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Age, successive waves, immunization, and mortality in elderly COVID-19 hematological patients: EPICOVIDEHA findings ☆,☆☆

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ABSTRACT

Objectives: Elderly patients with hematologic malignancies face the highest risk of severe COVID-19 outcomes. The infection's impact on different age groups remains unstudied in detail.
Methods: We analyzed elderly patients (age groups: 65-70, 71-75, 76-80, and >80 years old) with hematologic malignancies included in the EPICOVIDEHA registry between January 2020 and July 2022. Univariable and multivariable Cox regression models were conducted to identify factors influencing death in COVID-19 patients with hematological malignancy.
Results: The study included data from 3,603 elderly patients (aged 65 or older) with hematological malignancy, with a majority being male (58.1%) and a significant proportion having comorbidities. The patients were divided into four age groups, and the analysis assessed COVID-19 outcomes, vaccination status, and other variables in relation to age and pandemic waves. The 90-day survival rate for patients with COVID-19 was 71.2%, with significant differences between groups. The pandemic waves had varying impacts, with the first wave affecting patients over 80 years old, the second being more severe in 65-70, and the third being the least severe in all age groups. Factors contributing to 90-day mortality included age, comorbidities, lymphopenia, active malignancy, acute leukemia, less than three vaccine doses, severe COVID-19, and using only corticosteroids as treatment.
Conclusion: These data underscore the heterogeneity of elderly hematological patients, highlight the different impacts of COVID-19 waves and the pivotal importance of vaccination, and may help in planning future healthcare efforts.

Introduction

The impact of the SARS-CoV-2 pandemic has caused excess mortality worldwide. Its severity and clinical consequences varied according to differences in the characteristics of infected subjects. Both, age [1] and hematologic malignancy [2–17] proved to be adverse prognostic factors in most studies reported, making elderly patients affected by hematological malignancy among the categories of patients most vulnerable to severe infection. A better knowledge of the clinical characteristics of COVID-19 [18] together with the availability of effective prophylactic and therapeutic agents and the benefits of widespread vaccination policies have allowed a progressive improvement in COVID-19 prognosis.

To which extent the improvement in COVID-19 prognosis and the efficacy of prophylactic interventions affects elderly patients with hematological malignancy is only partially known [9]. Also, differences in the viral strain involved [2,19–21] and in vaccination status [12,14,15,19] likely influence the risk of COVID-19 progression to severe episodes among elderly hematologic patients. The potential role of differences in the age of elderly patients with hematological malignancy on the outcome of COVID-19 and their relationship with other prognostic variables have been only partially analyzed, including time of infection [5], viral strain [2,19–21], vaccination status [12,14,15,19], and hematologic diagnosis [3,4,6–8,10,11,17].

This analysis was conducted by the collaboration of the EPICOVIDEHA registry [22] from the European Hematology Association (EHA) Infections in Hematology Scientific Working Group (SWG) and the EHA Hematology and Aging SWG. The characteristics of patients aged >65 with hematological malignancy developing COVID-19 throughout different periods of the pandemic have been analyzed in detail. Results may provide scientific knowledge useful for improved management of elderly patients and for adopting rationale interventions to face the tasks that the pandemic may present in the future. The aim of this study is to assess the impact of age, vaccination status, viral strain, and other variables on the prognosis of elderly patients with hematological malignancy who contracted COVID-19 during different phases of the pandemic, addressing a critical gap in knowledge regarding the optimal management of this vulnerable population.

Methods

Patients aged ≥65 registered in the EPICOVIDEHA registry [22] between March 2020 and July 31, 2022, were included in the present analysis. They were divided into four groups according to the following age ranges: 65-70 years, 71-75 years, 76-80 years, and >80 years. Additionally, the patients included in analysis had to have a laboratory-based diagnosis of COVID-19 and a docu-

mented history of active hematological malignancy within the last 5 years before COVID-19 diagnosis for participation in this study.

In addition to age, other variables were collected: sex, comorbidities, diagnosis of hematological malignancy, malignancy status at COVID-19 onset and last hematological treatment received before COVID-19 diagnosis, neutrophil and lymphocyte count at COVID-19 onset, number and type of vaccine doses received, timing of COVID-19 diagnosis subdivided according to the following pandemic waves: first wave from January to April 2020, second wave from September 2020 to March 2021, third wave from September 2021 to March 2022 and fourth wave from May to July 2022. Furthermore, COVID-19 etiology, clinical severity, need for hospitalization and intensive care unit admission, treatment, death, and cause of death were also documented.

Categorical variables are presented as frequencies and percentages and continuous variables as median, interquartile range, and absolute range. A univariable Cox regression model was built and run with variables expected to play a role in mortality in hematological malignancy patients with COVID-19. Variables with a *P*-value ≤0.1 were included in the multivariable analysis. The multivariable Cox regression model was calculated using the Wald backward method. Survival probability was verified with Kaplan-Meier survival curves. Log-rank test was used to compare the survival probabilities of patients included in the different models. A *P*-value ≤0.05 was considered statistically significant. SPSS version 25.0 was used for statistical analysis (SPSS, IBM Corp, Chicago, IL, United States).

Results

A total of 3603 patients registered in the EPICOVIDEHA registry were studied. Median age was 74 years (interquartile range 70-80; absolute range 65-97). Males represented 58.1% (n = 2093/3603) of cases. Only 25.2% (n = 909/3603) of the patients had no comorbidities. Increasing age negatively correlated with the proportion of patients without comorbidities from 30.6% (n = 319/1044) in patients aged 65-70 to 20.0% (n = 164/819) in patients aged >80 (P <0.001). The coexistence of three or more comorbidities increased with age from 12.3% (n = 128/1044) in patients aged 65-70 to 22.7% (n = 186/819) in patients >80 years old. Cardiac (P = 0.001) and renal (P <0.001) comorbidities showed the same increasing trend, whereas the frequency of obesity (P = 0.004) and a history of smoking (P = 0.003) progressively decreased from the youngest to the eldest age group (Table 1).

