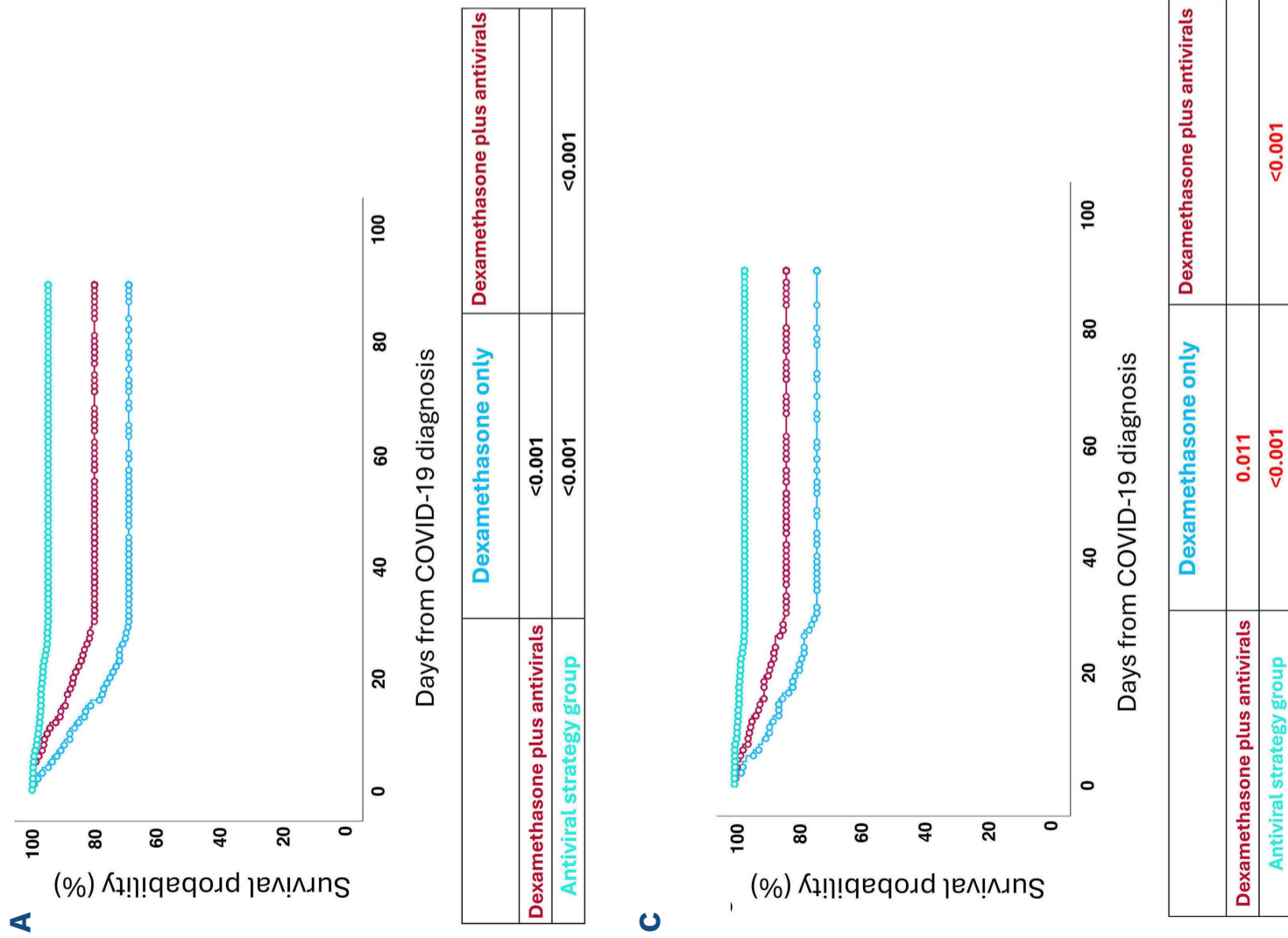


# Dexamethasone treatment for COVID-19 is related to increased mortality in hematologic malignancy patients: results from the EPICOVIDEHA registry

