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The mortality of COVID-19 in CML patients from 2020 until 2022: results from the EPICOVIDEHA survey

Shaimaa El-Ashwah[a*], Jon Salmanton-García[b,c*], Yavuz M. Bilgin[d*], Federico Itri[e], Pavel Žák[f], Barbora Weinbergerová[g], Luisa Verga[h,i], Ali S. Omrani[j], Maria Gomes da Silva[k], Tomáš Szotkowski[l], Monia Marchetti[m], Caterina Buquicchio[n], Marcio Nucci[o], Martin Schönlein[p], Francesca Farina[q], Caroline Besson[r,s], Lucia Prezioso[t], Summiya Nizamuddin[u], Julio Dávila-Valls[v], Sonia Martín-Pérez[v], Valentina Bonuomo[w,x], Jaap Van Doesum[y], Maria Chiara Tisi[z], Francesco Passamonti[aa], Gustavo-Adolfo Méndez[ab], Stef Meers[ac], Johan Maertens[ad,ae], Alberto López-García[af], Andreas Glenthøj[ag], Matteo Bonnani[ah], Ikhwan Rinaldi[ai], Irati Ormazabal-Vélez[aj], Jorge Labrador[ak], Austin Kulasekararaj[al], Ildefonso Espigado[am], Fatih Demirkan[an], Nick De Jonge[ao], Graham P. Collins[ap], Maria Calbacho[aq], Ola Blennow[ar], Murtadha Al-Khabori[as], Tatjana Adžić-Vukičević[at], Elena Arellano[am], Bojana Mišković[at,au], Miloš Mladenović[at,au], Anna Nordlander[ar], ZdeněkRáčil[av], Emanuele Ammatuna[y], Raul Cordoba[aw], Ditte Stampe Hersby[ax], Stefanie Gräfe[b,c,ay,az], Ziad Emarah[a], Michaela Hanakova[av], Maria Vittoria Sacchi[m], Marriyam Ijaz[bb], Laman Rahimli[b,c], Raquel Nunes Rodrigues[k], Giovanni Paolo Maria Zambrotta[i,bc], Francesco Marchesi[bd†], Oliver A. Cornely[b,c,be,bf,bg†] and Livio Pagano[ah,bh†]

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ABSTRACT

Since the beginning of the COVID-19 pandemic, there has been an overall improvement in patient mortality. However, haematological malignancy patients continue to experience significant impacts from COVID-19, including high rates of hospitalization, intensive care unit (ICU) admissions, and mortality. In comparison to other haematological malignancy patients, individuals with chronic myeloid leukemia (CML) generally have better prognosis. This study, conducted using a large haematological malignancy patient database (EPICOVIDEHA), demonstrated that the majority of CML patients experienced mild infections. The decline in severe and critical infections over the years can largely be attributed to the widespread administration of vaccinations and the positive response they elicited. Notably, the mortality rate among CML patients was low and exhibited a downward trend in subsequent years. Importantly, our analysis provided confirmation of the effectiveness of vaccinations in CML patients.

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Introduction

Chronic myeloid leukemia (CML) is a rare myeloproliferative neoplasm that affects approximately 1–2 individuals per 100,000 adults. It is characterized by the presence of BCR-ABL1 protein resulting from the fusion of the BCR gene on chromosome 22 and the ABL1 gene on chromosome 9 [1]. Following the introduction of tyrosine kinase inhibitors (TKIs) as a treatment for CML, there have been substantial changes in therapeutic options. This advancement has led to a remarkable improvement in overall survival rates, increasing from 20% to 90% [2,3]. As a result, the life expectancy of CML patients has now become comparable to that of the general population across all age groups [4]. Generally, TKIs are well tolerated [5]. However, during the initial months of TKIs treatment, some patients may experience grade 3–4 neutropenia, with a toxicity incidence of 14%–17% [6]. Infections, primarily viral, can occur in around 14% of patients treated with imatinib, while the incidence varies between 1 and 8% with second-generation TKIs [6].

The emergence of coronavirus disease 2019 (COVID-19) in December 2019 led to a global pandemic with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) acquiring multiple mutations, resulting in variants of concern such as Alpha, Beta, Gamma, Delta, and Omicron [7,8]. TKIs have demonstrated antiviral efficacy against coronaviruses *in vitro*. However, some TKIs may produce effects similar to those caused by COVID-19 [9]. The mortality for patients with high-risk hematologic malignancies has ranged from 14% to 34% [10–12]. With the introduction of COVID-19 vaccinations in subsequent years, the overall mortality rate has decreased. However, among patients with haematological malignancy, the mortality rate remains higher compared to other malignancies [13]. Despite this, CML patients with COVID-19 generally have better prognosis compared to those with other hematologic malignancies [10].

