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Letters to Blood

TO THE EDITOR:

COVID-19 in vaccinated adult patients with hematological malignancies: preliminary results from EPICOVIDEHA

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Coronavirus disease 2019 (COVID-19) is a life-threatening condition of high relevance for comorbid patients, such as those with baseline hematological malignancies (HM).[1-3] In April 2020, the European Hematology Association - Infectious Diseases Working Party opened an open web-based registry to collect all cases of HM adult patients that developed COVID-19 infections (EPICOVIDEHA survey).[4] This registry aimed to describe the epidemiology, risk factors, and mortality rates of HM patients. Overall, we collected 3801 valid cases, and we observed an overall mortality rate of 31%.[5]

Nearly 1 year after the first described COVID-19 case, in December 2020, the first vaccines against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were available,[6,7] and administration to the highest risk populations including HM patients started.[8,9] From 1 January 2021, we prospectively collected registry data on adult fully or partially vaccinated HM patients that developed COVID-19 to assess the vaccine efficacy and potentially identify categories of patients that may be less protected by vaccines. With this report, we share our findings of the first 113 patients included in the registry.

EPICOVIDEHA survey has been approved centrally by the Institutional Review Board and Ethics Committee of Fondazione Policlinico Universitario A. Gemelli – IRCCS – Università Cattolica del Sacro Cuore (Rome, Italy) and by the respective local partners as appropriate. EPICOVIDEHA has been registered at www.clinicaltrials.gov with the identifier NCT04733729.[4] From 1 January 2021 until 31 December 2021, all participating institutions document episodes of COVID-19 in their patients with baseline HM that received a vaccination against SARS-CoV-2. Data are collected via the EPICOVIDEHA electronic case report form, available at www.clinicalsurveys.net. This online survey is provided by Enterprise Feedback Suite Fall 2018 (Questback, Cologne, Germany). Clinical and epidemiological data from

Table 1. Clinical characteristics of 113 vaccinated HM patients that developed COVID-19 infection

	Patients, n	%
Sex		
Female/male	44/69	38.9/61.1
Age (y.o.) (IQR) [range]	66 (58 - 78) [21 - 94]	
50/>50 y.o.	16/97	14.2/85.8
Comorbidities		
None/1-2-3 comorbidities	36/77	31.9/68.1
Smoking history	17	15.0
Malignancy		
Acute lymphoid leukemia	3	2.6
Chronic lymphoid leukemia	28	24.8
Acute myeloid leukemia	5	4.4
Chronic myeloid leukemia	1	0.9
Myelodysplastic syndrome	7	6.2
Hodgkin lymphoma	4	3.5
Non-Hodgkin lymphoma	36	31.9
Myelofibrosis	3	2.7
Polycythemia vera	2	1.8
Systemic mastocytosis	2	1.8
Multiple myeloma	20	17.7
Aplastic anemia	2	1.8
Malignancy status before COVID-19		
Controlled disease*	51	45.1
Active disease	60	53.1
Not reported	2	1.8
Last malignancy treatment (in the last 3 mo)		
alloHSCT (in the last 6 mo)	1	0.9
Chemotherapy	77	68.1
Conventional chemotherapy	13	11.5
Hypomethylating agents	4	3.5
Immunotherapy	9	8.0
Immunochemotherapy	30	26.5
Targeted therapy	21	18.6
No treatment	35	31.0
Patients with previous COVID-19 infections	2	1.8
Yes/no	2/111	1.8/98.2
Vaccination		
One dose	25	22.1
Two doses	88	77.8
Patient that received vaccination at least 14 d before COVID-19 infection	87	77.0
Type of vaccine		
mRNA + LNP		
BioNTech/Pfizer	79	69.9
Moderna COVE	20	17.7
Vector-based		
AstraZeneca Oxford	10	8.8
Inactivated		
Sinovac	4	3.5
Antispike protein Ig dosage after vaccination (referring to WHO international standards, BAU/mL)		
No response (<30)	27	23.9
Weak response (31-250)	5	4.4
Optimal response (>250)	8	7
Unknown/not measured	73	64.7
COVID-19 infection		
WT	11	9.7
English: alpha (α)	16	14.2
South African: beta (β)	1	0.9
Indian: delta (δ)	9	8.0
Not tested	76	67.3
Severity		
Asymptomatic	22	19.5
Mild infection	12	10.6
Severe infection	63	55.8
Critical infection	16	14.2
Symptomatology at onset		
Asymptomatic	23	20.4
Pulmonary symptoms	37	32.7
Extrapulmonary symptoms	14	12.4
Pulmonary and extrapulmonary	39	34.5
Neutrophil count		
≥500/mm^3	98	86.7
Lymphocyte count		
≥200/mm^3	92	81.4

alloHSCT, allogeneic hematopoietic stem cell transplantation; BAU, binding antibody units; COVE, Coronavirus Efficacy and Safety Study; IQR, interquartile range; LNP, lipid nanoparticles; mRNA, messenger RNA; N, number; WT, wild type; y.o., years old.