Myelodysplastic syndrome was the only hematologic malignancy correlating with age (P = 0.001). Its frequency increased from 6.5% (n = 68/1044) in patients aged 65-70 to 17.3% (n = 142/819) in patients aged >80. Most patients (n = 3059/3603, 84.9%) had received some treatment for their baseline hematological malignancy, which was active in 32.9% (n = 1186/3603) of patients at COVID-19 diagnosis. The proportion of patients receiving no treatment (n = 181/819, 22.1%), treatment with demethylating agents (n = 67/819, 8.2%), or best supportive/palliative care (n = 61/819, 7.4%) was highest above 80 years of age, whereas the proportion of patients treated with immunochemotherapy was lowest (n = 168/819, 20.5%, P = 0.001). Allogeneic or autologous stem cell transplants had been performed only in patients under the age of 75, while two patients aged 75-80 years had been treated with chimeric antigen receptor T-cell (CAR-T) cells. Peripheral blood cell counts showed severe neutropenia (absolute neutrophil count $<0.5 \times 10^9$/l) in 7.1% (n = 256/3603) and lymphopenia (lymphocyte count $<0.2/10^9$/l) in 9.3% (n = 334/3603) of cases. Both, severe neutropenia (P = 0.017) and lymphopenia (P = 0.001) were more pronounced in patients aged 65-70 and decreased in elder age groups (Table 1).

The first wave affected particularly the eldest age groups (75+ years) whereas the second wave was the youngest (65-75 years, P <0.001). No further differences were observed during the subsequent pandemic waves. The viral strain causing COVID-19 was identified in 19.6% (n = 706/3603) of patients, with the Omicron variant accounting for COVID-19 etiology in 12.1% (n = 437/3603). Before developing COVID-19, 31.5% of patients had received at least one vaccine dose, in 90.6% (n = 1025/1135) of the cases with a messenger RNA vaccine. Many patients had received two (n = 442/3603, 12.3%) or three doses (n = 570/3603, 15.8%). Severe or critical infection was experienced by 58.5% (n = 2109/3603) of the patients. Vaccination rates did not change significantly with increasing age (P = 0.172, Table 1).

The frequency of COVID-19 diagnosis during screening was lower in the eldest patients (P = 0.010). Hospitalization was needed by 73.2% (n = 2638/3603) of the patients and intensive care was required by 21.2% (n = 560/3603). COVID-19 was gradually more severe based on the age of the patient, requiring more frequent hospitalization and reporting more often pulmonary symptoms at increasing age (P <0.001). The eldest patients were less commonly admitted to intensive care unit (P <0.001). Potential treatment for COVID-19 was collected from 51.7% (n = 1864/3603) of the patients. One-fifth (n = 752/3603, 20.9%) of the patients did not get any treatment, and among those receiving any drug, corticosteroids alone were the most prevalent (n = 385/3603, 10.7%, Table 1).

At day 30 post-COVID-19 diagnosis, 23.6% (n = 852/3603) had died; (n = 1038/3603), this rose to 28.8% at day 90 (Table 2). The mortality rate raised at one year to 30.4% (n = 1095/3603). At day 90, mortality rate was 21.9% (n = 229/1044) in patients aged 65-70, 26.2% (n = 244/932) in those aged 71-75, 31.1% (n = 251/808) in those aged 76-80 and 38.3% (n = 314/819) in those aged >80, respectively. In the survival probability analysis, a statistically significant difference was observed (P <0.001), with an age-based gradient from younger to elder patients (Figure 1a). COVID-19 was involved in the overall mortality in 91.9% (n = 753/1107) of patients; hematologic malignancy contributed in 23.8% (n = 264/1107). These proportions did not differ in the different age groups (P = 0.755, Table 2).

The 90-day mortality rate was markedly higher in patients diagnosed with COVID-19 during the first wave of the pandemic (n = 374/820 45.6%) than in the second (n = 385/1198, 37.3%, P <0.001). Day 90 mortality dropped significantly for patients diagnosed during the third wave (n = 178/1055, 16.9%, P <0.001). During the first wave, the 90-day mortality rate of patients aged 65-70 was 29.7% (n = 310/1044) and it progressively increased in the elder groups, being 39.6% (n = 369/932) in those aged 71-75, 48.7% (n = 393/808) in those aged 76-80 and 60.1% (n = 492/819) in those aged >80 (P <0.001). Conversely, the increase in 90-day mortality from the youngest to the eldest age group was less marked during the second wave (27.9% (n = 291/1044) in patients aged 65-70 and 41.0% (n = 336/819) in patients aged >80, P <0.001). Association between the age of the patients and the pandemic wave was also observed in the survival probability analysis (P <0.001, Figure 1b, Figure 2a, Supplementary Table 1).

Vaccination status and number of vaccine doses received significantly impacted survival probability at 90-day (P <0.001), which progressively increased among patients receiving zero, one, two, three, or four doses, with differences being statistically significant for each pairwise comparison between groups (Supplementary Table 1).

Considering patients whose viral strain was genotyped, those with wild-type, Alpha, or Delta variants, had a comparable survival probability at day 90, although significantly worse than in patients with Omicron variant (P <0.001, Figure 1c).

Table 1
Demographic and clinical characteristics of the whole series of older hematologic patients with COVID-19 and of the four groups of different age.