The primary objective of this study is to evaluate the mortality of CML patients with COVID-19 during the years 2020, 2021, and 2022. Additionally, the study examines the COVID-19 vaccination rate and its impact on mortality and other prognostic factors in CML patients.

Methods

In February 2020, the EPICOVIDEHA was established as an international cooperative registry by the European Hematology Association (EHA) Specialized Working Group 'Infection in Hematology'. The multicenter, non-interventional study (Study ID: 3226) received approval from the local Institutional Review Board and Ethics Committee of the Fondazione Policlinico Universitario Agostino Gemelli—IRCCS, Università Cattolica del Sacro Cuore in Rome, Italy. Additionally, the EPICOVIDEHA project may require authorization from the local ethics committee of each participating institution. The registration number for EPICOVIDEHA on ClinicalTrials.gov is NCT 04733729 (http://www.clinicaltrials.gov).

Researchers from any location were invited to report any instances of COVID-19 recorded in patients with haematological malignancies at their respective institutions since the onset of the pandemic. The electronic case report form was accessible online at www.clinicalsurveys.net (EFS Summer 2021, TIVIAN GmbH,

Cologne, Germany). Participating institutions could contribute anonymized clinical data through a survey covering various topics, including identification, demographics, underlying conditions, hematological malignancy, COVID-19, and mortality. Cases meeting the following inclusion criteria were eligible for registration: (1) age 18 or older, (2) a history of active hematological malignancy at any stage within the five years preceding COVID-19, and (3) confirmation of SARS-CoV-2 infection through real-time reverse transcriptase polymerase chain reaction (RT-PCR) diagnostic panels or antigen test kits.

COVID-19 severity was set as follows: asymptomatic (absence of clinical signs or symptoms); mild (non-pneumonia and mild pneumonia); severe (characterized by dyspnea, respiratory rate ≥30 breaths per minute, SpO2 ≤ 93%, PaO2/FiO2 < 300, or lung infiltrates >50%); and critical, primarily encompassing patients requiring intensive care (experiencing respiratory failure, septic shock, or multiple organ dysfunction or failure) (which also encompassed critical cases).

Qualitative demographic and clinical data were described using frequencies and percentages, while quantitative variables were summarized using medians and interquartile ranges (IQR). Appropriate statistical tests such as the Chi-squared test, Fisher's exact test, and Mann-Whitney U test were employed for making comparisons. The use of Cox multivariable regressions allowed for the identification of predictors of mortality. The statistical analysis was performed using SPSS software (version 25.0, Chicago, IL, United States).

Results

From February 2020 to September 2022, a total of 231 CML patients with COVID-19 were enrolled in the EPICOVIDEHA registry. Among them, males accounted for 55.8% ($n = 129$) of the entire cohort. The median age at the time of infection was 56 years, with an IQR of 21–90 and a range of 44–70. Out of all the patients, 56 (24.2%) had received a vaccination before contracting COVID-19. Specifically, in 2021, 21 out of 43 patients (48.8%) had been vaccinated, while in 2022, 35 out of 46 patients (76.1%). In terms of SARS-CoV-2 variants, 6 patients (2.6%) were infected with the Wild type, 2 patients (0.9%) with the Delta variant, and 26 patients (11.3%) with the Omicron variant. In 2022, the Omicron variant was the only documented variant and affected 20 patients (43.5%). As for the severity of infection, 50 patients (21.6%) experienced asymptomatic SARS-CoV-2 infection, while 99 patients (42.9%) had a mild infection. Severe and critical infections were observed in a total of 82 patients (35.5%). The rate of severe and critical infections significantly decreased over time, with 61/142 patients (43%) in 2020, 13/43 patients (30.3%) in 2021, and 8/46 patients (17.4%) in 2022. During the course of COVID-19, CML patients were monitored for haematological grade 3-4 TKIs-related adverse events, which revealed a prevalence of 3% for anemia ($n = 7$), 2.2% for neutropenia ($n = 5$), 1.7% for thrombocytopenia ($n = 4$), 0.9% for thrombosis ($n = 2$), and 0.9% for hemorrhage ($n = 2$). Non-haematological TKIs-related adverse events