The optimal treatment strategies for hematological malignancy patients with COVID-19 are still unclear with respect to the selection and timing of anti-viral as well as anti-inflammatory therapies. Most COVID-19 management recommendations have been adapted from the ones used in immunocompetent patients.<sup>1,2</sup> However, immunosuppressed patients often have substantial alterations in their adaptive and innate immunity that affect the pathophysiology of SARS-CoV-2 infection and often have reduced anti-viral immunity as well as dysfunctional inflammatory response. As a result, we hypothesize that these patients mainly benefit more from antiviral treatment, whereas dexamethasone may perpetuate the intrinsic immunosuppression and be even detrimental. Our study demonstrates that dexamethasone treatment for SARS-CoV-2 infection is related to increased mortality in hematological malignancy patients, even during the omicron wave with most patients being fully vaccinated. Data included were exported from the EPICOVIDEHA registry (*clinicaltrials.gov*. Identifier: NCT04733729). The corresponding local ethics committee of each participating institution has approved the EPICOVIDEHA study when applicable. The local Institutional Review Board and Ethics Committee of the Fondazione Policlinico Universitario Agostino Gemelli—IRCCS, Università Cattolica del Sacro Cuore of Rome, Italy, approved the multicenter, non-interventional EPICOVIDEHA study (study ID: 3226). Both hospitalized and non-hospitalized patients were eligible for inclusion. Each patient was reviewed for validity following the inclusion criteria: i) patient >18 years old, ii) hematological malignancies with activity during the 5 years before COVID-19, iii) confirmed diagnosis for COVID-19 and iv) COVID-19 treatment information. Mortality rate was reported at 90 days after COVID-19 diagnosis. Classification of COVID-19 role in patient's death was made by the reporting physician. Patients in the study population were classified as following: i) "dexamethasone only" group, for patients treated with dexamethasone exclusively, ii) "dexamethasone plus antivirals" group, for patients having received dexamethasone in addition to antivirals, and iii) in the "antiviral strategy group", with patients treated with antivirals exclusively. With regard to antivirals regimens, in both antiviral strategy group and the dexamethasone plus antivirals group, antivirals were used in monotherapy or in combination with monoclonal antibodies and convalescent plasma. Differences between treatment groups were assessed by  $\chi^2$  or Fisher's exact test. Factors associated with mortality were analyzed by Cox regression. Given the

lack of randomization of therapies, a propensity score of receiving dexamethasone was estimated using a backward stepwise logistic regression model that included variables with  $P$  values  $\leq 0.05$  in the univariable analysis: age, renal dysfunction, smoking history, status of the malignancy, lymphopenia, previous COVID-19 vaccination, season of COVID-19 diagnosis and COVID-19 severity. The propensity score for receiving dexamethasone was then used as a covariable in a multivariable analysis to adjust for potential confounding factors associated with initial anti-COVID-19 treatment. The goodness of fit of the final multivariable model was assessed by the Hosmer-Lemeshow test and the area under the receiver operating characteristic curve (AUC). Sensitivity analyses were performed by repeating the propensity score approach with different methods, including 1:1 matching with replacement and a calliper of 0.25, as well as quintile stratification. A  $P$  value  $< 0.05$  was considered statistically significant. Statistical analysis was run with SPSS v25.0 (IBM Corp. Chicago, IL, USA). A total of 5,962 patients with COVID-19 and hematological malignancies were enrolled in EPICOVIDEHA registry. Finally, 2,267 patients were included in the analysis, of whom 500 (22.1%) patients were assigned to the dexamethasone only group, 470 (20.7%) to the dexamethasone plus antivirals group and 1,297 (57.2%) to the antiviral strategy group (Table 1; *Online Supplementary Table S3*; *Online Supplementary Figure S1*). Anti-SARS-CoV-2 strategies were administered based on internal criteria of the respective treatment team (*Online Supplementary Tables S1, S2*). Overall, day-90 mortality was 20.5% (464 patients), 9.8% (223 patients) exclusively related to COVID-19, 6.0% (137) related to both hematological malignancies and SARS-CoV-2 infection and 1.6% (36 patients) not related to the COVID-19 episode. Figure 1A-C detailed the survival probability curves for the three treatment groups of the study, regardless of the pandemic waves and in those patients with omicron infection. Figure 1B detailed the survival probability curves for the groups according to the need of hospital admission, intensive care unit (ICU) admission or outpatients' care. In the dexamethasone only group, 138 patients (27.6%) died at the end of follow-up *versus* 86 patients (18.3%) in the dexamethasone plus antivirals group ( $P > 0.001$ ) and 55 patients (4.2%) in the antiviral strategy group ( $P < 0.001$ ). The independent factors associated to mortality were age, chronic liver disease, absence of neutropenia, active hematological malignancy, less than three vaccine doses, need of hospital and ICU admission (Table 2). The dexamethasone only group was an



