapy (CIT) displayed the worst outcome than patients on BTK inhibitors (BTKi, i.e., ibrutinib or acalabrutinib) or venetoclax. Lower middle and right panels: overall non-reinfection probability (E) and overall survival of patients who developed post-COVID condition (Yes) or not (No) (F).

3 | RESULTS

3.1 | Characteristics of the patients

We gathered data on 1677 patients from 91 institutions. After excluding cases without a qRT-PCR positive test for SARS-CoV-2, 1540 patients were included in the final analysis (Figure 1B), of whom 941 (61%) were reported in the previous studies.

Most patients were diagnosed with CLL (1449/1540, 94.1%), while 63 (4.1%) and 32 (2.1%) were affected by SLL and high-count MBL, respectively (Figure 1A). Patient characteristics are summarized in Table 1. Most patients were male (998, 64.8%), the median age at COVID-19 was 69 (IQR 62–77) years, and the median CIRS score was 4 (IQR 2–7). Half of the patients had received treatment for CLL in the last 12 months before COVID-19, and 599 (38.9%) were on active treatment at COVID-19 onset (Bruton's tyrosine kinase inhibitor-based [BTKi] 51.9%, BCL2 inhibitor-based [BCL2i] 21.9%, chemo/chemoimmunotherapy [CIT] 21.9%, PI3K inhibitors [PI3Ki] 3.3%, others 1.1%). After the infection, 122 (39.2%), 28 (21.4%), 21 (16%), and 2 (11%) patients on BTKi, BCL2i, CIT, and PI3Ki restarted therapy, respectively. Continuation of BTKi was slightly lower during the first waves (29%) than the last phases of the pandemic (35.7%); however, the difference did not reach statistical significance.

Overall, 34.6% of patients were managed at home, whereas 65.4% needed hospitalization, of whom 15.6% (23.8% of the hospitalized patients) were admitted to the ICU (Table 2). The infection resolved in 1172/1540 (76.1%) cases, while 360 (23.4%) died and 8 (0.5%) were still under medical observation due to persistent SARS-CoV-2 RNA positivity at the time of data analysis. The overall survival of the whole population is shown in Figure S1A.

After variables' selection in univariate analysis (Table S2), in the multivariate analysis we confirmed previous observations[5,7] that age (as a continuous variable) and comorbidities (expressed as continuous CIRS score) were independent risk factors for both hospitalization and

TABLE 1 Characteristics of the entire cohort and patients in each of the four different pandemic waves.

Variables	All patients, $n = 1540$	WAVES				p Values
		First, $n = 304$	Second, $n = 737$	Third, $n = 235$	Fourth, $n = 264$	
Age, years (IQR)	69 (62–77)	70 (63–80)	68 (61–76)	69 (61–76)	71 (62–76)	0.015
Sex						0.447
Female	542 (35.2%)	104 (34.2%)	259 (35.1%)	76 (32.3%)	103 (39.0%)	
Male	998 (64.8%)	200 (65.8%)	478 (64.5%)	159 (67.7%)	161 (61.0%)	
Median CIRS score (IQR)	4 (2–7)	4 (2–7)	4 (2–7)	5 (2–7)	4 (2–7)	0.146
Comorbidities, any	1354 (87.9%)	266 (87.5%)	653 (88.6%)	204 (86.8%)	231 (87.5%)	0.840
Arrhythmias	175 (11.4%)	25 (8.2%)	77 (10.5%)	36 (15.3%)	37 (14.0%)	0.014
Heart failure	59 (3.8%)	13 (4.3%)	20 (2.7%)	12 (5.1%)	14 (5.3%)	0.126
Coronary artery disease	154 (10.0%)	28 (9.2%)	81 (11.0%)	27 (11.5%)	18 (6.8%)	0.239
Hypertension	733 (47.6%)	137 (45.1%)	356 (48.3%)	118 (50.2%)	122 (46.2%)	0.493
COPD	103 (6.7%)	18 (5.9%)	48 (6.5%)	16 (6.8%)	21 (8.0%)	0.743
Asthma	49 (3.2%)	11 (3.6%)	17 (2.3%)	10 (4.3%)	11 (4.2%)	0.257
Chronic renal disease	103 (6.7%)	12 (3.9%)	44 (6.0%)	19 (8.1%)	28 (10.6%)	0.006
Diabetes mellitus	282 (18.3%)	60 (19.7%)	131 (17.8%)	43 (18.3%)	48 (18.2%)	0.905
Obesity	230 (14.9%)	42 (13.8%)	117 (15.9%)	31 (13.2%)	40 (15.2%)	0.775
IgG <5 g/L	762 (49.5%)	150 (49.3%)	358 (48.6%)	119 (50.6%)	135 (51.1%)	0.917
Other hem. malignancies	28 (1.8%)	1 (0.3%)	13 (1.8%)	5 (2.1%)	9 (3.4%)	0.032
Other non-hem cancers	161 (10.5%)	23 (7.6%)	78 (10.6%)	29 (12.3%)	31 (11.7%)	0.163
IGHV gene unmutated[a]	423 (43.9%)	76 (45.5%)	201 (44.5%)	68 (44.2%)	78 (40.8%)	0.812
TP53 gene abnormalities[a]	214 (24.0%)	37 (25.2%)	97 (24.6%)	32 (21.2%)	48 (24.2%)	0.843
Vaccinated	327 (21.3%)	0 (0.0%)	3 (0.4%)	101 (43.0%)	223 (84.5%)	<0.001
CLL therapy < 12 months	774 (50.3%)	134 (44.1%)	327 (44.4%)	135 (57.4%)	178 (67.4%)	<0.001
Active CLL treatment	599 (38.9%)	90 (29.6%)	249 (33.8%)	110 (46.8%)	150 (56.8%)	<0.001

