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CLINICAL TRIALS AND OBSERVATIONS

Breakthrough COVID-19 in vaccinated patients with hematologic malignancies: results from the EPICOVIDEHA survey

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KEY POINTS

- **Mortality rate in patients with hematologic malignancy with breakthrough COVID-19 is ~9%, lower than in the prevaccination era.**
- **Patients who received monoclonal antibodies, alone or combined with antivirals, showed a better clinical outcome.**

Limited data are available on breakthrough COVID-19 in patients with hematologic malignancy (HM) after anti–severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination. Adult patients with HM, ≥1 dose of anti-SARS-CoV-2 vaccine, and breakthrough COVID-19 between January 2021 and March 2022 were analyzed. A total of 1548 cases were included, mainly lymphoid malignancies (1181 cases, 76%). After viral sequencing in 753 cases (49%), the Omicron variant was prevalent (517, 68.7%). Most of the patients received ≤2 vaccine doses before COVID-19 (1419, 91%), mostly mRNA-based (1377, 89%). Overall, 906 patients (59%) received COVID-19-specific treatment. After 30-day follow-up from COVID-19 diagnosis, 143 patients (9%) died. The mortality rate in patients with the Omicron variant was 7.9%, comparable to other variants, with a significantly lower 30-day mortality rate than in the prevaccine era (31%). In the univariable analysis, older age ($P < .001$), active HM ($P < .001$), and severe and critical COVID-19 ($P = .007$ and $P < .001$, respectively) were associated with mortality. Conversely, patients receiving monoclonal antibodies, even for severe or critical COVID-19, had a lower mortality rate ($P < .001$). In the multivariable model, older age, active disease, critical COVID-19, and 2-3 comorbidities were correlated with a higher mortality, whereas monoclonal antibody administration, alone ($P < .001$) or combined with antivirals ($P = .009$), was protective. Although mortality is significantly lower than in the prevaccination era, breakthrough COVID-19 in HM is still associated with considerable mortality. Death rate was lower in patients who received monoclonal antibodies, alone or in combination with antivirals.

Introduction

Coronavirus disease 2019 (COVID-19) is a life-threatening infection in patients with hematologic malignancies (HM), associated with severe clinical presentation and high risk of death.[1-3] In April 2020, the European Hematology Association's Specialized Working Group, Infections in Hematology, opened the EPICOVIDEHA (Epidemiology of COVID-19 Infection in Patients with Hematological Malignancies: European Haematology Association) registry to collect data on all adult patients with HM who developed COVID-19. It aimed to describe the epidemiology and risk factors, and reported a mortality rate of 31.2% among 3801 patients.[4] In December 2020, nearly 1 year after the first described COVID-19 case, vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were approved and became available first to patients at high risk, including patients with HM.[5-8] The recently published recommendations from the European Conference of Infections in Leukemia (ECIL-9) identify the critical role of messenger RNA (mRNA)-based vaccines in the fight against COVID-19 and recommend their use in HM, although they may have more limited efficacy among severely immunocompromised patients.[9]

We collected data on adults with HM who developed breakthrough COVID-19, to assess the vaccine efficacy and the potential role of new emergent treatments against SARS-CoV-2. Our preliminary data, regarding the first 113 patients included, showed a significant decrease in the overall mortality rate in the postvaccination era (12.4%), which was, however, still remarkably higher than the rate observed in the overall population.[10] To date, few reports have been published on the severity and outcomes of breakthrough COVID-19 in patients with cancer in general[11,12] and HM specifically,[13] all showing high rates of severe clinical presentation, hospitalization, and death among these patients. This suggests that HM require close monitoring and increased medical attention when COVID-19 is diagnosed, regardless of previous anti-SARS-CoV-2 vaccine administration.

In this study, we analyzed the epidemiology and outcome of breakthrough COVID-19 in a large cohort of patients with HMs and evaluated anti-SARS-CoV-2 treatment received by these patients.

Methods

Study design, patients, and procedures

From 1 January 2021 to 10 March 2022, participating institutions documented episodes of COVID-19 in patients with HM that received anti-SARS-CoV-2 vaccination. Our analysis comprised data from the EPICOVIDEHA registry. EPICOVIDEHA (www.clinicaltrials.gov; National Clinical Trials identifier NCT04733729) is an international open web-based registry for patients with HMs infected with SARS-CoV-2.[14] The EPICOVIDEHA registry was approved by the local ethics committee of the Fondazione Policlinico Universitario Agostino Gemelli, RCCS, Università Cattolica del Sacro Cuore of Rome, Italy (Study ID: 3226). When applicable, the respective local ethics committee of each participating institution had approved the project. EPICOVIDEHA methods have been described elsewhere.[4,14] The electronic case report form is accessible online at www.clinicalsurveys.net (EFS Summer 2021, Tivian, Cologne, Germany). Each patient that had been documented was reviewed and validated by infectious diseases and

Table 1. Clinical characteristics of 1548 vaccinated patients with HM who developed COVID-19

	n	%
Sex		
Female/male	661/887	42.7/57.3
Age		
Median, y (IQR) [range]	66 (55-75) [18-96]	
<50/>50 y	301/1247	19.5/80.5
Comorbidities		
None/1-2-3 comorbidities	608/940	39.3/60.7
Smoking history	180	11.6
Malignancy		
Lymphoid malignancies	1181	76.3
Acute lymphoid leukemia	64	4.1
Chronic lymphoid leukemia	211	13.6
Hodgkin lymphoma	65	4.2
Non-Hodgkin lymphoma	549	35.5
Low grade	289	18.7
High grade	260	16.8
Multiple myeloma	275	17.8
Amyloid light-chain amyloidosis	10	0.6
Hairy cell leukemia	7	0.5
Myeloid malignancies	356	23.0
Acute myeloid leukemia	140	9.0
Chronic myeloid leukemia	44	2.8
Essential thrombocythemia	18	1.2
Myelodysplastic syndromes	93	6.0
Low-intermediate risk	69	4.5
High risk	23	1.5
Myelofibrosis	39	2.5
Polycythemia vera	16	1.0
Systemic mastocytosis	6	0.4
Aplastic anemia	11	0.7
Malignancy status before COVID-19		
Controlled disease	821	53.0
Complete remission	524	33.9
Partial remission	297	19.2
Stable disease	322	20.8
Active disease	365	23.6
Onset	185	12.0
Refractory/resistant	180	11.6
Unknown	40	2.6
Last malignancy treatment		
Allo-HSCT	76	4.9
Auto-HSCT	16	1
CAR-T	8	0.5
Chemotherapy		
Conventional chemotherapy	234	15.1
Demethylating agents	80	5.2
Immunotherapy	146	5.7
Immuno-chemotherapy	562	36.3
Targeted therapy	311	20.1
Supportive measures	36	2.3
No treatment	136	8.8
Vaccination		
1 dose	129	8.3
2 doses (or J&J)	770	49.7
3 doses	639	41.3
4 doses	10	0.6
Type of vaccine		
mRNA	1377	89.0
BioNTech/Pfizer	1121	72.4
Moderna COVE	256	16.5
Vector-based	133	8.6
AstraZeneca Oxford	99	6.4
Sputnik	13	0.8
J&J (Janssen)	21	1.4
Inactivated	38	2.5
CoronaVac/Sinovac	21	1.4
Sinopharm	17	1.1
Spike protein dosage after vaccination*		
No response	135	8.7
Weak response	34	2.2
Optimal response	75	4.8
Not tested	1304	84.2
COVID-19 infection		
Wild type	40	2.6
Alpha	34	2.2
Beta	1	0.1
Delta	161	10.4
Omicron	517	33.4
Not tested	795	51.4
Severity		
Asymptomatic	283	18.3
Mild infection	604	39.0
Severe infection	509	32.9
Critical infection	152	9.8
Symptomatology at onset		
Asymptomatic	306	19.8
Pulmonary	528	34.1
Pulmonary + extrapulmonary	400	25.8
Extrapulmonary	314	20.3
Stay during COVID-19		
Hospital	823	53.2
ICU	152	9.8
Home	800	51.7