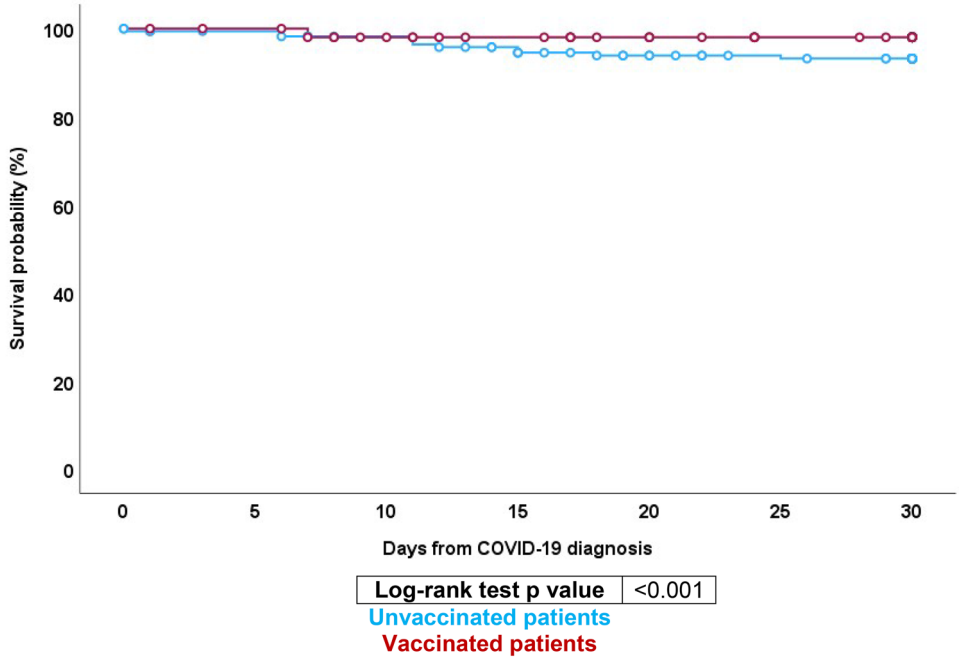

Figure 1. Overall survival for vaccinated vs not vaccinated.

included 2.2% pulmonary events ($n=5$), 1.7% musculoskeletal events ($n=4$), 1.3% gastrointestinal events ($n=3$), 0.4% hepatotoxic events, and non-viral infections ($n=1$). Out of all the patients, 96 (41.6%) were admitted to the hospital, with a median stay duration of 13 d, with an IQR of 6.5–21.5 and a range of 1–130. The rate of hospital admission was significantly higher in 2020 compared to 2021 and 2022 ($p=.004$). Additionally, 16 CML patients were admitted to the intensive care unit (ICU) for a median duration of 12 d, with 13 patients (9.2%) in 2020 and 3 patients (7%) in 2021 (Tables 1 and 2).

The study examined the overall survival rate, revealing that 92.2% (213/231) of individuals were alive at the end of the follow-up period. Significant variations were observed in the distribution of patients based on their age, with a median age of 55 among those who survived, compared to 72 among those who did not ($p=.005$). The presence of comorbidities at the onset of COVID-19 also had a notable impact on mortality. Patients without comorbidities had a higher survival rate ($n=115$, 54.0%) compared to those with comorbidities, which ranged from 8.5% ($n=18$) to 24.9% ($n=53$, $p=.005$). Chronic cardiopathy and diabetes mellitus were particularly concerning, with the latter significantly affecting survival ($p=.007$). The history of malignancy treatment also exhibited significant differences. Patients who received drug-based therapies had an 86.1% ($n=199$) survival rate. However, the specific type of treatment played a crucial role, with first-generation TKIs like imatinib showing better survival rates compared to other TKIs. Furthermore, patients treated within the last month before the onset of COVID-19 had a higher survival rate ($n=158$, 68.4%) compared to those treated further in the past. Survival rates among patients also varied based on their malignancy status at the onset of COVID-19. Patients with controlled malignancy had a higher survival rate ($n=165$, 77.5%) compared to those with active malignancy ($n=22$, 10.3%) or stable malignancy ($n=23$, 10.8%). Regarding vaccination status, there were noticeable trends, with vaccinated patients showing a lower mortality rate ($n=1$, 5.6%) compared to those who were not vaccinated ($n=17$, 94.4%), although the difference did not reach statistical significance ($p=.081$). More specifically, Six patients had received just one vaccine dose, and all of them successfully recovered (100%). In the group that received two vaccine doses, consisting of 16 patients, only one patient did not survive (93.75% survival rate). On the other hand, among the 32 patients who received three vaccine doses, all of them made a full recovery (100% survival rate). Additionally, one patient who had received four vaccine doses also emerged as a survivor in our study (100% survival rate) (Figure 1). Across the study duration, the hospital admission rate stood at 41.5% ($n=96$), with 36.6% ($n=78$) among surviving patients and a full 100.0% ($n=18$) among deceased patients ($p<.001$, Tables 1 and 2).