Abbreviations: COPD, chronic obstructive pulmonary disease; IQR, interquartile range; Obesity, body mass index ≥ 30 kg/m^2; Other hem. malignancies, other hematological malignancies; Other non-hem. cancers, other non-hematological cancers.

[a]Data available from 964 and 890 patients for IGHV mutational status and *TP53* gene abnormalities (including gene mutation and/or deletion of chromosome 17p). The p values were calculated for patients infected during the different waves.

death (Table S3). CLL treatment in the previous 12 months, hospitalization and ICU admission were also risk factors for death. Stratifying the OS of patients according to the type of treatment, those treated with CIT had the worst outcome (median OS 1.8 months), followed by those on BTKi (median OS 9 months), BCL2i, and untreated patients (median OS not reached, Figure 1C, $p < .001$). Patients who continued BTKi treatment were less likely to be hospitalized, had a statistically better outcome than those who discontinued treatment ($p = .038$), while both groups had a worse outcome compared with untreated patients ($p < .001$; Table S4). However, once hospitalized, the majority of the patients stopped BTKi or BCL2i. In detail, during the early waves, the death rates were 33.3% and 44.8% among patients who continued or stopped BTKi, while in the latter waves (i.e., third and fourth), the death rates were 28.6% and 49.3%, respectively (revised Table S4). However, the difference was not statistically significant, likely due to the low number of the patients ($p = .3792$). As shown in Figure S1B, vaccinated patients had a better OS than unvaccinated ones ($p = .013$). However, vaccination was not an independent risk factor of survival in multivariate analysis (Table S3).

3.2 | Characteristics of the patients among waves

The distribution of patients over time is shown in Figure 1A. Three hundred and four (19.7%) patients were infected during the first, 737 (47.9%) patients during the second, 235 (15.3%) patients during the third, and 264 (17.1%) patients during the last fourth wave. Comparing the features of patients infected during the different waves, gender and biological markers (i.e., IGHV mutational status and presence of *TP53* abnormalities) were similar. However, more patients in the latter phases were elderly (median age 70 vs. 68 vs. 69 vs. 71 years, $p = .015$), suffered from arrhythmias (8.2% vs. 10.5% vs. 15.3% vs. 14.0%, $p = .014$), chronic renal disease (3.9% vs. 6.0% vs. 8.1% and 10.6%, $p = .006$) and other hematological malignancies (0.3% vs. 1.8% vs. 2.1% vs. 3.4%, $p = .032$; Table 1). In addition, vaccinated patients (0% vs. 0.4% vs. 43.0% vs. 84.5%, $p < .001$), those treated for CLL in the last 12 months (44.1% vs. 44.4% vs. 57.4% vs. 67.4%, $p < .001$), and those on active treatment at COVID-19 (29.6% vs. 33.8% vs. 46.8% vs. 56.8, $p < .001$) were also more common in the last waves rather than the first ones (Table 1).

TABLE 2 Features of SARS-CoV2 infection in the entire cohort and patients in each of the four different pandemic waves.