	Overall		65-70 years old		71-75 years old		76-80 years old		>80 years old		*P*-value
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	
Sex											
Female	1510	41.9%	432	41.4%	344	36.9%	345	42.7%	389	47.5%	**<0.001**
Male	2093	58.1%	612	58.6%	588	63.1%	463	57.3%	430	52.5%	
Age	74 (70-80) [65-97]		68 (66-69) [65-70]		73 (72-74) [71-75]		78 (77-79) [76-80]		84 (82-87) [81-97]		
<71 years old	1044	29.0%	1044	100.0%	0	0.0%	0	0.0%	0	0.0%	
71-75 years old	932	25.9%	0	0.0%	932	100.0%	0	0.0%	0	0.0%	
76-80 years old	808	22.4%	0	0.0%	0	0.0%	808	100.0%	0	0.0%	
>80 years old	819	22.7%	0	0.0%	0	0.0%	0	0.0%	819	100.0%	
Comorbidities											
No comorbidities	909	25.2%	319	30.6%	247	26.5%	179	22.2%	164	20.0%	**<0.001**
1 comorbidity	1241	34.4%	355	34.0%	327	35.1%	296	36.6%	263	32.1%	
2 comorbidities	834	23.1%	242	23.2%	195	20.9%	191	23.6%	206	25.2%	
3 or more comorbidities	619	17.2%	128	12.3%	163	17.5%	142	17.6%	186	22.7%	
Chronic cardiopathy	1826	50.7%	419	40.1%	436	46.8%	449	55.6%	522	63.7%	**0.001**
Chronic pulmonary disease	654	18.2%	150	14.4%	171	18.3%	143	17.7%	190	23.2%	**<0.001**
Diabetes mellitus	706	19.6%	168	16.1%	197	21.1%	189	23.4%	152	18.6%	**<0.001**
Liver disease	156	4.3%	49	4.7%	45	4.8%	34	4.2%	28	3.4%	0.465
Obesity	244	6.8%	89	8.5%	69	7.4%	50	6.2%	36	4.4%	**0.004**
Renal impairment	388	10.8%	80	7.7%	92	9.9%	85	10.5%	131	16.0%	**<0.001**
Smoking history	453	12.6%	157	15.0%	122	13.1%	97	12.0%	77	9.4%	**0.003**
No risk factor identified	900	25.0%	316	30.3%	246	26.4%	176	21.8%	162	19.8%	**<0.001**
Hematological maligancies											
Leukemia	1456	40.4%	405	38.8%	342	36.7%	325	40.2%	384	46.9%	**0.001**
Acute lymphoid leukemia	47	1.3%	22	2.1%	8	0.9%	11	1.4%	6	0.7%	
Chronic lymphoid leukemia	616	17.1%	154	14.8%	166	17.8%	146	18.1%	150	18.3%	
Acute myeloid leukemia	328	9.1%	127	12.2%	76	8.2%	64	7.9%	61	7.4%	
Chronic myeloid leukemia	95	2.6%	27	2.6%	27	2.9%	17	2.1%	24	2.9%	
Myelodisplastic syndrome	353	9.8%	68	6.5%	63	6.8%	80	9.9%	142	17.3%	
Hairy cell leukemia	17	0.5%	7	0.7%	2	0.2%	7	0.9%	1	0.1%	
Lymphoma	1128	31.3%	346	33.1%	318	34.1%	249	30.8%	215	26.3%	
Hodgkin lymphoma	45	1.2%	23	2.2%	10	1.1%	9	1.1%	3	0.4%	
Non-Hodgkin lymphoma	1083	30.1%	323	30.9%	308	33.0%	240	29.7%	212	25.9%	
PH negative myeloproliferative diseases	264	7.3%	69	6.6%	72	7.7%	58	7.2%	65	7.9%	
Essential thrombocythemia	65	1.8%	8	0.8%	16	1.7%	19	2.4%	22	2.7%	
Myelofibrosis	126	3.5%	41	3.9%	36	3.9%	22	2.7%	27	3.3%	
Polycythemia vera	66	1.8%	16	1.5%	19	2.0%	16	2.0%	15	1.8%	
Systemic mastocytosis	7	0.2%	4	0.4%	1	0.1%	1	0.1%	1	0.1%	
Plasma cell disorders	740	20.5%	219	21.0%	197	21.1%	174	21.5%	150	18.3%	
Multiple myeloma	725	20.1%	215	20.6%	190	20.4%	171	21.2%	149	18.2%	
Amyloid light-chain amyloidosis	15	0.4%	4	0.4%	7	0.8%	3	0.4%	1	0.1%	
Other hematological malignancies	15	0.4%	5	0.5%	3	0.3%	2	0.2%	5	0.6%	
Aplastic anemia	15	0.4%	5	0.5%	3	0.3%	2	0.2%	5	0.6%	
Last haematological treatment before COVID-19											
No treatment	574	15.9%	138	13.2%	138	14.8%	117	14.5%	181	22.1%	**0.001**
alloHSCT	53	1.5%	41	3.9%	12	1.3%	0	0.0%	0	0.0%	
autoHSCT	34	0.9%	26	2.5%	8	0.9%	0	0.0%	0	0.0%	
Chimeric antigen receptor T-cell	16	0.4%	10	1.0%	4	0.4%	2	0.2%	0	0.0%	

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Table 1 (*continued*)