CAR-T, chimeric antigen receptor T cells; HSCT, hematopoietic stem cell transplantation.

*Referring to the World Health Organization international standards, binding antibody units per milliliter (https://www.who.int/news-room/feature-stories/detail/standardization-of-vaccines-for-coronavirusdisease-covid-19).

hematology experts from the coordination team. Inclusion criteria were: (1) active HM within the last 5 years before COVID-19 diagnosis, (2) aged ≥18 years, (3) laboratory-based diagnosis of SARS-CoV-2 infection, and (4) last vaccine dose ≥15 days before PCR confirmed SARS-CoV-2 infection. Data on baseline conditions pre-COVID-19 (ie, age, sex, status of HM at COVID-19 diagnosis, COVID-19–predisposing factors), HM clinical management (ie, last HM treatment strategy), vaccine type, spike protein concentration at diagnosis of COVID-19, COVID-19 diagnosis and management (ie, reason for diagnostic test, symptoms at onset, hospital stay during infection, treatments received for infection), and outcome (ie, mortality, attributable mortality [assessed by the medical team in charge of the patient], and last day of follow-up) were collected. Status of HM at COVID-19 onset and last follow-up was defined as active (onset and refractory/resistant), stable disease, or controlled (complete and partial response) based on the reports from the respective participating institution.

Study objectives

The primary objective of this study was to assess the epidemiology and the outcome of HM affected by breakthrough COVID-19. Secondary objectives were: (1) to estimate the relative frequency of disease severity, graded according to international standards in our patient population;[15,16] (2) to evaluate the relative frequency of intensive care unit (ICU) admission among participating patients; (3) to evaluate the overall case-fatality rate; (4) to explore the effect of cancer treatment phase (induction, consolidation, maintenance, palliative, or reinduction) on patient outcomes; (5) to explore the effect of vaccine doses administered on patient outcomes; and (6) to explore the effect of COVID-19 treatment on patient outcomes. Moreover, data collected were compared with data reported in our previously published study performed in the prevaccine era by using the same registry.[4]

Sample size and statistical analysis

No a priori sample size calculation was performed for this analysis. Categorical variables are presented with frequencies and percentages, and continuous variables with median, interquartile range (IQR), and absolute range. A univariable Cox regression model was performed with variables suspected to play a role in the mortality of patients with HM with COVID-19. Variables with a P value ≤.1 were considered for multivariable analysis. A multivariable Cox regression model was calculated with the Wald backward method. Mortality was analyzed by using Kaplan–Meier survival plots. A log-rank test was used to compare the survival probability of the patients included in the different models. A P value ≤.05 was considered statistically significant. No a priori sample size calculation was done for this exploratory study. SPSS version 25.0 was employed for statistical analyses (SPSS, IBM Corp, Chicago, IL). Patients with missing data in essential fields (ie, HM, chemotherapeutic program, vaccination status, COVID-19 management, or survival status) were considered as "not valid" and excluded from the final analysis. Among the valid cases, if a value in a specific variable was missing or unknown, it is indicated as such in the descriptive analysis. Patients with missing data in a certain variable were excluded from regression analyses in case that variable was included into such analyses.

Results

Study population

A total of 94 centers in 26 countries, mainly from Europe, participated and registered 1583 cases. A list of enrolled cases from each participating country is available in the supplemental material (supplemental Figures 1 and 2A, available on the *Blood* website). Out of these 1583 cases, 35 were excluded because COVID-19 was diagnosed within 14 days from the first vaccine dose. Clinical characteristics of 1548 evaluable cases are reported in Table 1. Lymphoid malignancies were the largest subgroup, accounting for 1181 cases (76.3%); the most frequently reported diagnosis was non-Hodgkin lymphoma (NHL, 549 cases). Among myeloid malignancies, the most frequent diagnosis was acute myeloid leukemia (AML, 140 cases). We found a significantly different distribution of lymphoid/myeloid malignancies from that reported in the prevaccination era (prevaccination lymphoid malignancy cases, 67.3%, vs postvaccination, 76.3%, P < .001). At the time of COVID-19 diagnosis, most patients had a controlled

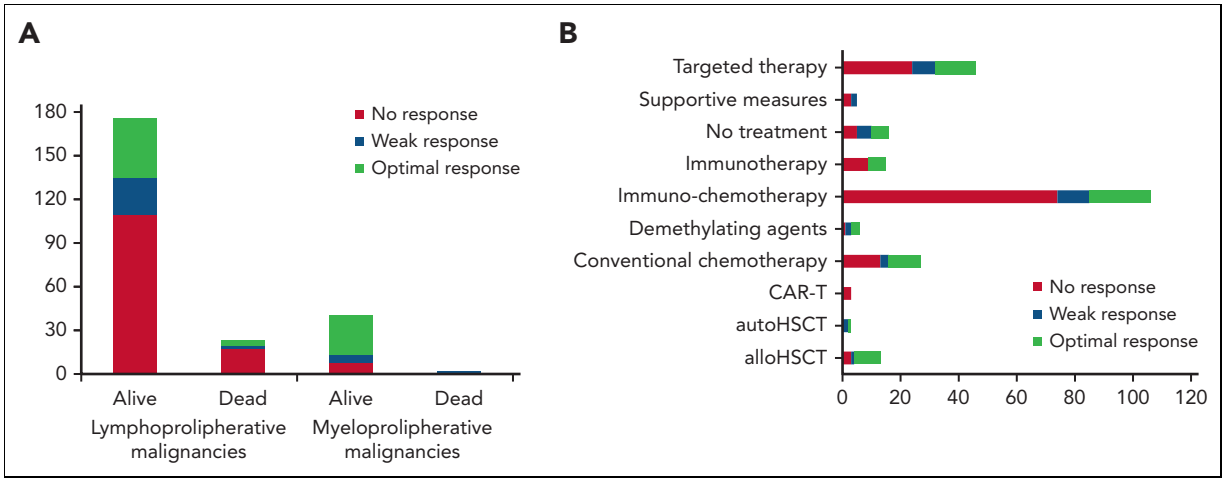

Figure 1. Patient distribution by serological response after last COVID-19 vaccination before COVID-19 diagnosis. (A) By baseline malignancy; (B) by last treatment for HM immediately before COVID-19 diagnosis.

