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COVID-19 in vaccinated adult patients with hematological malignancies. Preliminary results from EPICOVIDEHA

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Abstract:

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

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

143 EPICOVIDEHA survey has been approved centrally by the Institutional Review Board and
144 Ethics Committee of Fondazione Policlinico Universitario A. Gemelli – IRCCS – Università
145 Cattolica del Sacro Cuore (Rome, Italy), and by the respective local partners as appropriate.
146 EPICOVIDEHA has been registered at www.clinicaltrials.gov with the identifier NCT04733729.⁴
147 From January 1, 2021, until December 31, 2021, all participating institutions document episodes of
148 COVID-19 in their patients with baseline HM that received a vaccination against SARS-CoV-2.
149 Data are collected via the EPICOVIDEHA electronic case report form (eCRF), available at
150 www.clinicalsurveys.net. This online survey is provided by EFS Fall 2018 (Questback, Cologne,
151 Germany). Clinical and epidemiological data from patients with the laboratory-based diagnosis of
152 SARS-CoV-2 infection after partial or complete vaccination are collected. Data captured included
153 underlying conditions before SARS-CoV-2, HM status and management before SARS-CoV-2,
154 SARS-CoV-2 vaccination, and infection details and mortality. The diagnosis of COVID-19 accords
155 to the international recommendations of the WHO.¹⁰ The severity of COVID-19 at admission is
156 graded according to the China Centers for Disease Control and Prevention definitions.¹¹ Patients

157 are considered fully vaccinated if the final dose was administered at least 14 days before symptom
158 onset or a positive PCR test for SARS-CoV-2.

159 As of 31 August 2021, 113 COVID-19 episodes among partially or completely vaccinated
160 patients with HM have been registered in EPICOVIDEHA. These patients have been reported from
161 42 out of 163 centres in 14 out of 38 European and non-European countries participating in the
162 survey. The clinical characteristics of these patients are reported in Table 1. The majority of them
163 were males (61.1%) and over 50 years of age (85.8%). More than 80% of patients had underlying
164 lymphoproliferative malignancies (chronic lymphoid leukemia [CLL], non-Hodgkin lymphoma [NHL],
165 acute lymphoblastic leukemia [ALL], Hodgkin's lymphoma [HL], and multiple myeloma [MM]).
166 Seventy-eight (68.1%) patients received active treatment for underlying HM at the time of COVID-
167 19 or within the prior 3 months. Following the recommendations of major international scientific
168 societies,^{8,9} the majority of our patients received an mRNA vaccine (BioNTech/Pfizer N=79
169 (69.9%), Moderna N=20 (17.7%)), whereas the remaining 14 (12.4%) received a vector-based
170 vaccine (AstraZeneca Oxford, N=10) or an inactivated vaccine (Sinovac CoronaVac, N=4); overall,
171 the median time from the last dose of vaccine and COVID-19 diagnosis was of 64 days (IQR: 33.5-
172 108). Eighty-seven patients (77%) were considered fully vaccinated, whereas the remaining 26
173 received only one shot; in all fully vaccinated patients, COVID-19 was diagnosed more than two
174 weeks after the second vaccine dose. Viral genomes of infection were analyzed in only 37 (32.7%)
175 cases and the alpha-variant was the most frequently observed (Supplemental Figure 1). Post-
176 vaccine IgG levels against SARS-CoV-2 spike protein were analyzed in 40 (35.4%) fully vaccinated
177 patients, 2-4 weeks from the last vaccine dose. Among these patients, only 13 (32.5%) presented
178 an antibody response to vaccine (optimal: 8; weak: 5), whereas the remaining 27 (67.5%) were
179 considered no responders (Binding Antibody Units, BAU < 30/ml). Overall, 79 (60.4%) patients had
180 a severe or critical infection. Seventy-five patients (66.4%) were admitted to the hospital, 16
181 (21.3%) of them to an ICU, and 10/16 required mechanical ventilation (Table 2); detailed data
182 about COVID-19 symptoms and severity according HM diagnosis have been described in
183 Supplemental Table 1. After a follow-up of 30 days post COVID-19 diagnosis, the overall mortality
184 rate was 12.4% (N=14). COVID-19 was the main or a secondary cause of death for all but one

185 patients; interestingly, we did not observe any statistical difference in terms of mortality between
186 partially or fully vaccinated patients (15.4% vs 11.5%; $P=0.734$) and between patients achieving a
187 serological response to vaccine vs non responders (13.3% vs 15.6%; $P=1$). In addition, we did not
188 find any significant differences in terms of age or comorbidities comparing responder vs non
189 responder patients. Moreover, our multivariable analysis showed that the only factor independently
190 related to the risk of death in our cohort of vaccinated patients was the age ($P=0.035$; HR 1.053,
191 95%CI: 1.004-1.105) (Supplemental Table 2). Ten of 14 (71.4%) patients who died had underlying
192 lymphoproliferative malignancies. With the caution due to the limited number of reported cases, it
193 is worth to underline that none of the patients who died had underlying acute myeloid leukemia,
194 which in our previous analysis in non-vaccinated patients was the category with one of the highest
195 mortality rates.⁵