*Controlled disease: partial remission or better.

patients with the laboratory-based diagnosis of SARS-CoV-2 infection after partial or complete vaccination are collected. Data captured included underlying conditions before SARS-CoV-2, HM status and management before SARS-CoV-2, SARS-CoV-2 vaccination, and infection details and mortality. The diagnosis of COVID-19 accords to the international recommendations of the World Health Organization (WHO).[10] The severity of COVID-19 at admission is graded according to the China Centers for Disease Control and Prevention definitions.[11] Patients are considered fully vaccinated if the final dose was administered at least 14 days

Table 2. Outcome of vaccinated patients that developed COVID-19 infection

	N patients	%
Stay during COVID-19		
Hospital	75	66.4
COVID-19 ward	59	83.8
ICU	16	14.2
Of which, invasive mechanical ventilation	10	8.8
Home	38	33.6
Overall mortality at 30 d	14	12.4
Attributable to COVID-19	9/14	64.3
+ Hematological malignancy	3/14	21.4
Contributable by COVID-19	4/14	28.6
+ Other reasons*	2/14	14.3
Not related to COVID-19	1/14	7.1
+ Hematological malignancy	1/14	7.1
Mortality according to severity		
Asymptomatic	1/14	7.1
Mild infection	1/14	7.1
Severe infection	7/14	50.0
Critical infection	5/14	35.7
Mortality for stay		
Hospital	13/14	11.5
ICU	5/14	35.7
Of which, invasive mechanical ventilation	5/5	100.0
Home	1/14	7.1
Mortality according to type of vaccine		
BioNTech/Pfizer	12/79	15.2
Moderna COVE	1/20	5.0
AstraZeneca Oxford	1/10	10.0
Sinovac	0/4	0.0
Mortality according to SARS-CoV-2 variant		
WT	0/14	0.0
English: alpha (α)	4/14	28.6
South African: beta (β)	0/14	0.0
Indian: delta (δ)	0/14	0.0
Not tested	10/14	71.4
Mortality according to vaccine scheme		
1 dose	4/25	28.6
Full dose	10/78	71.4
Mortality according to type of hematological malignancy		
Acute lymphoid leukemia	0/3	0.0
Chronic lymphoid leukemia	2/28	7.1
Acute myeloid leukemia	0/5	0.0
Chronic myeloid leukemia	0/1	0.0
Myelodysplastic syndrome	2/7	28.6
Hodgkin lymphoma	1/4	25.0
Non-Hodgkin lymphoma	6/36	16.7
Myelofibrosis	1/3	33.3
Polycythemia vera	0/2	0.0
Systemic mastocytosis	1/2	50.0
Multiple myeloma	1/20	5.0
Aplastic anemia	0/2	0.0
Mortality for patients with active hematological malignancy		
Yes/no	7/7	50.0/50.0
Mortality for patients with chemo-immuno or radiotherapy		
in the last 3 mo	10/14	71.4
more than 3 mo/w&w	4/14	28.6

alloHSCT, allogeneic hematopoietic stem cell transplantation; COVE, Coronavirus Efficacy and Safety Study; ICU, intensive care unit; w&w, watch and wait.

*Renal impairment plus bacterial infection; intestinal subocclusion.

before symptom onset or a positive polymerase chain reaction test for SARS-CoV-2.

As of 31 August 2021, 113 COVID-19 episodes among partially or completely vaccinated patients with HM have been registered in EPICOVIDEHA. These patients have been reported from 42 out of 163 centers in 14 out of 38 European and non-European countries participating in the survey. The clinical characteristics of these patients are reported in Table 1. The majority of them were males (61.1%) and over 50 years of age (85.8%). More than 80% of patients had underlying lymphoproliferative malignancies (chronic lymphoid leukemia [CLL], non-Hodgkin lymphoma [NHL], acute lymphoblastic leukemia, Hodgkin's lymphoma, and multiple myeloma). Seventy-eight (68.1%) patients received active treatment of underlying HM at the time of COVID-19 or within the prior 3 months. Following the recommendations of major international scientific societies,[8,9] the majority of our patients received an mRNA vaccine (BioNTech/Pfizer n = 79 [69.9%], Moderna n = 20 [17.7%]), whereas the remaining 14 (12.4%) received a vector-based vaccine (AstraZeneca Oxford, n = 10) or an inactivated vaccine (Sinovac CoronaVac, n = 4); overall, the median time from the last dose of vaccine and COVID-19 diagnosis was of 64 days (IQR: 33.5-108). Eighty-seven patients (77%) were considered fully vaccinated, whereas the remaining 26 received only 1 shot; in all fully vaccinated patients, COVID-19 was diagnosed more than 2 weeks after the second vaccine dose. Viral genomes of infection were analyzed in only 37 (32.7%) cases and the α-variant was the most frequently observed (supplemental Figure 1). Postvaccine IgG levels against SARS-CoV-2 spike protein were analyzed in 40 (35.4%) fully vaccinated patients, 2 to 4 weeks from the last vaccine dose. Among these patients, only 13 (32.5%) presented an