Variables	All patients, $n = 1540$	Waves				p values
		First, $n = 304$	Second, $n = 737$	Third, $n = 235$	Fourth, $n = 264$	
COVID-19 signs/symptoms						
Fever	1065 (69.2%)	242 (79.6%)	504 (68.4%)	164 (69.8%)	155 (58.7%)	<0.001
Dyspnea	653 (42.4%)	152 (50.0%)	299 (40.6%)	108 (46.0%)	94 (35.6%)	0.026
Cough	862 (55.9%)	157 (51.6%)	368 (49.9%)	154 (65.5%)	183 (69.3%)	<0.001
Fatigue	525 (34.1%)	70 (23.0%)	200 (27.1%)	117 (49.8%)	138 (52.3%)	<0.001
Headache	173 (11.2%)	19 (6.3%)	55 (7.5%)	39 (16.6%)	60 (22.7%)	<0.001
Diarrhea	177 (11.5%)	41 (13.5%)	63 (8.5%)	39 (16.6%)	34 (12.9%)	0.003
Anosmia/ageusia	149 (9.7%)	12 (3.9%)	75 (10.2%)	32 (13.6%)	30 (11.4%)	<0.001
Myalgias/arthralgias	201 (13.1%)	29 (9.5%)	71 (9.6%)	53 (22.6%)	48 (18.2%)	<0.001
COVID-19 management						
Hospitalization	1007 (65.4%)	254 (83.6%)	491 (66.6%)	142 (60.4%)	120 (45.5%)	<0.001
ICU admission	240 (15.6%)	62 (20.4%)	126 (17.1%)	31 (13.2%)	21 (8.0%)	<0.001
Days of hospitalization (IQR)	15 (9–25)	15 (8–27)	13 (7–21)	11 (4–22)	10 (3–17)	0.003
COVID-19 treatments, any	1116 (72.5%)	259 (85.2%)	523 (71.0%)	168 (71.5%)	166 (62.9%)	<0.001
Hydroxychloroquine	214 (13.9%)	197 (64.8%)	13 (1.8%)	4 (1.7%)	0 (0.0%)	<0.001
Steroids	792 (51.4%)	150 (49.3%)	422 (57.3%)	124 (52.8%)	96 (36.4%)	<0.001
Azithromycin	336 (21.8%)	122 (40.1%)	160 (21.7%)	31 (13.2%)	23 (8.7%)	<0.001
Antivirals	409 (26.6%)	126 (41.4%)	148 (20.1%)	56 (23.8%)	79 (29.9%)	<0.001
Anti-IL6/IL6R	117 (7.6%)	54 (17.8%)	34 (4.6%)	13 (5.5%)	16 (6.1%)	<0.001
Monoclonal antibodies	82 (5.3%)	0 (0.0%)	2 (0.3%)	43 (18.3%)	37 (14.0%)	<0.001
Survived	1172 (76.1%)	214 (70.4%)	553 (75.0%)	183 (77.7%)	222 (84.1%)	0.002
Reinfections	76 (4.9%)	11 (3.6%)	48 (5.6%)	10 (4.3%)	7 (2.7%)	0.003

Note: antivirals, remdesivir, molnupiravir, nirmatrelvir–ritonavir, or other investigational antiviral; monoclonal antibodies, sotrovimab, casirivimab–imdevimab, bamlanivimab–etesevimab, or other investigational antibodies. Anti-IL6/IL6R, siltuximab, tocilizumab or sarilumab, or other investigational drugs.

Abbreviations: ICU, intensive care unit; IQR, interquartile range.

3.3 | Characteristics of COVID-19 among waves

The presentation and frequency of COVID-19 signs and symptoms varied between early and late waves, with less fever ($p < .001$) and dyspnea ($p = .026$) but more cough ($p < .001$), fatigue ($p < .001$), headache ($p < .001$), diarrhea ($p = .003$), anosmia/ageusia ($p < .001$), and myalgia/arthralgia ($p < .001$) in the later phases (Table 2).

Progressively fewer patients were hospitalized (83.6% vs. 66.6% vs. 60.4% vs. 45.5%, $p < .001$) and needed ICU admission (20.4% vs. 17.1% vs. 13.2% vs. 8.0%, $p < .001$) through the waves (Table 2). The days of hospitalization decreased through the phases from a median of 15–10 days ($p = .003$, Table 2). The treatment of COVID-19 also changed over time, with fewer patients receiving a SARS-CoV-2 therapy (85.2% vs. 71.0% vs. 71.5% vs. 62.9%, $p < .001$). In particular, hydroxychloroquine (64.8% vs. 1.8% vs. 1.7% vs. 0.0%, $p < .001$), azithromycin (40.1% vs. 21.7% vs. 13.2% vs. 8.7%, $p < .001$), steroids (49.3% vs. 57.3% vs. 52.8% vs. 36.4%, $p < .001$), and anti-IL6/IL6R (17.8% vs. 4.6% vs. 5.5% vs. 6.1%, $p < .001$) were more commonly used in the first phase, while anti-SARS-CoV-2 monoclonal antibodies (e.g., sotrovimab, casirivimab–imdevimab, bamlanivimab, and etesevimab or other investigational antibodies; 0.0% vs. 0.3% vs. 18.3% vs. 14.0%, $p < .001$) were mainly administered in the last two waves (Table 2). The use of antivirals decreased in the second wave ($p < .001$), but increased in the third and fourth wave with the availability of oral antivirals such as molnupiravir and nirmatrelvir–ritonavir (Table 2).