**Figure 1. Survival curves for the three groups of patients with different treatment strategies.** (A) All patients. (B) Non-hospitalized (home) patients and hospitalized patients (non-intensive care unit [non-ICU] admitted patients and ICU-admitted patients). (C) SARS-CoV-2 Omicron variant-infected patients.

**Table 1.** Clinical characteristic by treatment group.

Characteristics	Dexamethasone plus antivirals N=470 N (%)	<i>P</i> dexamethasone only versus dexamethasone plus antivirals	Dexamethasone only N=500 N (%)	<i>P</i> dexamethasone only versus antivirals	Antiviral strategies N=1,297 N (%)
Sex		0.057		0.112	
Male	268 (57)		315 (63)		764 (59)
Age in years, median (IQR)	68 (58-75)	0.021	70 (57-79)	<0.001	63 (51-72)
Comorbidities at COVID-19 onset		0.776		<0.001	
No comorbidities	143 (30.4)		156 (31.2)		575 (44.3)
Three or more comorbidities	61 (13)		71 (14.2)		83 (6.4)
Chronic cardiopathy	218 (46.4)	0.896	234 (46.8)	<0.001	424 (32.7)
Chronic pulmonary disease	64 (13.6)	0.921	67 (13.4)	0.001	109 (8.4)
Diabetes mellitus	96 (20.4)	0.262	88 (17.6)	0.001	126 (9.7)
Obesity	33 (7.0)	0.362	28 (5.6)	0.614	65 (5.0)
Liver disease	21 (4.5)	0.421	28 (5.6)	0.032	44 (3.4)
Renal impairment	31 (6.6)	0.004	60 (12.0)	<0.001	59 (4.5)
Smoking history	63 (13.4)	0.002	44 (8.8)	0.166	143 (11.0)
Baseline hematological malignancy		0.013		0.092	
Leukemia	188 (40.0)		214 (42.8)		551 (42.5)
Lymphoma	191 (40.6)		164 (32.8)		484 (37.3)
PH-negative myeloproliferative diseases	17 (3.6)		21 (4.2)		39 (3.0)
Plasma cell disorders	74 (15.7)		94 (18.8)		216 (16.7)
Other hematological malignancies	-		7 (1.4)		7 (0.5)
Status malignancy at COVID-19 onset		0.020		<0.001	
Controlled malignancy	186 (39.6)		188 (37.6)		650 (50.1)
Stable malignancy	100 (21.3)		148 (29.6)		225 (17.3)
Active malignancy	166 (35.3)		145 (29.0)		376 (29.0)
Unknown	18 (3.8)		19 (3.8)		46 (3.5)
Neutrophils/mcL at COVID-19 onset		0.313		0.096	
<501	41 (8.7)		37 (7.4)		109 (8.4)
Lymphocytes/mcL at COVID-19 onset		<0.001		0.660	
<201	89 (18.9)		49 (9.8)		118 (9.1)
201-499	8 (18.3)		98 (19.6)		202 (15.6)
>499	259 (55.1)		328 (65.6)		760 (58.6)
CRP level mg/L at corticosteroid administration onset, median (IQR)	9.3 (4.8-16.0)	0.504	9.5 (3.9-15.8)		
SARS-CoV-2 vaccination before COVID-19 onset		<0.001		<0.001	
Not vaccinated	185 (39.4)		273 (54.6)		405 (31.2)
1 dose	18 (3.8)		24 (4.8)		47 (3.6)
2 doses	98 (20.9)		99 (19.8)		307 (23.7)
3 doses	145 (30.9)		91 (18.2)		441 (34.0)
4 doses	24 (5.1)		13 (2.6)		97 (7.5)
Season SARS-CoV-2 diagnosis		<0.001		<0.001	
Pre-Delta (before May 2021)	123 (26.2)		175 (35.0)		144 (11.1)
Delta (May-November 2021)	83 (17.7)		125 (25.0)		167 (12.9)
Omicron (December 2021-onwards)	264 (56.2)		200 (40.0)		986 (76.0)
SARS-CoV-2 variant		<0.001		<0.001	
Wild-type	16 (3.4)		24 (4.8)		11 (0.8)
Alpha	13 (2.8)		18 (3.6)		17 (1.3)
Beta	1 (0.2)		1 (0.2)		1 (0.1)
Delta	36 (7.7)		32 (6.4)		59 (4.5)
Omicron	143 (30.4)		67 (13.4)		355 (27.4)
Not tested	261 (55.5)		358 (71.6)		854 (65.8)