	Overall		65-70 years old		71-75 years old		76-80 years old		>80 years old		*P*-value
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	
Conventional chemotherapy	512	14.2%	173	16.6%	112	12.0%	111	13.7%	116	14.2%	
Demethylating agents	246	6.8%	52	5.0%	65	7.0%	62	7.7%	67	8.2%	
Immuno-chemotherapy	987	27.4%	295	28.3%	291	31.2%	233	28.8%	168	20.5%	
Immunotherapy	197	5.5%	60	5.7%	42	4.5%	51	6.3%	44	5.4%	
Supportive/Palliative	149	4.1%	23	2.2%	30	3.2%	35	4.3%	61	7.4%	
Targeted therapy	835	23.2%	226	21.6%	230	24.7%	197	24.4%	182	22.2%	
Status malignancy before COVID-19											
Controlled disease	1462	40.6%	485	46.5%	380	40.8%	337	41.7%	260	31.7%	**<0.001**
Stable disease	839	23.3%	186	17.8%	212	22.7%	186	23.0%	255	31.1%	
Active disease	1186	32.9%	334	32.0%	307	32.9%	266	32.9%	279	34.1%	
Unknown	116	3.2%	39	3.7%	33	3.5%	19	2.4%	25	3.1%	
Neutrophils at COVID-19 onset											
<501	256	7.1%	93	8.9%	63	6.8%	56	6.9%	44	5.4%	**0.017**
501 - 999	191	5.3%	64	6.1%	50	5.4%	37	4.6%	40	4.9%	
>999	2665	74.0%	726	69.5%	678	72.7%	613	75.9%	648	79.1%	
Lymphocytes at COVID-19 onset											
<201	334	9.3%	125	12.0%	82	8.8%	72	8.9%	55	6.7%	**0.001**
201 - 499	538	14.9%	149	14.3%	137	14.7%	133	16.5%	119	14.5%	
>499	2265	62.9%	615	58.9%	589	63.2%	502	62.1%	559	68.3%	
Vaccine doses before COVID-19											
Not vaccinated	2468	68.5%	721	69.1%	629	67.5%	541	67.0%	577	70.5%	0.172
One dose	81	2.2%	29	2.8%	23	2.5%	16	2.0%	13	1.6%	
Two doses	442	12.3%	135	12.9%	115	12.3%	107	13.2%	85	10.4%	
Three doses	570	15.8%	148	14.2%	148	15.9%	139	17.2%	135	16.5%	
Four doses	42	1.2%	11	1.1%	17	1.8%	5	0.6%	9	1.1%	
Last vaccination before COVID-19											
mRNA	1025	28.4%	272	26.1%	278	29.8%	242	30.0%	233	28.4%	**<0.001**
Vector-based	66	1.8%	35	3.4%	15	1.6%	13	1.6%	3	0.4%	
Inactivated	40	1.1%	16	1.5%	8	0.9%	10	1.2%	6	0.7%	
Time of COVID-19 diagnosis											
1st wave January-April 2020	820	22.8%	192	18.4%	192	20.6%	183	22.6%	253	30.9%	**<0.001**
1st interwaves	185	5.1%	66	6.3%	50	5.4%	31	3.8%	38	4.6%	
2nd wave September 2020-March 2021	1198	33.3%	384	36.8%	316	33.9%	269	33.3%	229	28.0%	
2nd interwaves	230	6.4%	70	6.7%	52	5.6%	60	7.4%	48	5.9%	
3rd wave September 2021-March 2022	1055	29.3%	298	28.5%	292	31.3%	245	30.3%	220	26.9%	
3rd interwaves	68	1.9%	19	1.8%	20	2.1%	10	1.2%	19	2.3%	
4th wave May-July 2022	47	1.3%	15	1.4%	10	1.1%	10	1.2%	12	1.5%	
SARS-CoV-2 variant											
Wild type	113	3.1%	37	3.5%	31	3.3%	27	3.3%	18	2.2%	**0.001**
Alpha	45	1.2%	13	1.2%	8	0.9%	13	1.6%	11	1.3%	
Delta	111	3.1%	32	3.1%	32	3.4%	31	3.8%	16	2.0%	
Omicron	437	12.1%	120	11.5%	115	12.3%	104	12.9%	98	12.0%	
Not tested	2897	80.4%	842	80.7%	746	80.0%	633	78.3%	676	82.5%	
COVID-19 severity											
Asymptomatic	557	15.5%	187	17.9%	144	15.5%	116	14.4%	110	13.4%	**<0.001**
Mild infection	937	26.0%	276	26.4%	227	24.4%	210	26.0%	224	27.4%	
Severe infection	1554	43.1%	377	36.1%	389	41.7%	369	45.7%	419	51.2%	
Critical infection	555	15.4%	204	19.5%	172	18.5%	113	14.0%	66	8.1%	
COVID-19 symptoms at onset											
Pulmonary	1429	39.7%	379	36.3%	369	39.6%	327	40.5%	354	43.2%	**0.010**

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Table 1 (*continued*)

	Overall		65-70 years old		71-75 years old		76-80 years old		>80 years old		*P*-value
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	
Pulmonary + extrapulmonary	912	25.3%	250	23.9%	235	25.2%	210	26.0%	217	26.5%	
Extrapulmonary	605	16.8%	195	18.7%	152	16.3%	129	16.0%	129	15.8%	
Screening	657	18.2%	220	21.1%	176	18.9%	142	17.6%	119	14.5%	
Stay during COVID-19 episode											
Home	965	26.8%	309	29.6%	251	26.9%	217	26.9%	188	23.0%	**0.016**
Hospital	2638	73.2%	735	70.4%	681	73.1%	591	73.1%	631	77.0%	
Duration of the stay in hospital	14 (7-23) [1-190]		15 (8-27) [1-155]		14 (8-23) [1-179]		14 (7-23) [1-190]		12 (7-20) [1-135]		
Intensive care unit stay	560	21.2%	205	27.9%	174	25.6%	115	19.5%	66	10.5%	**<0.001**
Duration of the intensive care unit stay	10 (5-18) [1-115]		11 (6-20) [1-74]		10 (5-16) [1-80]		9 (4-15) [1-115]		7 (3-14) [1-68]		
COVID-19 treatment											
No specific treatment reported	752	20.9%	201	19.3%	204	21.9%	157	19.4%	190	23.2%	**0.002**
Antivirals ± corticosteroids ± plasma	332	9.2%	97	9.3%	104	11.2%	67	8.3%	64	7.8%	
Antivirals + monoclonal antibodies ± corticosteroids ± plasma	106	2.9%	34	3.3%	34	3.6%	23	2.8%	15	1.8%	
Monoclonal antibodies ± corticosteroids ± plasma	255	7.1%	89	8.5%	64	6.9%	64	7.9%	38	4.6%	
Plasma ± corticosteroids	34	0.9%	11	1.1%	10	1.1%	9	1.1%	4	0.5%	
Corticosteroids	385	10.7%	94	9.0%	88	9.4%	97	12.0%	106	12.9%	
Unknown	1739	48.3%	518	49.6%	428	45.9%	391	48.4%	402	49.1%	

The 90-day mortality in patients receiving only corticosteroids was 35.6% (n = 137/385. In patients receiving antivirals with or without other treatments, 90-day mortality was significantly lower (n = 126/438, 25.7%) and in those receiving only monoclonal antibodies with or without other treatments, it was 12.5% (n = 32/255, P <0.001, Figure 2b, Supplementary table 1).

In the multivariable regression analysis (Table 3), age was a significant independent risk factor for 90-day mortality. The presence of a cardiac (hazard ratio [HR] 1.262, 95% confidence interval [CI] 1.107-1.438), hepatic (HR 1.573, 95% CI 1.204-2.054), or renal (HR 1.233, 95% CI 1.029-1.476) comorbidity had a significantly negative impact on patient outcome, as well as lymphopenia at COVID-19 diagnosis. Acute leukemia had a significantly worse prognosis than any other malignancy. Moreover, an active hematologic malignancy at COVID-19 diagnosis (HR 1.651, 95% CI 1.421-1.918) also had an adverse impact on patient survival, so did baseline pulmonary involvement and critical COVID-19 (HR 2.903, 95% CI 2.517-3.347). Among COVID-19 treatments, receiving only corticosteroids increased the risk of death (HR 1.407, 95% CI 1.077-1.837), whereas the incorporation of monoclonal antibodies significantly decreased it (HR 0.589, 95% CI 0.380-0.915). In patients >80 years old, male sex also had significantly worse prognosis (HR 1.355, 95% CI 1.074-1.709).