3.4 | Outcome of patients

After a median follow-up of 2.76 months, 90 (29.6%), 184 (25%), 52 (22.3%), and 42 (15.7%) patients died during the first, second, third, and fourth wave ($p = .002$), respectively. The median OS was not reached in all waves, but the 2-month OS improved, from 70% to 74%, 81% and 83%, and so did the 4-month OS, from 68% to 73%, 79% and 83%, of patients diagnosed during the first, second, third, and fourth waves, respectively ($p = .0015$, Figure 1D). In multivariate analysis, SARS-CoV-2 infection during the last waves as compared to the first wave of the pandemic was a protective factor against hospitalization but not of death (Table S3, $p < .001$).

Seventy-six (6.65%) patients out of 1143 survivors who resolved the infection had a reinfection (Table 1 and Table S5). The median time to reinfection was 12.9 months. The estimated 3-month overall reinfection probability was 1% (Figure 1E). Reinfection was usually milder than the first SARS-CoV-2 infection, with only 33.8% of patients hospitalized ($p = .0001$ comparing the whole population, $p = .007$ comparing the rates of paired first and second infection), only 4.5% admitted to ICU ($p < .023$ comparing the whole population, $p = .99$ comparing the rates of paired first and second infection), and 4.5% deceased ($p < .001$ comparing the whole population; Table S6).

3.5 | Post-COVID condition

One hundred thirty-seven patients fulfilled the WHO criteria of post-COVID condition (Figure 1A). Considering that 864 patients survived acute COVID-19 and had at least 3 months of follow-up, the crude prevalence of the post-COVID condition among CLL survivors was 15.8%. The estimated cumulative incidence of post-COVID after 3 and 6 months from COVID-19 onset was 7.5% and 9.2%, respectively. Interestingly, we observed that 35% of patients infected in the last wave developed post-COVID compared to 16.7% versus 13.8% versus 14.7% of patients infected in the third, second, and first wave, respectively ($p = .005$).

Detailed information on the post-COVID condition was available for 134/137 patients (97.8%) and is reported in Table 3. The median number of signs or symptoms was 4, 26.8% of patients reported one or two conditions and 73.2% three or more conditions. Overall, the most common symptoms were fatigue (67.9%), dyspnea (59%), lasting cough (41.8%), muscle weakness (37.3%), inability to concentrate (26.9%), memory lapses (26.1%), sleep difficulties (23.9%), bronchiectasis (23.9%), complete or partial loss of smell (22.3%), oxygen need at home (19.4%), weight loss (17.9%), lung fibrosis (16.4%), and headache (12.7%; Table 3). In univariate analyses, CIRS as a continuous variable ($p = .03$), hospitalization ($p < .0001$), and ICU admission ($p < .001$) were associated with the development of post-COVID. In multivariate analyses, only severe COVID-19 (hospitalization with need of oxygen or ICU admission) emerged as a risk factor for developing the post-COVID condition (Table S7). The median time to resolution of the post-COVID condition was 4.7 months. The OS of patients with post-COVID was similar to that of those who did not experience this complication ($p = .33$; Figure 1F).

TABLE 3 Post-COVID signs and symptoms.

Systems and apparatus	Patients	%
Pneumological	99	73.9
Shortness of breath	79	59
Lasting cough	56	41.8
Bronchiectasis	32	23.9
Oxygen need at home	26	19.4
Lung fibrosis	22	16.4
Neurological	61	45.5
Inability to concentrate	36	26.9
Memory lapses	35	26.1
Sleep difficulties	32	23.9
Headaches	17	12.7
Changes in mood and mental health problems	12	9
Needle pains in arms and legs	8	6
Tremors	1	0.7
Ear, nose, and throat	33	24.6
Persistent lack of sense of smell	16	11.9
Loss of smell	14	10.4
Difficulties swallowing	6	4.5
Tinnitus	1	0.7
Hematological	22	16.4
Anemia	16	11.9
Thrombocytopenia	7	5.2
Lymphopenia	8	6
Deep vein thrombosis and/or pulmonary embolism	1	0.6
Cardiological	14	10.4
Arrhythmia	5	3.7
Hypertension	4	3
Palpitations	4	3
Chest pains	3	2.2
Heart failure	2	1.5
Orthostatic hypotension	1	0.7
Gastroenterological	13	9.7
Diarrhea	5	3.7
Gastroesophageal reflux disease	4	3
Vomit	3	2.2
Increased hepatic enzymes	2	1.5
Other symptoms	92	68.7
Fatigue	91	67.9
Low grade fever	6	4.5
Muscle weakness	50	37.3
Weight loss	24	17.9
Joint pain	20	14.9
Hair loss	7	5.2
Skin rash	3	2.2
New onset chronic kidney disease	2	1.5
New onset of diabetes	1	0.7
Dizziness	1	0.7

4 | DISCUSSION

To the best of our knowledge, this is the largest published cohort investigating the differences in the clinical course and management of COVID-19 between the sequential pandemic phases, also focusing on reinfection and post-COVID conditions.