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Characteristics	Dexamethasone plus antivirals N=470 N (%)	<i>P</i> dexamethasone only versus dexamethasone plus antivirals	Dexamethasone only N=500 N (%)	<i>P</i> dexamethasone only versus antivirals	Antiviral strategies N=1,297 N (%)
COVID-19 severity		0.012		<0.001	
Asymptomatic	44 (9.4)		21 (4.2)		251 (19.4)
Mild infection	44 (9.4)		44 (8.8)		329 (25.4)
Severe infection	254 (54.0)		296 (59.2)		654 (50.4)
Critical infection	128 (27.2)		139 (27.8)		63 (4.9)
Stay during COVID-19 episode		0.051		<0.001	
Home	12 (2.6)		28 (5.6)		529 (40.8)
Hospital no ICU	330 (70.2)		333 (66.6)		704 (54.3)
Hospital ICU	128 (27.2)		139 (27.8)		63 (4.9)
Outcome day 90		<0.001		<0.001	
Dead	86 (18.3)		138 (27.6)		55 (4.2)
Dead, observation time in days, median (IQR)	15 (10-22)		12 (6-17)		12 (8-23)
Reason for death			0.798		0.003
COVID-19	55 (64.0)		90 (65.2)		24 (43.6)
COVID-19 + hematological malignancy	28 (32.6)		41 (29.7)		21 (38.2)
Hematological malignancies and/or other reasons	3 (3.5)		7 (5.1)		10 (18.2)

Hematological malignancy status at coronavirus disease 2019 (COVID-19) onset: “stable disease” indicated patients at watch and wait, “controlled disease” patients in complete or partial remission, and “active diseases” patients on active treatment. Concerning COVID-19 severity: asymptomatic (no clinical signs or symptoms); mild (non-pneumonia and mild pneumonia); severe (dyspnea, respiratory frequency  $\geq 30$  breaths per minute,  $SpO_2 \leq 93\%$ ,  $PaO_2/FiO_2 < 300$ , or lung infiltrates  $> 50\%$ ), and critical (patients admitted in intensive care for respiratory failure, septic shock, or multiple organ dysfunction or failure). Asymptomatic patients were diagnosed by COVID-19 after testing as part of routine hospital admission screening or prior to hematologic specific treatment regimen. IQR: interquartile range; CRP: C-reactive protein; PH-negative: Philadelphia chromosome-negative; ICU: intensive care unit.

independent factor related to mortality (absolute hazard ratio [aHR]=0.562, 95% confidence interval [CI]: 0.418-0.754 in the antiviral strategy group; aHR=0.284, 95% CI: 0.191-0.422 in the dexamethasone plus antivirals group,  $P < 0.001$ ). This finding remained by incorporating the propensity score for receiving dexamethasone into the model. The goodness of fit was assessed by the Hosmer-Lemeshow test ( $P=0.099$ ), and the discriminatory power of the score, as evaluated by the area under the curve (AUC), was 0.77 (95% CI: 0.75-0.79). The consistency of this result was confirmed by repeating the propensity score analyses by 1:1 matching with replacement and a calliper of 0.25, and by quintile stratification. The main finding of this study is that the use of dexamethasone treatment for COVID-19 was associated with the worse outcomes in patients suffering from hematological malignancies, especially when antiviral strategies were not concomitantly applied (Figure 1A-C). It is increasingly acknowledged that patients with COVID-19 can present with different clinical phenotypes depending on the pathophysiology complicating the infection.<sup>3-5</sup> Low cycle threshold values of the real-time reverse transcription polymerase chain reaction (rRT-PCR) can guide us about the fact that our patients have a high viral load. Conversely, acute elevations in C-reactive protein, ferritin, or lactate dehydrogenase (LDH) values may indicate a hyper-inflammatory syndrome. Personalizing the treatment that