The univariable Cox regression model revealed that older age, baseline active malignancy, baseline cardiopathy, diabetes mellitus, liver disease, COVID-19 diagnosis *via* screening, and admission in the ICU unit were associated with a higher mortality. In the multivariable Cox regression analysis, however, age-stable malignancy at COVID-19, and ICU admission (Table 3).

There was no significant difference in overall survival probability across years (Figure 2).

Discussion

The data presented in this study indicate that CML patients predominantly experienced mild infections. The rates of severe and critical infections, as well as hospital and ICU admissions, were higher in 2020 compared to 2021 and 2022. Furthermore, the mortality rate was higher in 2020 and among unvaccinated patients. Multivariable analysis identified age, CML disease status, and ICU admission as significant independent predictors of mortality.

Following the onset of the COVID-19 outbreak, a study conducted in Hubei, China, focused on 530 CML outpatients who completed questionnaires, revealing a low prevalence of COVID-19 (0.9%) [14]. This observation was corroborated by other studies, which also demonstrated a mild course of COVID-19 in CML patients [15–17]. In the current study, it was found that 21.6% of patients had asymptomatic COVID-19, while 42.9% experienced a mild infection. Severe and critical infections were confirmed in approximately one-third of patients (35.5%). These findings are consistent with previous studies involving smaller numbers of CML patients [17–19].

During the initial year of the pandemic, a total of 3,801 patients were analyzed by EPICOVIDEHA, revealing an overall mortality rate of 31% [20]. In the present analysis, which included 231 CML patients, the mortality rate was approximately 8%. A study focusing on 217 CML patients with COVID-19 reported a mortality rate of 5.5% during the first year of the pandemic [21]. In other studies, with smaller patient populations, the mortality rates ranged between 6.3% and 11.1% [16,17,19]. Notably, the incidence of mortality among CML patients was lower compared to other hematologic malignancies, suggesting a potential protective

Table 1. Demographic, clinical characteristics, and summary of received treatments for CML at the time of COVID-19 diagnosis.