Table 2. Outcome of vaccinated patients with HM who developed COVID-19

	Alive		Deceased		*P* value
	n	%	n		%
Outcome at 30 d after COVID-19 diagnosis					
Alive	1405	90.8			
Deceased			143	9.2	
Reason for death					
COVID-19			97	67.8	
COVID-19 + HM			39	27.2	
HM ± other reasons			7	4.8	
Sex					
Female	591	89.4	70	10.6	ns
Male	814	91.8	73	8.2	
Age					
18-25 y	46	100.0	0	0.0	<.001
26-50 y	250	98.0	5	2.0	
51-69 y	585	94.2	36	5.8	
>70 y	524	83.7	102	16.3	
Comorbidities					
No comorbidities	581	95.6	27	4.4	<.001
1 comorbidity	471	91.5	44	8.5	
2 comorbidities	223	84.8	40	15.2	
≥3 comorbidities	130	80.2	32	19.8	
Smoker or ex-smoker	158	87.8	22	12.2	
Malignancies					
Lymphoid malignancies	1070	92.8	111	7.2	ns
Acute lymphoid leukemia	62	96.9	2	3.1	
Chronic lymphoid leukemia	186	88.2	25	11.8	
Hodgkin lymphoma	63	96.9	2	3.1	
Non-Hodgkin lymphoma	497	90.5	52	9.5	
Low grade	261	90.3	28	9.7	
High grade	236	90.8	24	9.2	
Multiple myeloma	246	89.5	29	10.5	
Amyloid light-chain amyloidosis	10	100.0	0	0.0	
Hairy cell leukemia	6	85.7	1	14.3	
Myeloid malignancies	324	91.0	32	9.0	
Acute myeloid leukemia	127	90.7	13	9.3	
Chronic myeloid leukemia	43	97.7	1	2.3	
Essential thrombocythemia	18	100.0	0	0.0	
Myelodysplastic syndromes	81	87.1	12	12.9	
Low-intermediate risk	63	91.3	6	8.7	
High risk	18	78.3	5	21.7	
Myelofibrosis	34	87.2	5	12.8	
Polycythemia vera	15	93.8	1	6.3	
Systemic mastocytosis	6	100.0	0	0.0	
Aplastic anemia	11	100.0	0	0.0	

CAR-T, chimeric antigen receptor T cells; HSCT, hematopoietic stem cell transplantation; ns, not statistically significant.

*1 to 2 doses vs 3 to 4 doses; *P* = .040.

†Referring to the World Health Organization international standards, binding antibody units per milliliter (https://www.who.int/news-room/feature-stories/detail/standardization-of-vaccines-for-coronavirusdisease-covid-19).

Table 2 (continued)

	Alive		Deceased		*P* value
	n	%	n		%
Malignancy status					
Controlled disease	768	93.5	53	6.5	<.001
Complete remission	505	96.4	19	3.6	
Partial remission	263	88.6	34	11.4	
Stable disease	294	91.3	28	8.7	
Active disease	307	96.3	58	3.7	
Onset	165	89.2	20	10.8	
Refractory/resistant	142	78.9	38	21.1	
Unknown	36	90.0	4	10.0	
Last malignancy treatment before COVID-19					
Allo-HSCT	72	94.8	4	5.2	ns
Auto-HSCT	16	100.0	0	0.0	
CAR-T	6	75.0	2	25.0	
Conventional chemotherapy	215	90.6	91.9	8.1	
Demethylating agents	73	90.5	7	9.5	
Immuno-chemotherapy	512	91.2	50	8.8	
Immunotherapy	78	87.6	11	12.3	
Targeted therapy	279	89.8	32	10.2	
Supportive measures	28	77.8	8	22.2	
No treatment	126	92.6	10	7.4	
SARS-CoV-2 vaccination before COVID-19*					
1 dose	115	89.1	14	10.9	ns
2 doses	689	89.5	81	10.5	
3 doses	591	91.9	48	8.1	
4 doses	10	100.0	0	0.0	
Type of SARS-CoV-2 vaccine					
mRNA	1250	90.8	127	9.2	ns
BioNTech/Pfizer	1011	90.2	110	9.8	
Moderna COVE	239	93.4	17	6.6	
Vector-based	123	92.5	10	7.5	
AstraZeneca Oxford	91	91.9	8	8.1	
Sputnik	13	100.0	0	0.0	
J&J (Janssen)	19	90.5	2	9.5	
Inactivated	32	84.3	6	15.7	
CoronaVac/Sinovac	18	85.7	3	14.3	
Sinopharm	14	82.4	3	17.6	
Spike protein dosage after vaccination†					
No response	118	87.4	17	12.6	ns
Weak response	31	91.2	3	8.8	
Optimal response	71	94.7	4	5.3	
Not tested	1185	90.9	119	9.1	

CAR-T, chimeric antigen receptor T cells; HSCT, hematopoietic stem cell transplantation; ns, not statistically significant.

*1 to 2 doses vs 3 to 4 doses; *P* = .040.

†Referring to the World Health Organization international standards, binding antibody units per milliliter (https://www.who.int/news-room/feature-stories/detail/standardization-of-vaccines-for-coronavirusdisease-covid-19).

Table 2 (continued)

	Alive		Deceased		*P* value
	n	%	n		%
COVID-19 variant					
Wild type	36	90.0	4	10.0	ns
Alpha	30	88.2	4	11.8	
Beta	1	100.0	0	0.0	
Delta	141	87.6	20	12.4	
Omicron	476	92.1	41	7.9	
Not tested	721	90.7	74	9.3	
COVID treatment					
No specific treatment reported	618	96.3	24	3.7	<.001
Antivirals + monoclonal antibodies	98	90.7	10	9.3	
Antivirals	186	85.3	32	14.7	
Corticosteroids	185	75.2	61	24.8	
Monoclonal antibodies	302	97.1	9	2.9	
Plasma	16	69.6	7	30.4	
COVID-19 infection					
Asymptomatic	270	95.5	13	4.5	.002
Mild infection	581	96.1	23	3.9	
Severe infection	456	89.6	53	10.4	
Critical infection	98	64.5	54	35.5	
COVID-19 symptoms					
Pulmonary	473	89.6	55	10.4	.002
Pulmonary + extrapulmonary	349	87.3	51	12.8	
Extrapulmonary	297	94.6	17	5.4	
Asymptomatic	286	93.5	20	6.5	

CAR-T, chimeric antigen receptor T cells; HSCT, hematopoietic stem cell transplantation; ns, not statistically significant.