Discussion

Increased age was the most frequent independent risk factor for an adverse outcome of COVID-19 reported in patients with hematological malignancy. In the present study, the large number of patients analyzed allowed us to demonstrate the negative impact of increasing age even in the elderly population and to dissect the prognosis of COVID-19 according to clinical and therapeutic variables. More importantly, the duration of the study encompassing three pandemic waves from January 2020 to March 2022 enabled us to show that prognosis gradually improved, particularly during the third wave mainly sustained by the Omicron variant, and that receiving three doses of vaccine further ameliorated patient's survival.

The present study confirms that chronological age significantly worsens the outcome of COVID-19 even within a population of hematological malignancy selected for age ≥65 years, whose median age was 74. Overall, the 90-day survival was 71.2% and survival rates decreased with age. Survival differences were significant between each 5-year group, underscoring the prominent importance of chronological age as a predictor of adverse outcomes, even within subjects collectively defined as advanced age. In previous research, age was a significant adverse prognostic factor in 19 of 25 worldwide epidemiological studies analyzed [23]. None of those studies evaluated the impact of increasing age specifically within the elderly patient population. However, some insights have emerged from a meta-analysis involving over 600,000 patients that specifically assessed the impact of advancing age on mortality within the elderly demographic [24].

The characteristics of elderly patients studied were similar to those of patients with hematological malignancy and COVID-19 of any age reported in larger studies. As expected, the frequency of comorbidities, particularly cardiac, was higher, and there were relatively more patients with chronic lymphoid leukemia and myelodysplastic syndrome and fewer with acute lymphoid leukemia, chronic myeloid leukemia and

Table 2
Outcome of the whole series of older hematologic patients with COVID-19 and of the four groups of different ages.

	Overall		65-70 years old		71-75 years old		76-80 years old		>80 years old		*P*-value
	n	%	n	%	n	%	n	%	n	%	
Follow up time	39 (14-133.5) [0-792]		50 (19-152) [0-792]		45 (17-139) [0-733]		35 (13-121) [0-760]		27 (10-103) [0-627]		**<0.001**
Follow-up time, alive	75.5 (26-191) [0-792]		82 (29-199) [0-792]		81 (27-206) [0-733]		69 (23-174.5) [0-760]		63 (23-191) [0-627]		0.099
Follow-up time, dead	15 (7-33) [0-657]		19 (10-37) [0-528]		16 (10-38) [0-657]		15 (7-30) [0-577]		12 (5-27) [0-584]		**<0.001**
Overall											**<0.001**
Mortality	1107	30.7%	252	24.1%	258	27.7%	261	32.3%	336	41.0%	
Reason for death											
COVID-19	753	20.9%	164	15.7%	176	18.9%	184	22.8%	229	28.0%	
COVID-19 + hematological malignancy	264	23.8%	66	6.3%	57	6.1%	59	7.3%	82	10.0%	
Hematological maligancies ± other reasons	90	2.5%	22	2.1%	25	2.7%	18	2.2%	25	3.1%	
Day 30											**<0.001**
Mortality	852	23.6%	175	16.8%	194	20.8%	209	25.9%	274	33.5%	
Reason for death											
COVID-19	598	16.6%	113	10.8%	138	14.8%	151	18.7%	196	23.9%	
COVID-19 + hematological malignancy	208	5.8%	49	4.7%	44	4.7%	47	5.8%	68	8.3%	
Hematological maligancies ± other reasons	46	1.3%	13	1.2%	12	1.3%	11	1.4%	10	1.2%	
Day 90											**<0.001**
Mortality	1038	28.8%	229	21.9%	244	26.2%	251	31.1%	314	38.3%	
Reason for death											
COVID-19	723	20.1%	152	14.6%	171	18.3%	179	22.2%	221	27.0%	
COVID-19 + hematological malignancy	252	7.0%	61	5.8%	55	5.9%	57	7.1%	79	9.6%	
Hematological maligancies ± other reasons	63	1.7%	16	1.5%	18	1.9%	15	1.9%	14	1.7%	
Day 365											**<0.001**
Mortality	1095	30.4%	249	23.9%	256	27.5%	260	32.2%	330	40.3%	
Reason for death											
COVID-19	745	20.7%	162	15.5%	175	18.8%	183	22.6%	225	27.5%	
COVID-19 + hematological malignancy	262	7.3%	65	6.2%	57	6.1%	59	7.3%	81	9.9%	
Hematological maligancies ± other reasons	88	2.4%	22	2.1%	24	2.6%	18	2.2%	24	2.9%	

Hodgkin's lymphoma, reflecting the epidemiology of the general population.

In our elderly patients, there were significant differences associated with increasing age in variables potentially impacting survival. The eldest patients had more comorbidities but less severe neutropenia and lymphopenia. More importantly, they were less likely to receive targeted antivirals and monoclonal antibodies for COVID-19 or to receive intensive care when hospitalized for severe disease. Nevertheless, multivariable analysis confirmed that age *per se* remains one of the most powerful independent predictors of adverse outcomes among elderly patients with COVID-19.

The role of hematological malignancy as a direct cause of death was limited, accounting for only 8.1% of deceased patients. This proportion was lower than that reported in hematological malignancy patients of any age suggesting that in elderly persons the clinical impact of COVID-19 was more severe than that of their underlying hematological malignancy [12–14,18,19]. Among the different hematological malignancies, the prognosis of COVID-19 was worst in patients with acute leukemia, where increasing age had a negative prognostic effect. In other hematological malignancies, this effect was less pronounced.

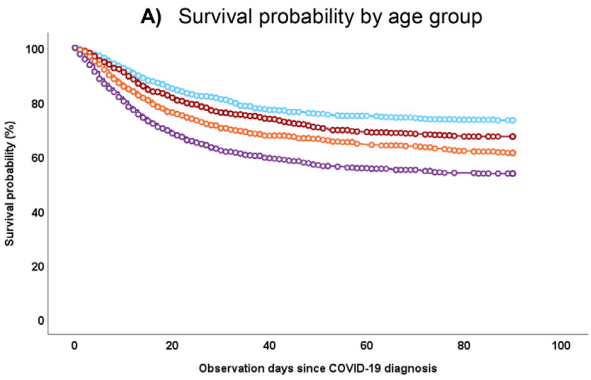
Similarly to the general population, the first wave of COVID-19 from January to April 2020 was more severe than the second from September 2020 to March 2021, which in turn was more severe than the third wave, from September 2021 to March 2022. The severity of COVID-19 during the first wave was particularly evident in patients >80 years old who were the largest group and whose 90-day survival did not reach 40%. On the contrary, the second wave affected primarily the youngest age group whose outcome did not differ from the first wave, whereas in the other age groups COVID-19 burden gradually decreased and its outcome improved. The third pandemic wave did not show an age predominance within elderly patients and its prognosis was markedly better with death rates below 20% in all age groups including patients >80 years old.