196 A generalized anti-SARS-CoV-2 vaccination policy has allowed a marked reduction in the
197 incidence of severe COVID-19 in the general population. However, some reports indicates the
198 occurrence of the infection in a limited number of vaccinated subjects.¹²⁻¹⁴ These are mostly
199 subjects who have not developed protective immunity. Our survey, involving 42 hematology
200 departments around the world, provides some preliminary insights. The majority of patients who do
201 not respond to vaccination are patients with lymphoproliferative diseases, mainly CLL and NHL.
202 This has also been observed for other vaccinations (e.g., influenza).¹⁵⁻¹⁶ Our results suggest that
203 the low serologic response rate to anti-SARS-CoV-2 vaccines in patients with HM may translate to
204 higher rates of infections. This has previously been described following monoclonal antibody
205 treatment.¹⁷⁻²³ Unfortunately, only little data is available on the genomic characterization of the
206 virus, we expect having a greater proportion of genotyping cases while continuing the survey.
207 Given policies that differ between sites, post-vaccination serology results were available in only
208 about 35% of patients and of those about two thirds were serologically non responders. It should
209 be taken into account that the methods differ from a center to anotherone, even though our attempt
210 of reducing inter-laboratory variation by referring to the WHO standardized method
211 ([https://www.who.int/news-room/feature-stories/detail/standardization-of-vaccines-for-coronavirus-](https://www.who.int/news-room/feature-stories/detail/standardization-of-vaccines-for-coronavirus-disease-covid-19)
212 [disease-covid-19](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

213 in the pre-vaccination period (~31%), remained high (12.4%). This percentage, on one hand
214 remains quite worrying for hematologists, but on the other hand should be interpreted as a
215 significant achievement following the spread of vaccination programs around the world. The
216 hospitalization and mortality are still higher than the one observed in the fully vaccinated general
217 population where the hospitalization rates of 2-3% have been reported.^{12,13,24,25} Our study reports
218 preliminary observations and the low number of vaccinated patients is the main weakness, for now
219 limiting the possibility to define the real incidence of breakthrough COVID-19 in HM.

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

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223

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

	N patients	%
Sex		
Female/male	44/69	38.9/61.1
Age (y.o.) (IQR) [range]		
<50/>50 y.o.	66 (58 - 78) [21 - 94]	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	
Last malignancy treatment (in the last 3 months)		
alloHSCT (in the last 6 months)	1	0.9
Chemotherapy	77	68.1
<i>Conventional chemotherapy</i>	13	11.5
<i>Hypomethylating agents</i>	4	3.5
<i>Immunotherapy</i>	9	8.0
<i>Immunochemotherapy</i>	30	26.5
<i>Targeted therapy</i>	21	18.6
No treatment	35	31.0
Patients with previous COVID-19 infections		
y/n	2/111	1.8/98.2
Vaccination		
One dose	25	22.1
Two doses	88	77.8
<i>Patient that received vaccination at least 14 days before COVID-19 infection</i>	87	77.0
Type of vaccine		
mRNA + LNP		
<i>BioNTech/Pfizer</i>	79	69.9
<i>Moderna COVE</i>	20	17.7
Vector-based		
<i>AstraZeneca Oxford</i>	10	8.8
Inactivated		
<i>Sinovac</i>	4	3.5

	N patients	%
Anti-spike 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		
Wild type - <i>WT</i>	11	9.7
English - <i>Alpha</i> (α)	16	14.2
South African - <i>Beta</i> (β)	1	0.9
Indian - <i>Delta</i> (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
Neutrophils count		
$\geq 500/\text{mm}^3$	98	86.7
Lymphocytes count		
$\geq 200/\text{mm}^3$	92	81.4

alloHSCT, allogeneic hematopoietic stem cell transplantation; **BAU**: binding antibody units; **COVE**, Coronavirus Efficacy and Safety Study; **COVID-19**, coronavirus disease 2019; **HM**, patients with hematological malignancy; **IQR**, interquartile range; **LNP**, lipid nanoparticles; **mm³**, cubic millimetre; **mRNA**, messenger ribonucleic acid; **N**, number; **WT**, wild type; **y.o.**, years old

^ Controlled disease: partial remission or better.

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 days	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		
Wild type - <i>WT</i>	0/14	0.0
English - <i>Alpha</i> (α)	4/14	28.6
South African - <i>Betha</i> (β)	0/14	0.0
Indian - <i>Delta</i> (δ)	0/14	0.0
Not tested	10/14	71.4
Mortality according to vaccine scheme		
One 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		
y/n	7/7	50.0/50.0

	N patients	%
Mortality for patients with chemo-immuno or radiotherapy		
in the last 3 months	10/14	71.4
more than 3 months/ w&w	4/14	28.6

* Renal impairment + Bacterial infection; Intestinal subocclusion

alloHSCT, allogeneic hematopoietic stem cell transplantation; **COVE**, Coronavirus Efficacy and Safety Study; **COVID-19**, coronavirus disease 2019; **HM**, patients with hematological malignancy; **ICU**, intensive care unit; **w&w**, watch and wait