*1 to 2 doses vs 3 to 4 doses; *P* = .040.

†Referring to the World Health Organization international standards, binding antibody units per milliliter (https://www.who.int/news-room/feature-stories/detail/standardization-of-vaccines-for-coronavirusdisease-covid-19).

malignancy (n = 821, 53%), 322 (20.8%) a stable disease, and the remaining 365 (23.6%) an active disease, with 185 cases registered at HM onset. The most frequently reported last HM treatment was immuno-chemotherapy or immunotherapy alone (n = 708, 42%), followed by targeted therapies (n = 311, 20.1%) and conventional chemotherapy (n = 234, 15.1%); 92 patients (5.9%) had received hematopoietic stem cell transplantation within 6 months before COVID-19 (allogeneic 76; autologous, 16) and 8 had chimeric antigen receptor T-cell therapy. Most patients presented at least 1 comorbidity (60.7%) and 180 (11.6%) had a history of smoking; a complete list of comorbidities and associated clinical outcomes is available in the supplemental material (supplemental Table 1).

COVID-19 severity, variants, and anti-SARS-CoV-2 spike proteins

COVID-19 was mild, severe, or critical in 39%, 32.9%, and 9.8% of cases, respectively. Of the 1548 patients, 283 (18.3%) were asymptomatic and in most of them the diagnosis was made in screening programs (Table 1). We found a significantly lower rate of severe or critical cases compared with what we reported in the prevaccination era (prevaccination, 2425/3801, 63.8%, vs postvaccination, 661/1545, 42.7%; $P < .001$). Overall, 823 (53.2%) patients required hospitalization and among them 152 (18.1%) required admission to ICUs. The hospitalization and ICU admission rate was significantly lower than reported in the prevaccination era (53.2% vs 73%; $P < .001$% and 9.8% vs 18.1%; $P < .001$, respectively). The percentage of asymptomatic cases was 18.3% (283/1548), similar to that reported in our previous publication with data from the prevaccine era (17.8%, 675/3801).[4] Viral genomes were studied in 753 cases (48.6%), with the different Omicron variant the most frequently detected viral strain (517/753, 68.7%). Most patients received 2 or 3 anti-SARS-CoV-2 vaccine doses (91%), mostly with mRNA-based technology (89%); only a few patients (8.6%) received a vector-based vaccine and a minority of them an inactivated vaccine (Table 1; supplemental Figure 2B-D). Anti-SARS-CoV-2 spike protein immunoglobulin G (IgG) levels were analyzed in 244 (15.8%) fully vaccinated patients, 2 to 4 weeks after the last vaccine dose; among these patients, 109 (44.7%) presented an antibody response (optimal, 75, 30.7%; weak, 34, 13.9%),

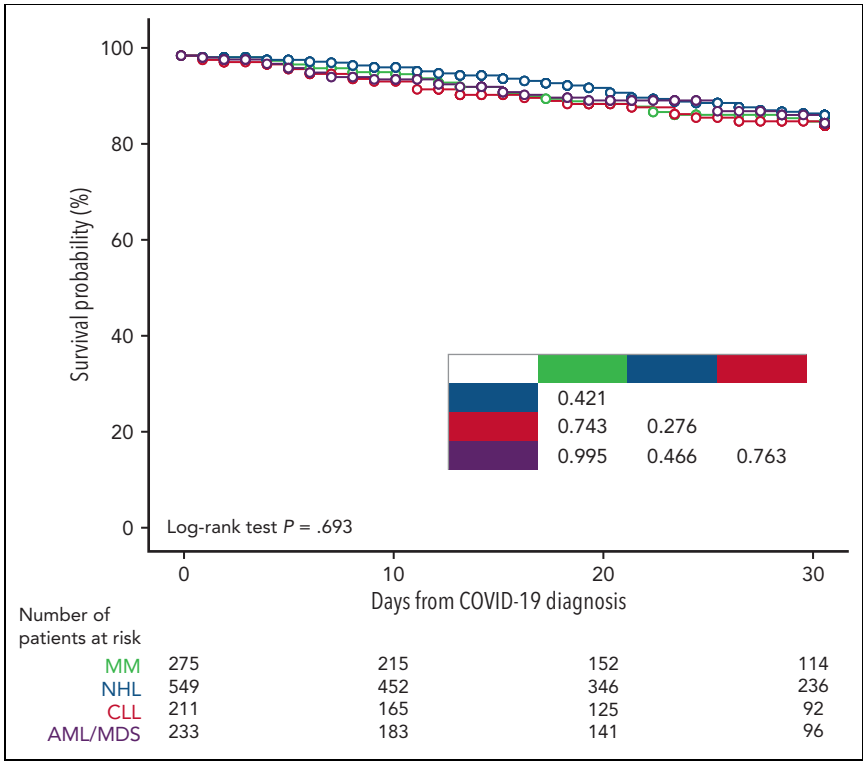

Figure 2. Survival probability by most prevalent underlying condition.

whereas the remaining 135 (55.3%) were nonresponders. Most patients who did not have a serological response to vaccines were affected by lymphoid malignancies, as expected (126/135, 93.3%; Figure 1).