Immune dysfunction in patients with CLL and MBL is well characterized in the literature. Quantitative and qualitative defects of both the innate and the adaptive immune systems compromise the

optimal seroconversion to vaccines,[27,28] including those against SARS-CoV-2,[29,30] and favor the development of life-threatening infections.[31–34] Accordingly, patients with CLL display a high risk of mortality by SARS-CoV-2 infection compared to the general population.[5,6]

We found that vaccinated patients had lower hospitalization rates and a better OS than unvaccinated ones in the entire cohort, but the protective effect of vaccination by itself was not confirmed in multivariate analyses. This finding points out that vaccination is not an independent factor of hospitalization or survival, suggesting that other variables affect the outcome of patients with CLL. Arguably, seroconversion and/or cellular memory are more likely to be protective variables rather than vaccination itself, though such data are not available in our study.

This study highlights different patterns of COVID-19 manifestations between waves. The initial waves were characterized by a higher rate of fever and dyspnea, while the latter ones were associated with milder symptoms (Table 2). Accordingly, fewer patients needed hospitalization and ICU admission or died in the latter waves, despite that during these waves, more patients had comorbidities and/or were on active treatment at the time of COVID-19. This observation is likely related to the emergence of milder SARS-CoV-2 variants[8,35,36] and the significantly higher number of patients who received preemptive therapies in the latter waves but also the more effective therapies. Accordingly, infection during the four waves was an independent protective factor for hospitalization, but not for survival, since COVID-19 can still be severe and cause death in patients with CLL, irrespective of the SARS-CoV-2 variant (Table S3). However, the steady decrease of the ORs through the sequential waves, suggests a trend toward a better outcome. Data on reinfections are also of interest, due to the lower rates of hospitalization and death compared to the first infection (Table S6). Acquired immunity after the infection reinforced by immunity elicited by the vaccine might conceivably be highly protective from reinfection and/or the development of severe COVID-19. Additionally, this observation may be linked to the emergence of the milder omicron SARS-CoV-2 variants: accordingly, a study from Denmark reported that patients with CLL had a milder course of COVID-19 during the era of the Omicron variant, corresponding to our fourth wave.[8]

The presence of persistent symptoms in previously infected patients is referred to by several terms, including post-COVID-19 condition, post-COVID syndrome, post-acute COVID-19 syndrome, post-acute sequelae of COVID-19 and long-COVID depending on the agency (i.e., WHO, NICE, or CDC).[26] Common symptoms include fatigue, shortness of breath, muscle pain, and cognitive dysfunctions. Symptoms might be of new onset after initial recovery from acute COVID-19 or persistent from the initial illness. In addition, symptoms might fluctuate or relapse over time.[14] In our study, almost 16% of patients with CLL who survived the acute SARS-CoV-2 infection developed the post-COVID condition throughout the different waves, in line with the frequency observed among patients with cancer in the OnCovid study.[15] Patients of our series experienced a plethora of different symptoms, which undoubtedly impaired their quality of life. Post-COVID was more common in patients with comorbidities and among those who needed hospitalization, similar to the general population.[16,17] In contrast to other studies,[13,37] vaccines did not have a protective effect against post-COVID conditions in our cohort, probably hinting again toward a more limited seroconversion occurring in patients with CLL. It is of particular concern that patients with CLL infected in the last waves experienced post-COVID condition at a more than double frequency, likely due to their advanced age and comorbidities. We cannot exclude that a greater knowledge among health professionals may have contributed to the higher recognition of post-COVID condition in later waves. Further investigation is required to address the specific needs of these patients who fortunately have now a better chance of survival but their quality of life remain highly affected by the consequences of the infection.

In this study, we confirmed previous observations, including ours, that a relevant fraction of patients with CLL and COVID-19 require hospitalization and even ICU admission.[3,5,7] In multivariate analysis, older age, increased CIRS score, and CLL-directed treatment were the only predictors of both hospitalization and death. Accordingly, untreated patients had a better OS than patients treated with CIT or protein inhibitors. Conversely to our previous publications, we found that treatment with venetoclax did not confer a worse prognosis but rather an intermediate one; moreover, we obtained evidence that continuing BTKi during the infection might prevent progression to severe COVID-19.[5,7] Adequate humoral responses to vaccination of patients treated with venetoclax monotherapy[30] may help explain this relevant difference. However, admittedly, the small number of patients treated with venetoclax in our cohort might have also confounded this result. Nonetheless, we must acknowledge the bias of such comparisons in a retrospective study.