patients receive based on the respective clinical phenotype of COVID-19 is essential to improve the prognosis.<sup>4,6</sup> In this scenario, hematological patients may be different compared with immunocompetent general population. First, the process of immune-mediated viral clearance is often distorted in immunosuppressed patients leading to insufficient viral control, which may end up in long-term persistent positive PCR. Thus, the day from the onset of symptoms may not give us optimal information about the need for antivirals. Secondly, hematologic patients with malignancies have commonly pre-existing elevations in LDH and ferritin. It is therefore important not to analyze the absolute value of these markers in COVID-19 but also to consider the longer-time evolution of these inflammatory biomarkers prior and during the infection. Since the beginning of the pandemic, hematological patients have had an increased mortality when compared to the general population.<sup>7,8</sup> Most factors associated with mortality identified in our study are well known.<sup>9</sup> Our study helps to identify that a delay in antiviral treatment until the patient manifests severe illness and the use of dexamethasone are related to increased mortality in hematological patients with malignancies. Importantly, most patients included in this study presented COVID-19 during the predominance of SARS-CoV-2 Omicron variant. Dexamethasone was the first drug reported as a treat-

ment option for COVID-19 patients.<sup>10</sup> In the RECOVERY study including mainly unvaccinated patients from the first pandemic wave with wild-type SARS-CoV-2, mortality decreased from 25.7% to 22.9%. In fact, a recent sub-analysis from this trial, including 1,272 patients admitted with COVID-19 for hypoxemia mainly receiving oxygen, showed that higher doses of dexamethasone in patients with high viral load significantly increased the risk of death, com-

**Table 2.** Factors related with mortality in univariate and multivariate analyses.

	Univariable analysis 95% CI				Multivariable analysis 95% CI			
	<i>P</i>	HR	Lower limit	Upper limit	<i>P</i>	HR	Lower limit	Upper limit
Sex	-	-	-	-	-	-	-	-
Female	-	-	-	-	-	-	-	-
Male	0.457	1.097	0.859	1.401	-	-	-	-
Age	<0.001	1.035	1.026	1.045	<0.001	1.036	1.026	1.047
Comorbidities at COVID-19 onset								
Chronic cardiopathy	<0.001	1.934	1.524	2.454	0.288	1.156	0.885	1.509
Chronic pulmonary disease	0.689	1.079	0.743	1.569	-	-	-	-
Diabetes mellitus	<0.001	1.981	1.502	2.614	0.567	1.094	0.805	1.485
Liver disease	0.009	1.860	1.167	2.965	0.040	1.641	1.024	2.629
Obesity	0.901	0.966	0.564	1.655	-	-	-	-
Renal failure	<0.001	2.017	1.402	2.902	0.362	1.197	0.813	1.763
Smoking history	0.806	0.952	0.644	1.408	-	-	-	-
Baseline malignancy at COVID-19 onset								
Leukemia	-	-	-	-	-	-	-	-
Lymphoma	0.009	0.696	0.529	0.915	0.363	0.866	0.636	1.180
PH-negative myeloproliferative diseases	0.815	1.073	0.594	1.938	0.412	1.288	0.704	2.358
Plasma cell disorders	0.239	0.815	0.579	1.146	0.701	0.928	0.636	1.356
Other hematological malignancies	0.535	0.536	0.075	3.835	0.651	0.628	0.084	4.724
Neutropenia at COVID-19 onset	0.003	1.721	1.207	2.454	0.001	1.829	1.262	2.653
Lymphopenia at COVID-19 onset	0.063	0.733	0.528	1.017	0.951	1.011	0.718	1.424
Status malignancy at COVID-19 onset								
Controlled malignancy	-	-	-	-	-	-	-	-
Stable malignancy	<0.001	1.943	1.382	2.732	0.297	1.211	0.845	1.736
Active malignancy	<0.001	2.785	2.083	3.724	<0.001	2.140	1.549	2.957
Unknown	0.001	2.650	1.467	4.787	0.123	1.693	0.867	3.306
SARS-CoV-2 vaccination status at COVID-19 onset								
Not vaccinated	-	-	-	-	-	-	-	-
1 dose	0.017	0.421	0.207	0.855	0.109	0.552	0.267	1.141
2 doses	<0.001	0.413	0.293	0.581	0.018	0.640	0.443	0.925
2+ doses	<0.001	0.387	0.287	0.521	0.025	0.685	0.492	0.953
Season SARS-CoV-2 diagnosis								
Pre- $\delta$ (before May 2021)	-	-	-	-	-	-	-	-
$\delta$ (May 2021-November 2021)	0.030	0.706	0.515	0.967	0.038	1.510	1.024	2.227
Omicron (December 2021-onwards)	<.001	0.319	0.244	0.418	0.861	0.967	0.665	1.406
Stay during COVID-19 episode								
Home	-	-	-	-	-	-	-	-
Hospital non-ICU ward	<0.001	18.741	5.970	58.828	<0.001	7.140	2.239	22.769
Hospital ICU ward	<0.001	83.729	26.662	262.943	<0.001	27.506	8.523	88.769
COVID-19 treatment								
Dexamethasone only	-	-	-	-	-	-	-	-
Antiviral strategy group	<0.001	0.572	0.436	0.751	<0.001	0.562	0.418	0.754
Dexamethasone plus antivirals	<0.001	0.140	0.102	0.192	<0.001	0.284	0.191	0.422