COVID-19 treatments and risk factors for mortality

Overall, 906 patients (58.5%) received a specific treatment for COVID-19, whereas 642 (41.5%) were not treated or received symptomatic therapies (nonsteroidal anti-inflammatories, painkillers, antipyretics). Among patients who received a specific treatment for COVID-19, 311 (34.3%) were treated with monoclonal antibodies only, 246 (27.1%) with corticosteroids only, 218 (24.1%) with antivirals only, 108 (11.9%) with antiviral plus monoclonal antibodies, and the remaining 23 with convalescent plasma. Details on COVID-19 treatments and outcomes are displayed in the supplemental material (supplemental Table 2). Overall day-30 mortality (ie, from COVID-19 diagnosis) was 9.2% (143/1548); if we only consider patients who were symptomatic, the day-30 mortality rate was 0.3% (130/1265). The primary cause of death was COVID-19 in 97 patients (67.8%), a combination of COVID-19 and progressive HM in 39 cases (27.2%), and HM alone or combined with other reasons in the remaining 7 patients (4.8%). The mortality rate was significantly lower than that reported in the prevaccine era (prevaccine 31.2% vs postvaccine 9.2%; $P < .001$). Looking at 2 of the largest patient cohorts (ie, chronic lymphocytic leukemia and NHL) we evaluated the potential effect of chemotherapeutic treatment type on mortality rate. In patients with chronic lymphocytic leukemia, we did not observe any significant difference in terms of 30-day mortality rate among patients who had received immuno-chemotherapy (13.4%), immunotherapy alone (12.5%), or new targeted therapies (16.1%). On the contrary, in NHL we did observe a slightly higher mortality rate for patients recently treated with chimeric antigen receptor T cells (20%), compared with those treated with immuno-chemotherapy (8%), immunotherapy alone (14.3%), or targeted therapies (9.5%). Patient outcomes according to clinical characteristics, vaccine received, and specific treatments against SARS-CoV-2 are detailed in Table 2. As shown in Figure 2, we did not find any significant difference in terms of 30-day mortality rate among the different HM ($P = .693$), in contrast to that observed in the prevaccination era in which we reported a higher number of fatalities in patients with AML/myelodysplastic syndrome. In univariable analysis, the factors associated with a worse mortality rate were older age ($P < .001$), active HM disease ($P < .001$), and presence of 2 to 3 comorbidities ($P < .001$) (Table 3). Regarding age, patients aged <60 years showed a more favorable outcome (30-day mortality rate, 2.6%), compared with patients aged 60 to 69 years (7%), 70 to 79 years (14.8%), and ≥80 years (19.6%) ($P < .001$). Conversely, we observed a better clinical outcome for patients who received monoclonal antibodies (with or without antivirals; Figure 3). Analyzing the severity of COVID-19 presentation, a better clinical outcome was observed in patients treated with monoclonal antibodies alone for asymptomatic, mild, or severe disease and with monoclonal antibodies combined with antivirals in critical cases (Figure 4). We did not find differences in terms of outcome according to the number of vaccine doses received; however, a slightly better clinical outcome was evident among patients who received 3 to 4 doses vs 1 to 2 doses ($P = .040$, Table 3). We did not observe differences in survival when sorting patients according to viral strain detected ($P = .664$; Figure 5), or postvaccine antispike IgG levels (Table 2).

Table 3. Univariable and multivariable analysis of factors influencing 30-day mortality

	Univariable				Multivariable			
			95% CI				95% CI	
	P value	HR	Lower	Upper	*P* value	HR	Lower	Upper
Sex								
Female	—	—	—	—				
Male	.148	0.785	0.566	1.090				
Age	<.001	1.059	1.044	1.075	<.001	1.042	1.024	1.061
Malignancy status at COVID-19 diagnosis								
Controlled disease	—	—	—	—	—	—	—	—
Stable disease	.183	1.364	0.863	2.157	.767	1.081	0.647	1.806
Active disease	<.001	2.494	1.718	3.619	.001	1.981	1.305	3.008
Baseline malignancy								
Aplastic anemia	—	—	—	—				
Lymphoid malignancies	.875	3032.714	0.000	—				
Myeloid malignancies	.876	2974.523	0.000	—				
Comorbidities								
0-1 comorbidities	—	—	—	—	—	—	—	—
≥2 comorbidities	<.001	2.802	2.019	3.889	.027	1.503	1.050	2.229
Type of last vaccination								
mRNA	—	—	—	—				
Vector-based	.359	0.740	0.389	1.409				
Inactivated	.122	1.907	0.841	4.326				
SARS-CoV-2								
Omicron	—	—	—	—				
Alpha	.800	1.142	0.409	3.190				
Beta	.960	0.000	0.000	—				
Delta	.210	1.408	0.825	2.403				
Wild type	.758	1.175	0.421	3.281				
Not tested	.399	1.179	0.805	1.726				
Vaccine doses before COVID-19								
1 dose	—	—	—	—				
2 doses	.870	1.049	0.595	1.849				
≥3 doses	.637	0.866	0.478	1.572				
Serological response before COVID-19								
No response	—	—	—	—				
Weak response	.632	0.740	0.217	2.529				
Optimal response	.124	0.425	0.143	1.264				
COVID-19 treatment								
Corticosteroids	—	—	—	—	—	—	—	—
Antivirals + monoclonal antibodies	.001	0.333	0.171	0.651	.010	0.407	0.206	0.803
Antivirals	.010	0.570	0.372	0.874	.099	0.680	0.431	1.075
Monoclonal antibodies	<.001	0.123	0.061	0.247	<.001	0.155	0.077	0.313
Plasma	.852	1.077	0.493	2.355	.243	1.605	0.726	3.549

CI, confidence interval; HR, Hazard ratio.

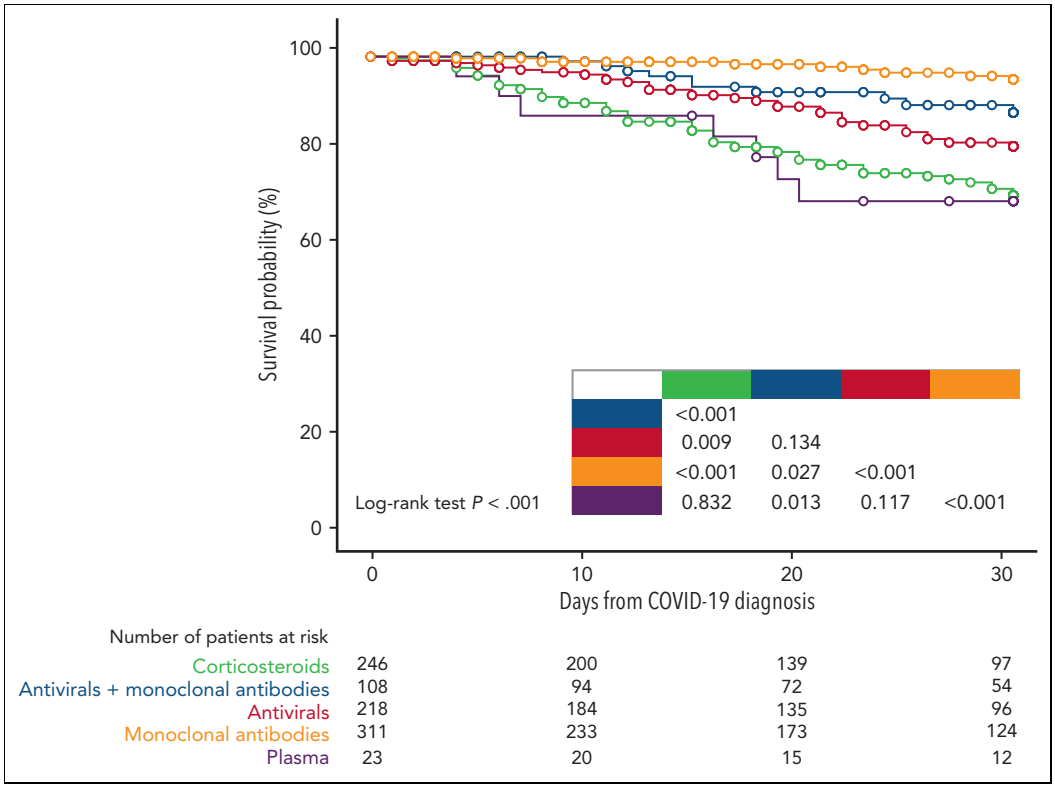

Figure 3. Survival probability of patients by COVID-19 treatment.