	Overall		Alive		Dead		
	n	%	*n*	%	*n*	%	*p* value
	231	100.0	213	92.2	18	7.8	
Sex							
Female	102	44.2	94	44.1	8	44.4	0.980
Male	129	55.8	119	55.9	10	55.6	
Age	56 (44–70) [21–90]		55 (43–67) [21–90]		72 (59–82) [29–90]		**0.005**
Comorbidities at COVID-19 onset							
No comorbidities	118	51.1	115	54.0	3	16.7	**0.005**
1 comorbidity	59	25.5	53	24.9	6	33.3	
2 comorbidities	32	13.9	27	12.7	5	27.8	
3 or more comorbidities	22	9.5	18	8.5	4	22.2	
Chronic cardiopathy	58	25.1	48	22.5	10	55.6	**0.004**
Chronic pulmonary disease	21	9.1	18	8.5	3	16.7	0.216
Diabetes mellitus	33	14.3	26	12.2	7	38.9	**0.007**
Liver disease	11	4.8	7	3.3	4	22.2	**0.006**
Obesity	25	10.8	24	11.3	1	5.6	0.701
Renal impairment	15	6.5	12	5.6	3	16.7	0.100
Smoking history	20	8.7	19	8.9	1	5.6	1.000
Chronic myeloid leukemia							
CCI	3 (2–6) [0–30]		3 (2–5) [0–30]		6 (6–6) [6–6]		0.375
Month of diagnosis prior to COVID-19 onset	48 (16–112) [0–372]		48 (17–108) [0–372]		58 (12–120) [0–245]		0.780
Last malignancy treatment immediately before COVID-19 onset							**0.033**
Drug-based therapies	215	93.1	199	86.1	16	6.9	
In the last month	172	74.5	158	68.4	14	6.1	
1G TKIs (Imatinib)	77	33.3	68	29.4	9	3.9	
Imatinib	77	33.3	68	29.4	9	3.9	
2G TKIs	76	32.9	74	32.0	2	0.9	
Bosutinib	11	4.8	11	4.8	0	0.0	
Dasatinib	36	15.6	35	15.2	1	0.4	
Nilotinib	29	12.6	28	12.1	1	0.4	
3G TKIs	12	5.2	11	4.8	1	0.4	
Asciminib	4	1.7	4	1.7	0	0.0	
Ponatinib	8	3.5	7	3.0	1	0.4	
Conventional chemotherapy	6	2.6	5	2.2	1	0.4	
Demethylating agents	1	0.4	0	0.0	1	0.4	
In the last 3 months	18	7.8	18	7.8	0	0.0	
1G TKIs	8	3.5	8	3.5	0	0.0	
Imatinib	8	3.5	8	3.5	0	0.0	
2G TKIs	6	2.6	6	2.6	0	0.0	
Bosutinib	4	1.7	4	1.7	0	0.0	
Nilotinib	2	0.9	2	0.9	0	0.0	
Conventional chemotherapy	1	0.4	1	0.4	0	0.0	
Demethylating agents	1	0.4	1	0.4	0	0.0	
Immunochemotherapy	1	0.4	1	0.4	0	0.0	
Immunochemotherapy + TKIs	1	0.4	1	0.4	0	0.0	
> 3 months	12	5.2	11	4.8	1	0.4	
1G TKIs	6	2.6	6	2.6	0	0.0	
Imatinib	6	2.6	6	2.6	0	0.0	
2G TKIs	4	1.7	4	1.7	0	0.0	
Bosutinib	1	0.4	1	0.4	0	0.0	
Dasatinib	1	0.4	1	0.4	0	0.0	
Nilotinib	2	0.9	2	0.9	0	0.0	
3G TKIs	1	0.4	1	0.4	0	0.0	
Ponatinib	1	0.4	1	0.4	0	0.0	
Demethylating agents	1	0.4	0	0.0	1	0.4	
Not reported	13	5.6	12	5.2	1	0.4	
1G TKIs	5	2.2	5	2.2	0	0.0	
Imatinib	5	2.2	5	2.2	0	0.0	
2G TKIs	7	3.0	6	2.6	1	0.4	
Dasatinib	2	0.9	2	0.9	0	0.0	
Nilotinib	5	2.2	4	1.7	1	0.4	
Conventional chemotherapy	1	0.4	1	0.4	0	0.0	
HSCT therapies	10	4.3	9	3.9	1	0.4	
In the last 6 months	4	1.7	4	1.7	0	0.0	
> 6 months	6	2.6	5	2.2	1	0.4	
No treatment	6	2.6	5	2.2	1	0.4	
Status malignancy at COVID-19 onset							**0.009**
Controlled disease	173	74.9	165	77.5	8	44.4	
Stable disease	27	11.7	23	10.8	4	22.2	
Active disease	27	11.7	22	10.3	5	27.8	
Unknown	4	1.7	3	1.4	1	5.6	
Vaccination status at COVID-19 onset							0.081
Not vaccinated	175	75.8%	158	74.2%	17	94.4%	
Vaccinated	56	24.2%	55	25.8%	1	5.6%	

CCI: Charlson comorbidity index; G TKIs: generation tyrosine kinase inhibitor; HSCT: hematopoietic stem cell transplantation

role of TKIs [22]. *In vitro* experiments have indicated that imatinib may block the fusion of the coronavirus's Spike protein with cell membranes, thereby preventing virus activation and endocytosis [23–25].

In this analysis, approximately one-fourth of the CML patients received vaccination, and among them, the mortality rate was 1.7% (1 out of 56 patients). In contrast, the mortality rate for unvaccinated patients was 9.7%. In 2022, out of 46 patients, 76.1% were vaccinated, and no critical infections, ICU admissions, or deaths were recorded among these vaccinated patients. A study evaluating the outcomes of serological testing

Table 2. Clinical features of COVID-19 in CML patients.