The main limitation of our study is its retrospective structure. To minimize selection, attrition biases, and inaccurate reporting of data inherent to observational studies, we asked the physicians to report all their patients with CLL/SLL or MBL with COVID-19. We analyzed the reported data, excluded cases without proven qRT-PCR for SARS-CoV-2 infection, and performed automatic and manual consistency checks on each case report form. Furthermore, the lack of harmonization of post-COVID definition,[14,26] together with the evolving spectrum of this often-overlooked condition, might have brought inter-sites heterogeneity into the research.

In conclusion, our analysis of the evolving landscape of COVID-19 documented a remarkable improvement in the survival of patients with CLL and COVID-19 likely due to the improvement of strategies employed to fight the SARS-CoV-2 and the change in SARS-CoV-2 variants over time have. However, the relevant rate of the post-COVID condition represents an area of concern because of its invalidating effects and the lack of evidence-based therapy, which mandates continued patient follow-up and the investigation of effective interventions even in the current post-pandemic era.

AUTHOR CONTRIBUTIONS

Andrea Visentin, Thomas Chatzikonstantinou, Lydia Scarfò, Anargyros Kapetanakis, and Christos Demosthenous collected data, coordinated

the study, wrote the paper, and performed the analysis. Georgios Karakatsoulis wrote the paper and performed the statistical analysis. Eva Minga, Dimitra Chamou, David Allsup, Alejandro Alonso Cabrero, Martin Andres, Darko Antic, Mónica Baile, Panagiotis Baliakas, Sotiria Besikli-Dimou, Dominique Bron, Antonella Capasso, Sofia Chatzileontiadou, Raul Cordoba, Juan-Gonzalo Correa, Carolina Cuéllar-García, Lorenzo De Paoli, Maria Rosaria De Paolis, Giovanni Del Poeta, Maria Dimou, David Donaldson, Michael Doubek, Maria Efstathopoulou, Barbara Eichhorst, Salma Elashwah, Alicia Enrico, Blanca Espinet, Lucia Farina, Angela Ferrari, Myriam Foglietta, Henrik Frederiksen, Moritz Fürstenau, José A. García-Marco, Rocío García-Serra, Massimo Gentile, Eva Gimeno, Andreas Glenthøj, Maria Gomes da Silva, Odit Gutwein, Yervand K. Hakobyan, Yair Herishanu, José Ángel Hernández-Rivas, Tobias Herold, Idanna Innocenti, Gilad Itchaki, Ozren Jaksic, Ann Janssens, Olga B. Kalashnikova, Elżbieta Kalicińska, Linda Katharina Karlsson, Arnon P. Kater, Sabina Kersting, Jorge Labrador, Deepesh Lad, Luca Laurenti, Mark-David Levin, Enrico Lista, Alberto Lopez-Garcia, Lara Malerba, Roberto Marasca, Monia Marchetti, Juan Marquet, Mattias Mattsson, Francesca R. Mauro, Ivana Milosevic, Fatima Mirás, Marta Morawska, Marina Motta, Talha Munir, Roberta Murru, Carsten U. Niemann, Raquel Nunes Rodrigues, Jacopo Olivieri, Lorella Orsucci, Maria Papaioannou, Miguel Arturo Pavlovsky, Inga Piskunova, Viola Maria Popov, Francesca Maria Quaglia, Giulia Quaresmini, Kristian Qvist, Gianluigi Reda, Gian Matteo Rigolin, Rosa Ruchlemer, Gevorg Saghumyan, Amit Shrestha, Martin Šimkovič, Martin Špaček, Paolo Sportoletti, Oana Stanca, Niki Stavroyianni, Tamar Tadmor, Doreen Te Raa, Sanne H. Tonino, Livio Trentin, Ellen Van Der Spek, Michel van Gelder, Roel van Kampen, Marzia Varettoni, Candida Vitale, Ewa Wasik-Szczepanek, Tomasz Wróbel, Lucrecia Yáñez San Segundo, Mohamed Yassin, Mark Catherwood, Alessandro Rambaldi, Emili Montserrat, RF, Antonio Cuneo, Julio Delgado, Barbara Pocali, Elisabeth Vandenberghe, Sunil Iyengar, and Mark Catherwood collected data and contributed to interpretation and manuscript editing. Kostas Stamatopoulos and Paolo Ghia designed and coordinated the study, reviewed the manuscript that was approved by all the authors.