In the multivariable model, older age, active disease, and 2 to 3 comorbidities were the factors significantly correlated with a higher mortality, whereas receiving anti-SARS-CoV-2 treatment with monoclonal antibodies alone or combined with antivirals was independently associated with a lower mortality (HR, 0.155; 95% CI, 0.077-0.313; $P < .001$ and HR, 0.407; 95% CI, 0.206-0.803; $P = .010$, respectively) (Table 3). Survival and severity according to vaccine doses administration and post-vaccine antispike IgG levels are shown in Figures 6 and 1, respectively.

Discussion

In the prevaccination era, several studies reported a high COVID-19 mortality in HM.[1-4] From December 2020, anti-SARS-CoV-2 vaccines have been administered in patients with cancer, including those with HM.[7,8] Most published studies on HM confirmed the efficacy and safety of vaccines, particularly those using mRNA, however, most showing less efficacy in patients with lymphoid malignancies treated with immunosuppressive drugs.[17-22]

This study was performed in a large cohort of vaccinated patients with HM to evaluate epidemiology, risk factors for adverse clinical outcome, and treatments of breakthrough COVID-19. We found a predominance of lymphoid malignancies, higher than observed in our previous survey during the prevaccine era; this difference might be explained by the lower efficacy of vaccines in this patient population, as further suggested by the high rate of serological nonresponders among patients with lymphoid malignancies when evaluating antispike IgG levels. These data are consistent with data in a recent report describing COVID-19 breakthrough infections in a large cohort of patients with HM, mostly consisting of patients with lymphoid malignancies.[13] Advanced age, presence of comorbidities, and active HM were confirmed in this study as factors that negatively influenced clinical outcome and survival; these were the same risk factors that had previously been reported in the prevaccination era.[1-4] Interestingly, in this study, the underlying malignancy did not have a significant effect on survival, which was different from our previous experience in nonvaccinated patients, where AML and myelodysplastic syndrome were associated with higher mortality risk.[4] A potential explanation for this difference might be the better efficacy of anti-SARS-CoV-2 vaccines in myeloid malignancies[23-25] than in lymphoid malignancies;[17-22] however, we may hypothesize new specific anti-SARS-CoV-2 drugs and better COVID-19 management to be particularly important for patients with AML at risk of increased mortality if urgent chemotherapy is delayed. Similarly, as reported by other studies,[13] we did not find any significant difference in terms of mortality among different treatments received for HM. As expected, severe and critical COVID-19 had a worse clinical outcome than mild cases, showing a strong correlation with an increased mortality rate both in univariable and multivariable analysis. Given the vaccine protection, the occurrence of respiratory symptoms, hospitalization rate, and severe or critical clinical presentations were significantly lower than in the prevaccination era but still substantially higher compared with that of the overall population.[26-29] However, it is worth underlining that ~20% of patients were asymptomatic and SARS-CoV-2 infection was detected in screening programs. Interestingly, this percentage is analogous to that reported in our previously published study referring to the prevaccination era.[4]