	Overall		Alive		Dead		
	n	%	*n*	%	*n*	%	*p* value
Symptoms at COVID-19 onset							**0.001**
Pulmonary	116	50.2	109	51.2	7	38.9	
Pulmonary + extrapulmonary	54	23.4	48	22.5	6	33.3	
Extrapulmonary	57	24.7	55	25.8	2	11.1	
Screening	4	1.7	1	0.5	3	16.7	
COVID-19 status							**<0.001**
Asymptomatic	50	21.6	50	23.5	0	0.0	
Mild infection	99	42.9	95	44.6	4	22.2	
Severe infection	66	28.6	61	28.6	5	27.8	
Critical infection	16	6.9	7	3.3	9	50.0	
Neutrophils at COVID-19 onset (×109/mm3)							1.000
<0.501	1	0.4	1	0.5	0	0.0	
0.501–0.999	5	2.2	5	2.3	0	0.0	
>0.999	161	69.7	145	68.1	16	88.9	
Lymphocytes at COVID-19 onset (×109/mm3)							**0.030**
<0.201	4	1.7	3	1.4	1	5.6	
0.201–0.499	9	3.9	6	2.8	3	16.7	
>0.499	157	68.0	144	67.6	13	72.2	
Stay during COVID-19							
Home	149	64.5	148	69.5	1	5.6	**<0.001**
Hospital	96	41.6	78	36.6	18	100.0	**<0.001**
Duration in days	13 (6.5–21.5) [1–130]		11 (6–21) [1v130]		14 (11–30) [2–50]		0.125
ICU	16	6.9	7	3.3	9	50.0	**<0.001**
Non-invasive ventilation	5	2.2	2	0.9	3	16.7	1.000
Invasive ventilation	8	3.5	4	1.9	4	22.2	
Duration in days	12 (6–20) [1–115]		27 (13–40) [1–115]		8 (5–12) [2–20]		0.073
COVID-19 treatment							0.385
No specific treatment reported	92	39.8	87	40.8	5	27.8	
Antivirals ± corticosteroids ± plasma	12	5.2	12	5.6	0	0.0	
Antivirals + monoclonal antibodies ± corticosteroids ± plasma	2	0.9	2	0.9	0	0.0	
Monoclonal antibodies ± corticosteroids ± plasma	8	3.5	8	3.8	0	0.0	
Plasma ± corticosteroids	0	0.0	0	0.0	0	0.0	
Corticosteroids	10	4.3	8	3.8	2	11.1	
Unknown	107	46.3	96	45.1	11	61.1	
Hematologic grade 3-4 TKIs-related adverse events during COVID-19							
Anemia	7	3.0	6	2.8	1	5.6	0.258
Bleeding	2	0.9	2	0.9	0	0.0	1.000
Neutropenia	5	2.2	4	1.9	1	5.6	0.189
Thrombocytopenia	4	1.7	3	1.4	1	5.6	0.154
Thrombosis	2	0.9	2	0.9	0	0.0	1.000
None of the above	63	27.3	62	29.1	1	5.6	0.065
Unknown	148	64.1	134	62.9	14	77.8	
Non-hematologic TKIs-related adverse events during COVID-19							
Cardiac	2	0.9	2	0.9	0	0.0	1.000
Gastrointestinal	3	1.3	3	1.4	0	0.0	1.000
Hepatotoxicity	1	0.4	1	0.5	0	0.0	1.000
Infections (bacterial, fungal)	1	0.4	1	0.5	0	0.0	1.000
Musculoskeletal	4	1.7	4	1.9	0	0.0	1.000
Neurological	1	0.4	1	0.5	0	0.0	1.000
Pulmonary	5	2.2	4	1.9	1	5.6	0.189
Renal impairment	2	0.9	2	0.9	0	0.0	1.000
Others	2	0.9	1	0.5	1	5.6	0.079
None of the above	62	26.8	61	28.6	1	5.6	0.076
Unknown	148	64.1%	133	62.4%	15	83.3%	
Mortality							
Observation days	68.5 (22–235) [0–815]		78 (24–252) [0–815]		15 (11–61) [0–509]		**0.001**
Reason for mortality							
COVID-19	14	6.1	0	0.0	14	77.8	
COVID-19 + haematological malignancy	4	1.7	0	0.0	4	22.2	

Table 3. Overall mortality predictors in COVID-19 CML patients.