The improved outcome of COVID-19, in parallel to the pandemic evolution, has been ascribed to a presumed lower virulence of the Omicron virus variant [2,19–21], mostly represented since the third wave of the pandemic. However, in hematological malignancy patients, Omicron was still associated with considerable attributable mortality [19]. Although the viral strain was known only in a limited number of patients, the present study confirms that survival with the Omicron variant was significantly higher in elderly patients. The increased survival rates were particularly evident in patients aged 65-70 years whereas in the elder groups, differences between Omicron and the other variants were less notable, suggesting that if a patient is frail due to coexisting conditions like hematological malignancy, the effects of the

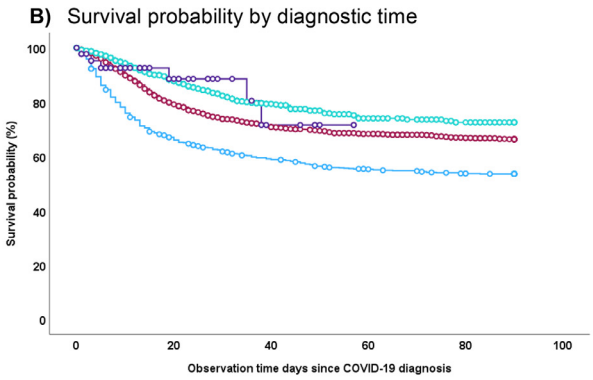
Table 3
Univariable and multivariable regression analysis on the effect of different parameters on 90-day mortality.

	UNIVARIABLE				MULTIVARIABLE			
	P-value	HR	95% C.I. Lower	Upper	*P*-value	HR	95% C.I. Lower	Upper
Age								
65-70 years old	-	-	-	-	-	-	-	-
71-75 years old	**0.011**	1.258	1.054	1.502	**0.005**	1.308	1.082	1.582
76-80 years old	**<.001**	1.584	1.327	1.889	**<.001**	1.706	1.411	2.063
>80 years old	**<.001**	2.119	1.792	2.506	**<.001**	2.542	2.107	3.067
Sex	0.137	1.097	0.971	1.239				
Comorbidities								
No comorbidities	-	-	-	-				
1 comorbidity	**0.024**	1.216	1.027	1.441				
2 comorbidities	**<.001**	1.440	1.206	1.720				
3 or more comorbidities	**<.001**	1.793	1.494	2.152				
Chronic cardiopathy	**<.001**	1.382	1.225	1.559	**<.001**	1.262	1.107	1.438
Chronic pulmonary disease	**<.001**	1.277	1.106	1.475	0.832	0.983	0.839	1.152
Diabetes	**0.024**	1.179	1.022	1.362	0.417	1.067	0.913	1.246
Liver disease	**0.003**	1.484	1.149	1.918	**<.001**	1.573	1.204	2.054
Obesity	0.175	1.166	0.934	1.455				
Renal impairment	**<.001**	1.645	1.392	1.943	**0.023**	1.233	1.029	1.476
Smoking history	0.083	1.162	0.981	1.376	0.078	1.177	0.982	1.411
Neutrophils								
<501	-	-	-	-	-	-	-	-
501 - 999	0.312	0.859	0.639	1.154	0.890	1.022	0.756	1.381
>999	**<.001**	0.643	0.526	0.785	0.157	0.846	0.671	1.067
Lymphocytes								
< 201	**-**	-	-	-	-	-	-	-
201 - 499	**0.013**	0.766	0.620	0.946	**0.019**	0.769	0.618	0.958
>499	**<.001**	0.582	0.487	0.694	**<.001**	0.605	0.501	0.731
Type of cancer								
Acute leukaemia	**-**	-	-	-	**-**	-	-	-
Chronic myeloproliferative neoplasms	**<.001**	0.494	0.378	0.645	**<.001**	0.586	0.436	0.787
Chronic lymphoid leukemia	**<.001**	0.633	0.510	0.786	**<.001**	0.632	0.495	0.807
Lymphoma	**<.001**	0.684	0.565	0.828	**<.001**	0.665	0.539	0.822
Myelodisplastic syndrome	**0.030**	0.765	0.600	0.975	**0.015**	0.714	0.545	0.937
Multiple myeloma	**<.001**	0.595	0.481	0.735	**<.001**	0.607	0.481	0.765
Other	0.141	0.424	0.135	1.329	0.361	0.579	0.179	1.871
Status malignancies								
Controlled disease	-	-	-	-	-	-	-	-
Stable disease	0.847	1.017	0.854	1.212	0.794	1.027	0.843	1.251
Active disease	**<.001**	1.927	1.678	2.212	**<.001**	1.651	1.421	1.918
Unknown	**<.001**	2.520	1.887	3.367	**<.001**	1.860	1.370	2.526
Time last malignancy treatment before COVID-19								
Chemotherapy - In the last month	-	-	-	-				
Chemotherapy - In the last 3 months	0.798	1.026	0.843	1.250				
Chemotherapy - > 3 months	0.134	0.872	0.729	1.043				
HSCT/Chimeric antigen receptor T-cell - In the last 6 months	0.663	1.110	0.695	1.774				
HSCT/Chimeric antigen receptor T-cell - > 6 months	0.053	0.540	0.289	1.008				
No treatment - Not applicable	**0.031**	0.824	0.691	0.982				
Not reported	0.077	0.676	0.437	1.044				
Vaccine doses								
Not vaccinated	-	-	-	-	-	-	-	-
One dose	0.071	0.658	0.418	1.037	0.785	0.932	0.561	1.548
Two doses	**<.001**	0.644	0.519	0.799	0.684	0.947	0.727	1.233
Three doses	**<.001**	0.439	0.347	0.555	**0.009**	0.683	0.513	0.910
Four doses	**0.002**	0.172	0.055	0.535	0.079	0.354	0.111	1.127
Variant								
Wild type	-	-	-	-	-	-	-	-
Alpha	0.994	0.998	0.558	1.785	0.699	0.880	0.459	1.687
Delta	0.577	0.873	0.543	1.406	0.069	1.645	0.962	2.812
Omicron	**0.004**	0.559	0.377	0.828	0.326	1.247	0.803	1.939
Not tested	0.864	0.972	0.706	1.340	0.220	1.232	0.883	1.719
Symptoms at COVID-19 onset								
Pulmonary	-	-	-	-	-	-	-	-
Pulmonary + extrapulmonary	0.304	0.928	0.805	1.070	0.358	0.931	0.799	1.084
Extrapulmonary	**<.001**	0.507	0.417	0.618	**<.001**	0.658	0.534	0.812
Screening	**<.001**	0.550	0.457	0.662	**<.001**	0.634	0.514	0.782
Intensive care unit admission	**<.001**	3.157	2.782	3.584	**<.001**	2.903	2.517	3.347
COVID-19 treatment								
No specific treatment reported	-	-	-	-	-	-	-	-
Antivirals ± corticosteroids ± plasma	**<.001**	1.968	1.508	2.569	0.345	1.152	0.859	1.544
Antivirals + monoclonal antibodies ± corticosteroids ± plasma	0.553	1.151	0.723	1.831	0.546	0.854	0.512	1.425
Monoclonal antibodies ± corticosteroids ± plasma	0.425	0.853	0.577	1.261	**0.018**	0.589	0.380	0.915
Plasma ± corticosteroids	**<.001**	2.871	1.702	4.840	0.159	1.485	0.857	2.575
Corticosteroids	**<.001**	2.303	1.799	2.947	**0.012**	1.407	1.077	1.837
Unknown	**<.001**	2.215	1.819	2.697	**<.001**	1.486	1.181	1.869