antibody response to vaccine (optimal: 8; weak: 5), whereas the remaining 27 (67.5%) were considered no responders (BAU <30/mL). Overall, 79 (60.4%) patients had a severe or critical infection. Seventy-five patients (66.4%) were admitted to the hospital: 16 (21.3%) of them to an ICU, and 10/16 required mechanical ventilation (Table 2); detailed data about COVID-19 symptoms and severity according HM diagnosis have been described in supplemental Table 1. After a follow-up of 30 days post-COVID-19 diagnosis, the overall mortality rate was 12.4% (n = 14). COVID-19 was the main or a secondary cause of death for all but 1 patient; interestingly, we did not observe any statistical difference in terms of mortality between partially or fully vaccinated patients (15.4% vs 11.5%; $P = .734$) and between patients achieving a serological response to vaccine vs nonresponders (13.3% vs 15.6%; $P = 1$). In addition, we did not find any significant differences in terms of age or comorbidities comparing responder vs nonresponder patients. Moreover, our multivariable analysis showed that the only factor independently related to the risk of death in our cohort of vaccinated patients was the age ($P = .035$; HR 1.053, 95% CI: 1.004-1.105) (supplemental Table 2). Ten of 14 (71.4%) patients who died had underlying lymphoproliferative malignancies. With the caution due to the limited number of reported cases, it is worth it to underline that none of the patients who died had underlying acute myeloid leukemia, which in our previous analysis in nonvaccinated patients was the category with one of the highest mortality rates.[5]

A generalized anti-SARS-CoV-2 vaccination policy has allowed a marked reduction in the incidence of severe COVID-19 in the general population. However, some reports indicate the occurrence of the infection in a limited number of vaccinated subjects.[12-14] These are mostly subjects who have not developed protective immunity. Our survey, involving 42 hematology departments around the world, provides some preliminary insights. The majority of patients who do not respond to vaccination are patients with lymphoproliferative diseases, mainly CLL and NHL. This has also been observed for other vaccinations (eg, influenza).[15,16] Our results suggest that the low serologic response rate to anti-SARS-CoV-2 vaccines in patients with HM may translate to higher rates of infections. This has previously been described following monoclonal antibody treatment.[17-23] Unfortunately, only little data are available on the genomic characterization of the virus. We expect to have more detailed data at the end of this survey. Given policies that differ between sites, postvaccination serology results were available in only ~35% of patients, and of those about two-thirds were serologically nonresponders. An important limitation of these data is that methods for evaluating anti-SARS-CoV-2 antibodies were different among enrolling centers; as a consequence we tried to reduce this interlaboratory variability by referring to the WHO standardized method (https://www.who.int/news-room/feature-stories/detail/standardization-of-vaccines-for-coronavirus-disease-covid-19). Importantly, the overall mortality observed in our patients, although lower than in the prevaccination period (~31%), remained high (12.4%). This percentage, on one hand, remains quite worrying for hematologists, but on the other hand should be interpreted as a significant achievement following the spread of vaccination programs around the world. The hospitalization and mortality rates are still higher than the ones observed in the fully vaccinated general population, where hospitalization rates of 2% to 3% have been reported.[12,13,24,25] Our study reports preliminary observations, and the low number of vaccinated patients is the main weakness, for now limiting the possibility to define the real incidence of breakthrough COVID-19 in HM.

Recruitment to this survey continues, and larger numbers of cases will enable us to draw more conclusions in order to develop strategies to prevent severe COVID-19 in this frail population.

Informed consent was collected as applicable.

Acknowledgment

Università Cattolica del Sacro Cuore contributed to the funding of this research project and its publication.

Authorship

Contribution: L.P. set up EPICOVIDEHA, conceived the study idea, provided clinical details from local patients, interpreted the data, wrote the initial draft of the manuscript, and revised and approved the final manuscript; J.S.-G. enrolled patients and performed formal validation of the clinical details, extracted data from EPICOVIDEHA patients, performed the statistical analysis and interpreted the data, wrote the initial draft of the manuscript, created tables, and revised and approved the final manuscript; F.M. provided clinical details from local patients interpreted the data, interpreted the data, wrote the initial draft of the manuscript, and revised and approved the final manuscript; A.L.-G., S.L., F.I., M.G.-S., G.D., I.F.-R., J.v.D., U.S., J.L., M.C., Y.M.B., B.W., L.S., J.-M.R.-S.S., S.M., J.L.-A., A.G., R.C.-M., R.N.-R., T.-J.G.-L., L.K.K., M.-J.J.-L., J.-A.H.-R., O.J., Z.R., and the researchers listed in the study group provided clinical details from local patients and revised and approved the final manuscript; and A.B., P.C., M.H., N.K., P.K., A.P., F.P., and O.A.C. set up EPICOVIDEHA, conceived the study idea, and revised and approved the final manuscript.

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

A list of the members of the EPICOVIDEHA study group appears in "Appendix."

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Footnotes

Submitted 15 September 2021; accepted 13 October 2021; prepublished online on *Blood* First Edition 8 November 2021.

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Requests for data sharing may be submitted to 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.

Appendix

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DOI 10.1182/blood.2021014124