	Univariable analysis				Multivariable analysis			
			95% CI				95% CI	
	p value	HR	Lower limit	Lower limit	*p* value	HR	Lower limit	Upper limit
Sex								
Female	–	–	–	–				
Male	0.976	0.986	0.389	2.500				
Age	**0.009**	1.043	1.010	1.076	**0.011**	1.043	1.010	1.078
Status malignancy at COVID-19 onset								
Controlled disease	–	–	–	–	–	–	–	–
Stable disease	0.066	3.092	0.929	10.286	**0.021**	4.680	1.256	17.438
Active disease	**0.011**	4.266	1.395	13.048	0.056	3.096	0.971	9.875
Unknown	**0.035**	9.615	1.176	78.581	0.266	3.483	0.386	31.412
Comorbidities at COVID-19 onset								
No comorbidities	–	–	–	–				
1 comorbidity	0.066	3.666	0.916	14.670				
2 comorbidities	**0.015**	5.887	1.404	24.676				
3 or more comorbidities	**0.009**	7.412	1.657	33.156				
COVID-19 status								
Asymptomatic	–	–	–	–				
Mild infection	0.926	.	0.000	.				
Severe infection	0.922	.	0.000	.				
Critical infection	0.906	.	0.000	.				
Chronic cardiopathy	**0.007**	3.629	1.430	9.209	0.804	0.848	0.232	3.103
Chronic pulmonary disease	0.271	2.008	0.581	6.939				
Diabetes mellitus	**0.005**	3.859	1.492	9.981	0.495	1.511	0.461	4.952
Liver disease	**0.002**	5.715	1.872	17.446	0.058	3.021	0.962	9.489
Obesity	0.348	0.380	0.050	2.871				
Renal impairment	0.080	3.048	0.877	10.599	0.374	2.024	0.428	9.571
Smoking history	0.718	0.689	0.092	5.187				
Last malignancy treatment immediately before COVID-19 onset								
No treatment	–	–	–	–				
1G TKIs (Imatinib)	0.622	0.593	0.074	4.740				
2G TKIs (Bosutinib, Dasatinib, Nilotinib)	0.131	0.174	0.018	1.688				
3G TKIs (Asciminib, Ponatinib)	0.580	0.457	0.029	7.324				
alloHSCT	0.978	0.962	0.060	15.492				
Conventional chemotherapy	0.972	0.952	0.059	15.268				
Demethylating agents	0.084	8.720	0.750	101.318				
Immunochemotherapy	0.985	0.000	0.000	.				
Immunochemotherapy + TKIs	0.996	0.000	0.000	.				
Anti-SARS-CoV-2 vaccination	0.237	0.293	0.038	2.243				
SARS-CoV-2 variant								
Wild type	–	–	–	–				
Delta	0.996	0.000	0.000	.				
Omicron	0.983	0.000	0.000	.				
Not tested	0.415	0.432	0.057	3.258				
Neutrophils at COVID-19 onset (×109/mm3)								
<0.501	–	–	–	–				
0.501–0.999	0.914	0.883	0.091	8.585				
>0.999	0.193	0.259	0.034	1.984				
Lymphocytes at COVID-19 onset (×109/mm3)								
<0.201	–	–	–	–				
0.201–0.499	–	–	–	–				
>0.499	0.632	21.218	0.000	.				
Symptoms at COVID-19 onset								
Pulmonary	–	–	–	–	–	–	–	–
Pulmonary + extrapulmonary	0.141	2.278	0.761	6.821	0.547	0.638	0.148	2.747
Extrapulmonary	0.533	0.607	0.126	2.923	0.957	0.953	0.169	5.385
Screening	**<0.001**	17.611	4.449	69.720	0.863	0.810	0.074	8.894
ICU admission	**<0.001**	15.125	5.934	38.553	**<0.001**	13.349	4.594	38.789
COVID-19 treatment								
No specific treatment reported	–	–	–	–				
Antivirals ± corticosteroids ± plasma	0.989	0.000	0.000	.				
Antivirals + monoclonal antibodies ± corticosteroids ± plasma	0.996	0.000	0.000	.				
Monoclonal antibodies ± corticosteroids ± plasma	0.990	0.000	0.000	.				
Corticosteroids	0.143	3.443	0.659	17.992				
Unknown	0.253	1.864	0.641	5.419				