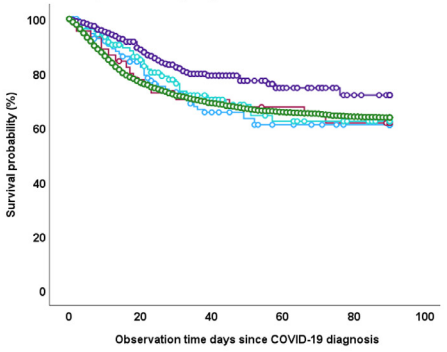
CI, confidence interval; HR, hazard ratio.



Overall comparison	p<0.001		
Pairwise comparisons	65-70 years old	71-75 years old	76-80 years old
71-75 years old	0.010		
76-80 years old	<.001	0.008	
>80 years old	<.001	<.001	<.001



Overall comparison	p=0.001		
Pairwise comparisons	1st wave	2nd wave	3rd wave
2nd wave	0.781		
3rd wave	0.055	<0.001	
4th wave	0.458	0.412	0.818



Overall comparison	p=0.001			
Pairwise comparisons	Wild type	Alpha	Delta	Omicron
Alpha	0.944			
Delta	0.650	0.778		
Omicron	0.010	0.096	0.071	
Not tested	0.967	0.900	0.456	0.001

Figure 1. Survival probability by age group, diagnostic time, and SARS-CoV-2 variant.

lower virulence of virus variant may be outbalanced by increasing age.

The vaccination status may have also played a substantial role in the better outcome of the more recent Omicron variants. An improvement both in 30-day and 90-day survival was documented in patients receiving at least one dose of vaccine compared to unvaccinated patients. The difference was highly significant despite a low vaccination rate. This result may be surprising as it is generally assumed that hematological malignancy is associated with a lack of serological response to vaccines, both against COVID-19 or other viruses, for example, influenza [25]. In addition, treatments commonly used in hematological malignancy, like anti-CD20 monoclonal antibodies and Bruton's tyrosine kinase inhibitors [7], are strong inhibitors of anti-SARS-CoV-2 antibody production after vaccination [26,27], and increasing age may contribute to a reduced response to vaccination in hematological malignancy [26], as reported already, with an age cut-off of 82 years, but not in other reports [27]. Nevertheless, our report strongly documents the paramount importance of vaccination in elderly patients with hematological malignancy as well as the increasingly favorable impact of vaccination in parallel to increasing age. The beneficial effect of vaccines was magnified by the worsening prognosis with increasing age of unvaccinated patients. In patients >80 years old, a single vaccine dose was sufficient to improve survival significantly compared to unvaccinated persons, whose 90-day survival was lower than 50%. Patients aged 75-80 required a two-dose vaccination course to have a significant survival advantage, while a third additional dose was necessary in the cohort of patients aged 71-75. Similarly, in patients aged 65-70, a third dose was associated with a marked survival improvement compared to receiving only two doses.

The efficacy of a booster dose in enhancing the serological response rate and also the cellular immune response in persistently seronegative patients has been already reported in patients with hematological malignancy, irrespective of age [28], except in those recently treated with anti-CD20 monoclonal antibodies [29]. In the present study, the importance of a third vaccine dose in elderly patients was further highlighted by the multivariable analysis showing that vaccination with three doses was the most important actionable variable conferring an independent survival advantage. A lower number of doses and infection with the Omicron virus variant did not reach statistical significance.