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CONFLICT OF INTEREST STATEMENT

Andrea Visentin received advisory board participation fees from Janssen, Abbvie, Beigene, CSL behring, Astrazeneca, Beigene, and Takeda. Candida Vitale received honoraria from Janssen. Lydia Scarfò received advisory boards fees from AbbVie and Janssen; educational activity AstraZeneca. David Allsup received funding to attend symposia from Gilead, CSL Behring, and Bayer. Martin Andres received advisory boards fees from AbbVie, AstraZeneca, and Janssen-Cilag; travel support from AbbVie and Novartis. Darko Antic received honoraria from AbbVie, Janssen, and Roche. Panagiotis Baliakas has received honoraria from Abbvie, Gilead, and Janssen and research funding from Gilead. Rosa Collado received speaker fees from Roche, Janssen, AbbVie, AstraZeneca, Celgene, BMS, Kite, and Takeda; received advisory board fees from Janssen, AbbVie, Celgene, BMS, Kite, Takeda, Incyte, Kyowa-Kirin, and ADCT; received travel and accommodation expenses from Roche, Janssen, AbbVie, Celgene, BMS, Kite, Takeda, and Pfizer; research grant from Pfizer. Michael Doubek received honoraria for advisory board and research support from AstraZeneca, AbbVie, Roche, Gilead, and Janssen. Barbara Eichhorst received consulting or advisory boards fees from Janssen, Roche, Novartis, AbbVie, Gilead, Celgene, ArQule, AstraZeneca, Oxford Biomedica (UK), and BeiGene; speaker/speaker's bureau fees from Janssen, Gilead, Roche, AbbVie, Novartis, Celgene, Adaptive Biotechnologies, BioGene, and AstraZeneca; research support/research funding from Janssen, Gilead, Roche, AbbVie, BeiGene, and AstraZeneca; travel, accommodations, expenses from Janssen, Roche, Novartis, AbbVie, Gilead, and Celgene. Myriam Foglietta received honoraria from Janssen and Gilead. José A. García-Marco received honoraria for advisory board and speaker's bureau from Mundipharma, Glaxo, AbbVie, Roche, Gilead, AstraZeneca, and Janssen; research support from Hoffman-La Roche, AbbVie, and Janssen. Rocío García-Serra received educational grants from AbbVie, Janssen, and Novartis. Eva Gimeno received travel grants, honoraria as a consultant, and/or speaker bureau for Janssen-Cilag, Roche, and AbbVie. Maria Gomes da Silva received honoraria for consultancy/advisory boards with Roche, Janssen Cilag, Gilead, AbbVie, and BMS; research Grant from Gilead and Astrazeneca. Yair Herishanu received honoraria from AbbVie, Janssen, AstraZeneca, and Roche, outside the submitted work. José Ángel Hernández-Rivas received honoraria and advisory boards fees from Janssen, AbbVie, AstraZeneca, Roche, Beigene, Gilead, and BMS-Celgene. Ozren Jaksic received honoraria from AbbVie, Janssen, and Roche. Arnon P. Kater received honoraria from Janssen, BMS, AstraZeneca, Roche/Genentech; research money from Janssen, BMS, AstraZeneca, and Roche/Genentech. Sabina Kersting received Travel grant from Celgene; received research funding from Janssen and AbbVie. Luca Laurenti received honoraria from Roche, AbbVie, Janssen, and AstraZeneca. Mark-David Levin received travel expenses and advisory board compensation from Janssen, AbbVie, and Roche. Alberto Lopez-Garcia received speaker's bureau fees from Roche, Janssen, AbbVie, Celgene, Fresenius, Novonordisk; received advisory board participation fees from Janssen, and AbbVie; received travel and accommodation expenses from Roche, Janssen, and AbbVie. Monia Marchetti received speaker bureau (invited speech) fees from Amgen; received honoraria as a consultant from Gilead. Juan Marquet received honoraria and travel grants from AbbVie, Janssen, Roche, Gilead, and Takeda. Mattias Mattsson received research grant from GILEAD. Francesca R. Mauro received research funding from Gilead; received advisory board participation fees from AbbVie, Gilead, Janssen, AstraZeneca,