HR: hazard ratio; G TKIs: generation tyrosine kinase inhibitor

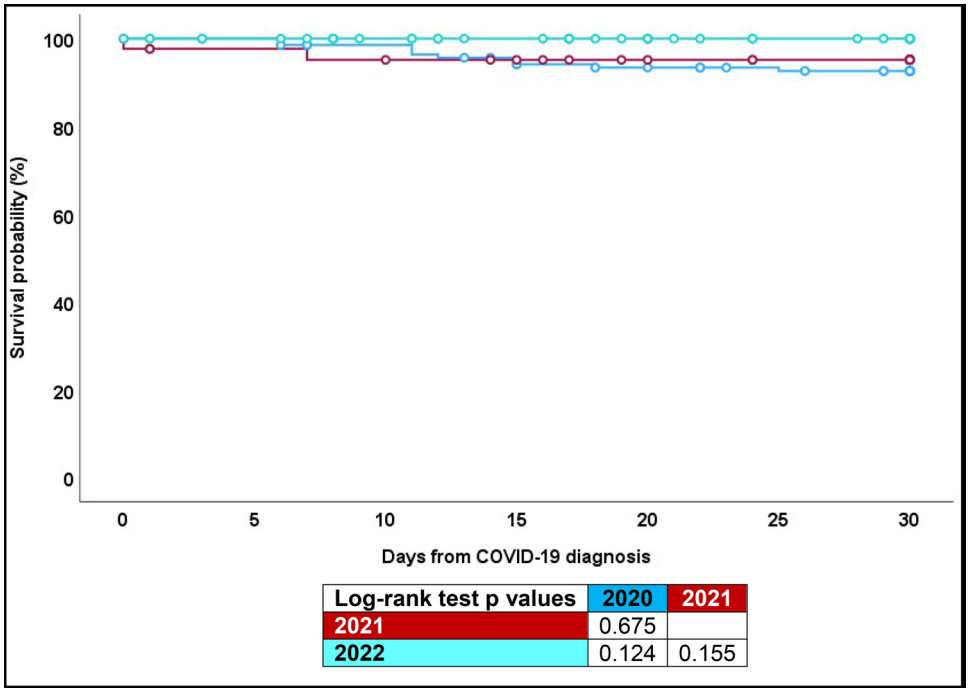

Figure 2. Overall survival across years.

in CML patients revealed similarities to the general population, indicating that CML patients can generate an adequate antibody response to SARS-CoV-2 [26–28]. Despite the risk of impaired antibody production in many patients with hematological malignancies, the rate of seronegative patients after COVID-19 vaccination was reported to be 2.9% in CML patients [29]. Furthermore, CML patients using TKIs exhibited a higher response to mRNA COVID-19 vaccination compared to other hematologic malignancies, and the response was nearly comparable to that observed in healthy individuals [30]. Additionally, after receiving the vector-based vaccine GamCOVIDVac (Sputnik V), chronic phase CML patients demonstrated a seroconversion rate of about 93–94% [31]. The robust response to COVID-19 vaccination may have a positive impact on the survival of CML patients following COVID-19 infection. In a matched cohort study involving chronic phase CML patients, those who did not receive a COVID-19 vaccination were found to have an increased risk of hospitalization compared to the control group [32].

In our study, approximately 40% of the patients were hospitalized, with a median hospital stay of 13 d. The overall mortality rate was 7.8%, and this rate decreased over the course of the pandemic. Among the patients identified in 2020 without a COVID-19 vaccine, 142 (61.5%) had a higher risk of experiencing severe and life-threatening infections, requiring hospitalization, ICU admission, and facing mortality compared to patients identified in 2021 and 2022. The results of the multivariable analysis revealed that age, stable malignancy status, and ICU admission were significant independent factors associated with mortality. These findings further confirm the beneficial effect of vaccination in CML patients. Moreover, the results illustrate that, within our patient sample, individuals with active malignancies faced a reduced risk of mortality in comparison to the patients with a stable malignancy. This observation might be attributed to the predominance of newly onset malignancies rather than refractory cases.

This study has several limitations, including its retrospective design and a small number of patients. Additionally, the survey did not clearly define the status of CML patients, as it relied on practitioners' indications of whether the disease was active, controlled, or stable. The Sokal or Hasford scores, which are commonly used to assess the severity and prognosis of CML, were not monitored in the database. It is important to note that our survey may not capture the entirety of CML cases from each participating institution, and there is no means to ascertain whether all institutions contributed all their CML cases. Additionally, given the longitudinal nature of our sample, it's noteworthy that the overall vaccination rate could be perceived as relatively low. Various factors may contribute to this, including vaccine availability in the respective country, medical advice provided by physicians, and individual patient decisions.

In conclusion, this large database supports the finding that the majority of CML patients experience mild cases of COVID-19 during the pandemic. The incidence

of mortality is low and has decreased over time. Furthermore, vaccinations have shown to be highly effective in CML patients. The beneficial effects of COVID-19 vaccinations in CML patients are reflected in the lower mortality rates and reduced occurrence of severe COVID-19 infections.

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