The potential further benefit of a fourth vaccine dose in hematological malignancy patients is still under investigation. In a small series of solid organ transplant patients, a 50% seroconversion of seronegative patients and a 100% boosting of patients with low-

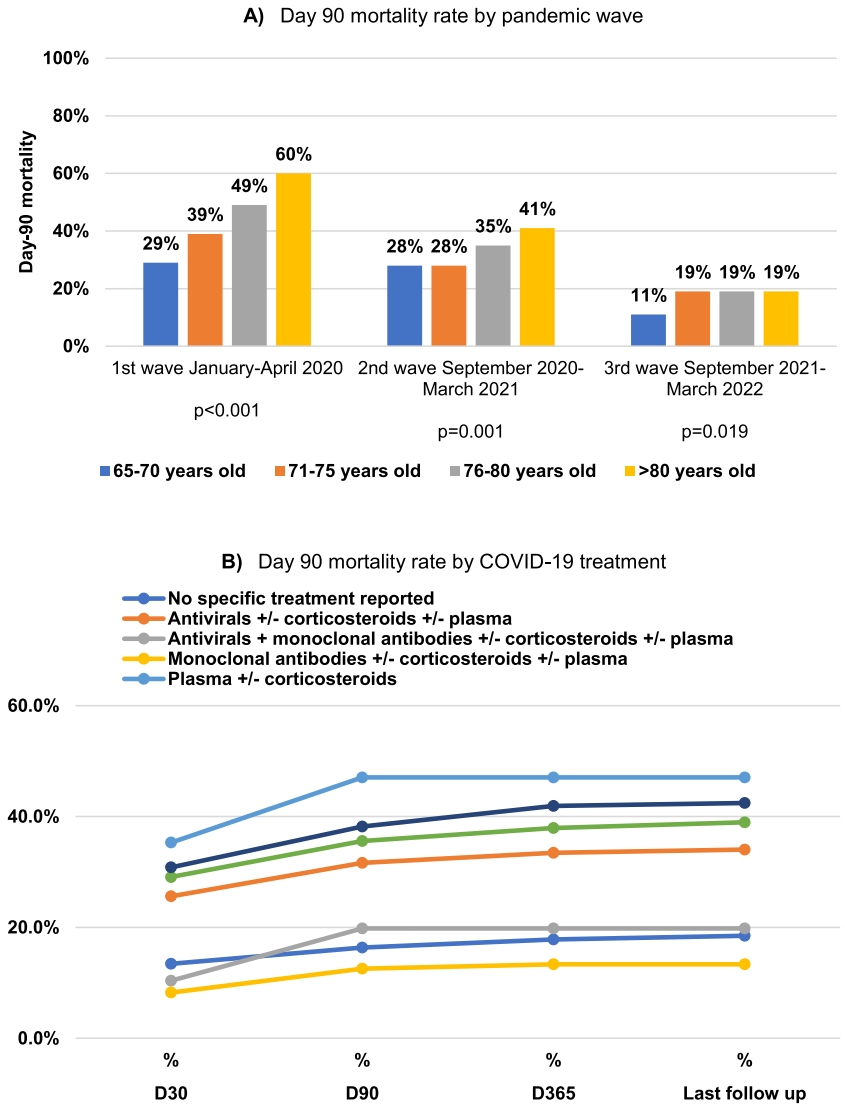


Figure 2. Day 90 mortality rate by pandemic wave and COVID-19 treatment.

positive antibody levels were shown [30]. Results of the present series are to be interpreted with caution since only 42 patients had received a fourth vaccine dose. Nevertheless, survival of these patients at 90 days reached over 90% overall and 100% in those aged 65-70 and 75-80 years, and it was consistently better than that of patients receiving three doses in all age groups.

Taken together, these data highlight the key importance of vaccination in a category of patients with a combination of multiple risk factors like comorbidities and hematological malignancy, whose difficulties in coping with COVID-19 are magnified by the increase in chronological age. Of note, age was recently demonstrated as the most significant adverse risk factor for survival in vaccinated patients with breakthrough COVID-19 [12,14]. Therefore, every improvement in the ability to effectively respond to the virus, including the immune response to multiple doses of vaccine, should be actively pursued.

In multivariable analysis, also an active hematologic malignancy, a diagnosis of acute leukemia, a more severe presentation of COVID-19, as well as comorbidities and severe lymphopenia were independently associated with mortality. They have been reported as potential risk factors in other reports on adult hematological malignancy patients with COVID-19 [31]. Unlike vaccination, most of these variables can be hardly addressed to improve the prognosis of our patients. However, the use of prolonged treatments for hematological malignancy, potentially causing lymphopenia, as well as optimal management of cardiac, renal, and hepatic comorbidities should be implemented to limit the dismal consequences of COVID-19 in elderly patients with hematological malignancy. Our data show that increasing age was associated with a suboptimal management of COVID-19. The use of antivirals and monoclonal antibodies, whose efficacy was highlighted also in our series, was apparently neglected particularly in patients >80 years old, although in this category of very frail patients, better infection management may maximize therapeutic benefits.

This large registry study has some limitations in addition to its retrospective nature. Data are incomplete particularly regarding the identification of SARS-CoV-2 variants, COVID-19 treatments, and potential thromboembolic phenomena. Other relevant limitations include the absence of sample size calculation due to its exploratory aims, and the potential bias stemming from the lack of data on functionality, cognition, and the prevalence of polypharmacy among elderly patients with hematological malignancy who contracted COVID-19, which could have provided additional insights into their overall health status and outcomes. Finally, the fact that antiviral and monoclonal antibody treatments were un-

derutilized in patients over 80, potentially limited benefits in this vulnerable group.

In conclusion, elderly COVID-19 patients with hematological malignancy are a heterogeneous group whose prognosis markedly worsens with age. Despite the above limitations, the data collected provide a framework to address the optimal healthcare management of elderly hematological malignancy patients using preventive and therapeutic strategies, including vaccination and antiviral agents, which may be modulated according to increasing chronological age. Additionally, this study underscores the significant impact of age on the prognosis of elderly COVID-19 patients with hematological malignancy, mirroring the worse vital prognosis observed in other elderly patients with COVID-19 and specific comorbidities. Furthermore, the data highlight the crucial role of monoclonal antibodies in reducing mortality among these vulnerable individuals.

CRediT authorship contribution statement

G.R., J.S.G., C.C., R.C., O.A.C. and L.P. contributed to study design, study supervision, did the statistical plan and data interpretation, and wrote the paper. J.S.G. performed the statistical analysis.All authors recruited participants and collected and interpreted data, 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, have read and agreed to the published version of the manuscript. All authors have read and agreed to the published version of the manuscript.

Declarations of competing interest

The authors have no competing interests to declare.

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Ethical approval

EPICOVIDEHA (www.clinicaltrials.gov; NCT04733729) is an international open web-based registry for patients with HM infected with SARS-CoV-2. This registry was centrally approved by the local ethics committee of the Fondazione Policlinico Universitario Agostino Gemelli—IRCCS, Università Cattolica del Sacro Cuore of Rome, Italy (Study ID: 3226). Additionally, if applicable, the respective local ethics committee of each participating institution might have approved the EPICOVIDEHA.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2023.10.013.

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