Neutropenia: absolute neutrophil count of less than  $0.5 \times 10^9/L$  during more than 7 days. Lymphopenia: absolute lymphocyte count of less than  $0.2 \times 10^9/L$  during more than 7 days. COVID-19; coronavirus disease 2019; CI: confidence interval; HR: hazard ratio, ICU: intensive care unit; PH-negative: Philadelphia chromosome-negative.

pared with patients receiving usual care.<sup>11</sup> No severe immunosuppressant patients were included. Data validating these results in immunocompromised patients has been never reported. Our study provides clear real-life evidence against the general use of dexamethasone in this population, specially without antivirals, regardless of SARS-CoV-2 variant predominance. Interesting, mortality in ICU patients is very high and seems not to be influenced by detailed treatment strategies. Dexamethasone potentially diminishes type I interferon (INF) response, an endogenous cytokine essential to avoid escape of SARS-CoV-2 and it may also increase SARS-CoV-2 viral load and prolongs SARS-CoV-2 viral shedding.<sup>12</sup> Our study contributes additional evidence to previously documented results supporting the improving outcomes related with the use of early antiviral strategies in patients with hematological malignancies and COVID-19.<sup>13-15</sup> The strengths of this study are the large number of patients included, the multicenter approach and the extensive data gathered. However, there are some limitations, this study was non-randomized and non-interventional, with treatment decisions made by attending physicians. The absence of randomization introduces the potential for selection bias. Nevertheless, we employed propensity score methodology to mitigate the impact of these limitations. The retrospective design of the study may inherently result in lower data quality. Additionally, the analysis spanned a dynamic period, making it impossible to completely rule out the presence of a calendar effect on certain aspects, such as the evolving medical expertise in COVID-19. Data on the cycling time (Ct) of rRT-PCR or other surrogate viral marker (subgenomic RNA) are not available. Finally, we report the limitation of missing information on the day of starting different treatments after symptoms onset. In conclusion, this real-life large multicenter study showed the potential worse effect of dexamethasone treatment for COVID-19 in hematological patients with malignancies, even in the omicron era with most vaccinated patients. General treatment recommendations for patients with COVID-19 can be used with caution in patients with immunosuppression. New studies to provide high quality recommendations and treatment guidelines addressed to solve the specific problems of COVID-19 in patients with hematological malignancies are needed.

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### Contributions

Conceptualization by CGV and TFA. Data curation by JSM, FM, BW, AG, JVP, FF, JDV, SMP, SEA, MS, IFR, JL, US, CB, AV, GP, VP, MB, TL, IE, JVD, OB, KP, CT, MS, YB, LF, FI, TV, NF, MD, MJ, FM, ALG, LP, NC,

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### Data-sharing statement

Data were collected via the EPICOVIDEHA electronic case report form (eCRF), available at [www.clinicalsurveys.net](http://www.clinicalsurveys.net) (EFS Summer 2021, TIVIAN, Cologne, Germany).

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