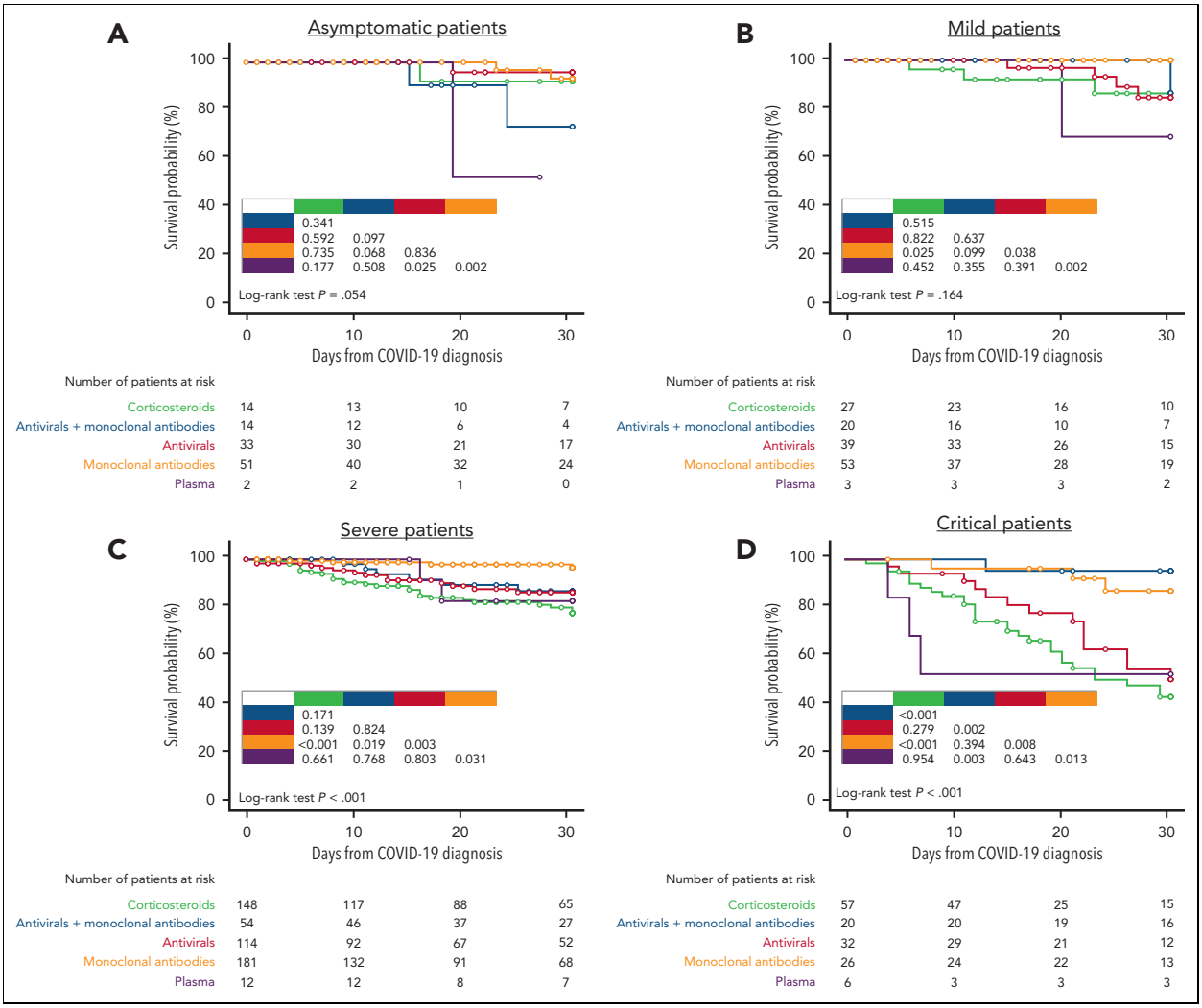

Figure 4. Survival probability by COVID-19 treatment and COVID-19 severity. (A) Patients who were asymptomatic; (B) patients with mild disease; (C) patients with severe disease; and (D) patients who were critically ill.

Unfortunately, it is not possible to estimate the true incidence of breakthrough infections nor the true number of patients who were asymptomatic with our data as only patients with COVID-19 were included in the registry; this is a potential selection bias, hypothetically hampering the reliability of our results. To the best of our knowledge, only few studies evaluated the incidence and cumulative COVID-19 risk among vaccinated patients with cancer, showing an increased risk in patients with HM compared with the overall population.[30-32] In particular, Lee and coworkers[32] recently published a comprehensive population-based test-negative case-control study in the United Kingdom, evaluating COVID-19 breakthrough infections among a large number of vaccinated patients with cancer and healthy control participants. The authors showed that vaccine efficacy at 3 to 6 months after the second dose was lower in the cancer cohort than in the control population and among patients with cancer, was lower in patients with HM, especially those affected by leukemia and lymphoma. Very recently, an Italian study evaluated the immunogenicity and clinical efficacy of anti-SARS-CoV-2 vaccine in 365 patients with HM. The authors showed an overall incidence of breakthrough infections of 2.98 per 10 000 person-days, significantly lower in patients who were seropositive after vaccination, whereas a clear correlation between T-cell immunity response and risk of postvaccine infection has not been found.[33]

In this study, we reported an overall 30-day-mortality rate of 9.2%, mainly driven by COVID-19 infection as a direct or contributing factor, which is significantly lower than in the pre-vaccination era.[1-4] Moreover, the 30-day mortality rate in patients who were symptomatic was 10.3%. The success of vaccination strategies is likely a major factor in the reported improvement but not the only factor. Previous reports suggest that COVID-19 management (eg, steroids, etc) have also affected outcomes, and newer variants may be less severe. Data reported in our study are comparable with other recently published reports that showed a significant mortality rate of COVID-19 breakthrough infections among patients with cancer.[11,12] or more specifically, among those affected by HM.[13]

In our study, we collected data on viral genotyping in approximately half of patients, among which the most prevalent variant was Omicron, accounting for more than two-thirds of patients. These data are not surprising if we consider the large number of

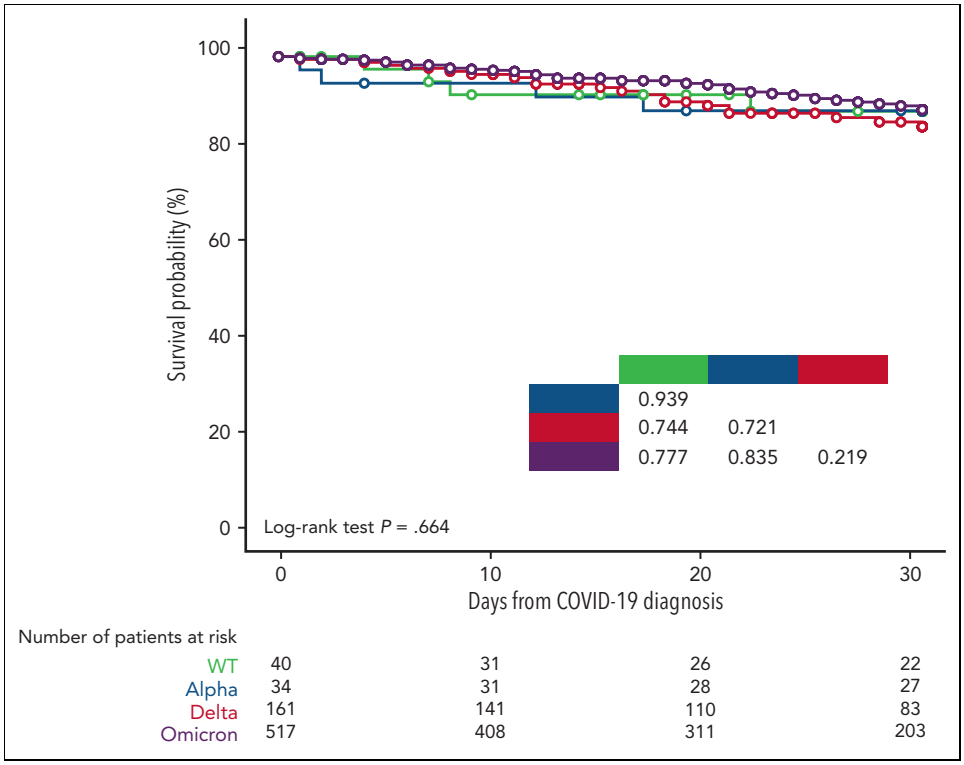

Figure 5. Survival probability by SARS-CoV-2 variant.

patients registered between late 2021 and early 2022, months in which the Omicron variant was rapidly spreading throughout Europe.[34] Interestingly, we did not find any significant difference in terms of severity of clinical presentation and mortality rate between Omicron and other variants, similar to other small, recently published reports on HM[35,36] but different to reports on immunocompetent patients in which Omicron presents with better outcome than other variants.[34,37]

Most of the patients enrolled in our study received 2 or 3 vaccine doses; comparing clinical presentation and outcomes, we did not find consistent data supporting a better clinical outcome for patients who had received a higher number of vaccine doses, although a slight difference in the proportion of deaths was observed comparing those who received 1 to 2 vs 3 to 4 doses. However, in multivariable analysis, the number of doses did not significantly effect on the overall 30-day