Takeda, and Roche; received speakers bureau fees from Gilead, Janssen, and AbbVie. Talha Munir received honoraria from AbbVie, Janssen, AstraZeneca, Gilead, Roche, and Alexion; received advisory board participation fees from AbbVie, AstraZeneca, Janssen, Alexion, Morphosys, and Sunesis. RM received honoraria from Janssen, and AbbVie. Carsten U. Niemann received research funding and/or consultancy fees from AbbVie, AstraZeneca, Janssen, CSL Behring, and Takeda. Miguel Arturo Pavlovsky received advisory board participation fees from Janssen, AbbVie, AstraZeneca, and Merck; received speaker's bureau fees from Janssen, AbbVie, AstraZeneca, Varifarma, and Merck. Francesca Maria Quaglia advisor role for AstraZeneca; speaker for Astra Zeneca and Janssen; consultant for Sandoz. Gianluigi Reda received consultancy fees and honoraria from AbbVie, AstraZeneca, and Janssen. Gian Matteo Rigolin received honoraria from AbbVie, AstraZeneca, Pfizer, Gilead, and Janssen; received research funding from Gilead. Martin Šimkovič received consultancy fees, advisory board participation fees, travel grants, and honoraria from Janssen, Gilead, Roche, AstraZeneca, and AbbVie. Martin Špaček received honoraria from AbbVie, AstraZeneca, Gilead, Janssen, and Roche. Paolo Sportoletti received funding from Gilead; received advisory board participation fees from AbbVie and Janssen; received honorarium AbbVie, Janssen, and AstraZeneca. Livio Trentin received advisory board participation fees from Janssen, Roche, AbbVie, Gilead, Takeda, Beigene, Astranezeca; research funding from Janssen, Roche, Takeda, Astrazeneca and Gilead. Ellen Van Der Spek participated in teaching activities for Amgen. Marzia Varettoni received advisory board participation fees from Janssen, Roche, AstraZeneca; received travel expenses from Janssen and AbbVie. Tomasz Wróbel received research funding from Roche; received honoraria for advisory board, and research funding from Janssen; received honoraria, advisory board participation fees, and travel grant from AbbVie; received speaker's bureau fees from Gilead. Lucrecia Yáñez San Segundo received advisory board participation fees from Gilead-Kite, Janssen, AbbVie, AstraZeneca, Beigene, Roche, Pfizer, Jazz, BMS, and Merck; received speaker's bureau fees from Janssen, AbbVie, AstraZeneca, Gilead-Kite, Roche, Pfizer, and Merck. Mark Catherwood received honoraria from AbbVie, Gilead, Janssen, and AstraZeneca. Antonio Cuneo received speaker's bureau fees and advisory board participation fees from Abbvie, Asta-Zeneca, Gilead, Janssen. Kostas Stamatopoulos received honoraria and research support from Janssen, Abbvie, AstraZeneca, Gilead. Paolo Ghia received honoraria from AbbVie, Arqule/MSD, AstraZeneca, Celgene/Juno/BMS, Janssen, Loxo/Lilly, Roche; Research support, AbbVie, AstraZeneca, Janssen, Gilead, Sunesis. Gilad Itchaki received honoraria and research grants from Abbvie and Janssen. Moritz Fürstenau received research funding from Roche, Abbvie, Janssen, Beigene and AstraZeneca and honoraria from Abbvie. Thomas Chatzikonstantinou, Anargyros Kapetanakis, Georgios Karakatsoulis, Christos Demosthenous, Emili Montserrat, Dimitra Chamou, Alejandro Alonso Cabrero, Mónica Baile, Sotiria Besikli-Dimou, Dominique Bron, Antonella Capasso, Sofia Chatzileontiadou, Juan-Gonzalo Correa, Carolina Cuéllar-García, Lorenzo De Paoli, Maria Rosaria De Paolis, Julio Delgado, Giovanni Del Poeta, Maria Dimou, David Donaldson, Maria Efstathopoulou, Salma Elashwah, Alicia Enrico, Blanca Espinet, Lucia Farina, Angela Ferrari, Henrik Frederiksen, Massimo Gentile, Andreas Glenthøj, Odit Gutwein, Yervand K. Hakobyan, Tobias Herold, Idanna Innocenti, Ann Janssens, Olga B. Kalashnikova, Elżbieta Kalicińska, Linda Katharina Karlsson, Luca Laurenti, Deepesh Lad, Enrico Lista, Lara Malerba, Roberto Marasca, Ivana Milosevic, Fatima Mirás, Mark Catherwood, Marta Morawska, Marina Motta, Raquel Nunes Rodrigues, Jacopo Olivieri, Lorella Orsucci, Maria Papaioannou, Inga Piskunova, Viola Maria Popov, Giulia Quaresmini, Kristian Qvist, Rosa Ruchlemer, Gevorg Saghumyan, Amit Shrestha, Oana Stanca, Niki Stavroyianni, Tamar Tadmor, Doreen Te Raa, Sanne H. Tonino, Michel van Gelder, Roel van Kampen, Ewa Wasik-Szczepanek, Mohamed Yassin, Alessandro Rambaldi, Emili Montserrat, Rosa Collado, Sunil Iyengar, Barbara Pocali, and Elisabeth Vandenberghe have no conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

All data created during this study are included in the manuscript and supporting material. The datasets generated and analyzed during the current study are not publicly available due to the data protection and lack of consent from the patients. Access to anonymous data can be available after contacting corresponding authors.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX A: ERIC COOPERATIVE GROUP MEMBERS.

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