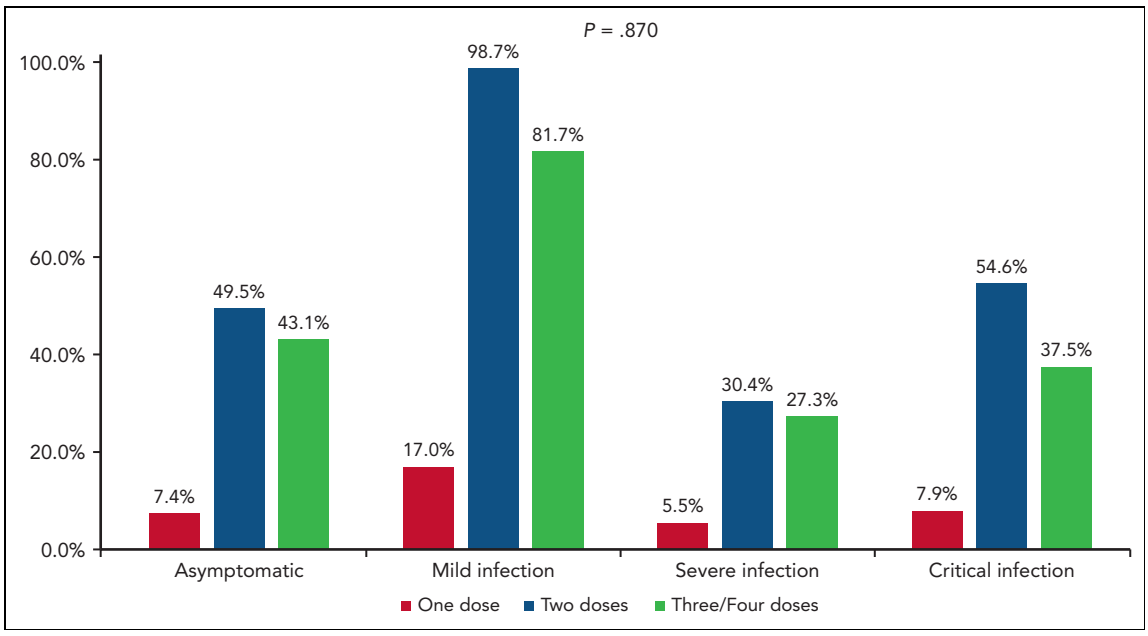

Figure 6. Patient distribution by number of SARS-CoV-2 vaccination doses administered before COVID-19 diagnosis, and COVID-19 severity.

mortality. Several studies highlighted the role of a third vaccine dose as capable of restoring the immune response in serologically less responsive patients with HM.[38,39] However, there are insufficient data to consider patients with low antispike antibody titers at high risk of worse outcomes. Indeed, in our study we did not find any differences in terms of outcomes stratifying patients according to serological response after 2 to 4 weeks from the last vaccine dose. By using the World Health Organization international standards (binding antibody units per milliliter), we did not find a significantly better survival for patients with optimal response, compared with those with weak or no response, although these data were only available in a small percentage of patients (16%). This lack of direct correlation between serological response and survival might be, at least in part, explained by the putative role of anti-SARS-CoV-2–induced cellular immunity, as suggested by several studies,[23,24,40] because the presence of memory T cells might control the infection and prevent severe COVID-19, even if high titers of long-lasting neutralizing antibodies are not elicited.[41] However, because a recently published study did not find a clear correlation between postvaccine T-cell immunity and vaccine clinical efficacy,[33] further studies are warranted to better understand this aspect. Another possible explanation is related to the role of the specific anti-SARS-CoV-2 treatments (ie, monoclonal antibodies and antivirals) that could have partially balanced the lack of protection of serological nonresponders. Indeed, from our survey, monoclonal antibodies with or without antivirals showed a high clinical activity irrespective of COVID-19 severity, showing the best efficacy when administered as single agents in patients with asymptomatic, mild, or severe disease, and when administered in combination with antivirals in patients with critical disease. The role of monoclonal antibodies in mitigating the negative effect of weak vaccine responses is supported by a recent randomized trial evaluating their role in immunocompetent people without serological response.[42] Moreover, our multivariable model confirmed the positive effect on 30-day mortality risk for patients who had received monoclonal antibodies alone or combined with antivirals. We are aware that this study has limitations owing to the retrospective observational design and the possible selection bias owing to the large number of participating institutions. Moreover, viral genotyping and serological data were not available for all enrolled patients, and we did not know whether COVID-19 was first diagnosed in hospital or in the community, potential key information for discriminating patient risk and infection natural history. Further prospective studies that better evaluate the role of vaccine response in patients with HM are needed.

In conclusion, our survey has shown that vaccination and novel COVID-19 treatments have brought significant improvements in terms of mortality in patients with HM. To further improve the prognosis of these patients, the role of additional booster vaccine doses and the role of prophylactic monoclonal antibodies in patients with an ineffective response to vaccination should be investigated.

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Authorship

Contribution: L.P. served as the principal investigator; J.S.-G. and F.M. served as project manager and research assistant, respectively. L.P., J.S.-G., and F.M. contributed to study design, study supervision, and data interpretation and wrote the paper; A.B., P.C., M.H., P.K., A.P., F.P., O.A.C., and L.P. conceived the registry idea. L.P., J.S.-G., and F.M. did the statistical plan, analysis, and interpreted the data; all the authors recruited participants and collected and interpreted data; all authors contributed to manuscript writing and review of the manuscript; and all authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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Footnotes

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Data are available on request from the corresponding author, Livio Pagano (livio.pagano@unicatt.it).

The online version of this article contains a data supplement.

There is a *Blood* Commentary on this article in this issue.

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Appendix

The EPICOVIDEHA Survey collaborators that contributed to this work are Laura Serrano, José-María Ribera-Santa Susana, Joseph Meletiadis, Panagiotis Tsirigotis, Nicola Coppola, Malgorzata Mikulska, Nurettin Erben, Caroline Besson, Maria Merelli, Tomás-José González-López, Jorge Loureiro-Amigo, Carolina García-Vidal, Elizabeth de Kort, Annarosa Cuccaro, Sofia Zompi, Florian Reizine, Olimpia Finizio, Rémy Duléry, Maria Calbacho, Ghaith Abu-Zeinah, Sandra Malak, Przemyslaw Zdziarski, Gina Varrichio, Athanasios Tragiannidis, Gaëtan Plantefeve, Rafael Duarte, François Danion, Maria Chiara Tisi, Ioanna Sakellari, Meinholf Karthaus, Ana Groh, Monica Fung, Ziad Emarah, Omar-Francisco Coronel-Ayala, Louis Yi Ann Chai, Mathias Brehon, Valentina Bonuomo, Dominik Wolf, Jana Wittig, Maria Vehreschild, Mario Virgilio Papa, Julia Neuhann, María-Josefa Jiménez-Lorenzo, Jan Grothe, Eleni Gavriilaki, Ramón García-Sanz, Nicole García-Poutón, Shaimaa Saber El-Ashwah, Matthias Eggerer, Raul Cordoba, Gökçe Melis Çolak, and Elena Arellano.

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