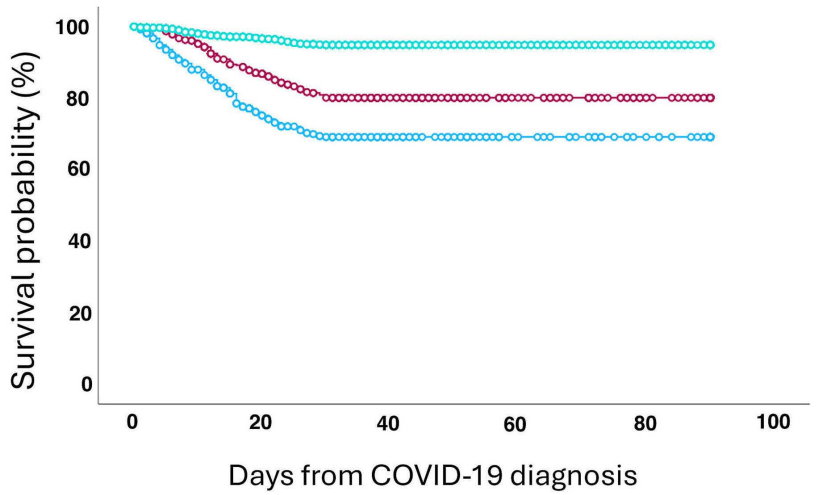
Dexamethasone treatment for COVID-19 is related to increased mortality in hematologic malignancy patients: results from the EPICOVIDEHA registry

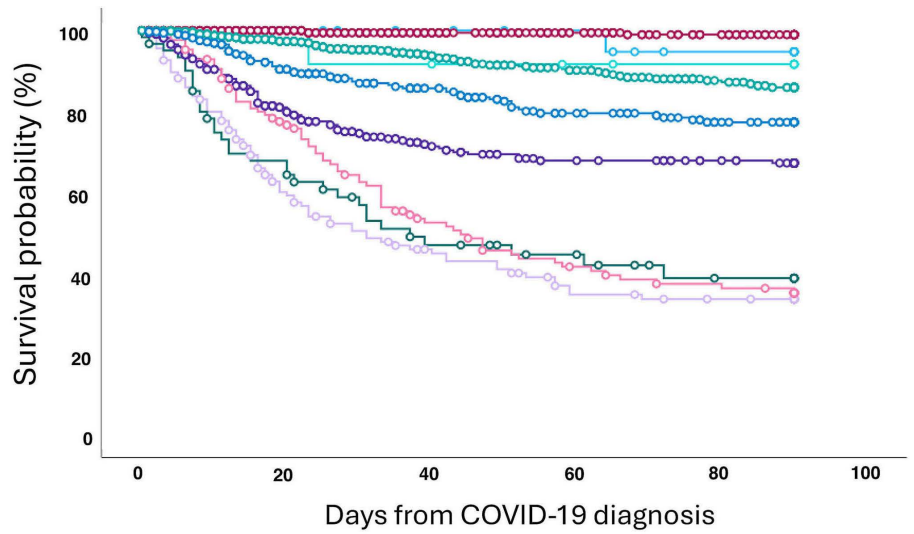
The optimal treatment strategies for hematological malignancy patients with COVID19 are still unclear with respect to the selection and timing of anti-viral as well as anti-inflammatory therapies. Most COVID-19 management recommendations have been adapted from the ones used in immunocompetent patients.[1,2] 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 χ^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 ≤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 independents 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

A



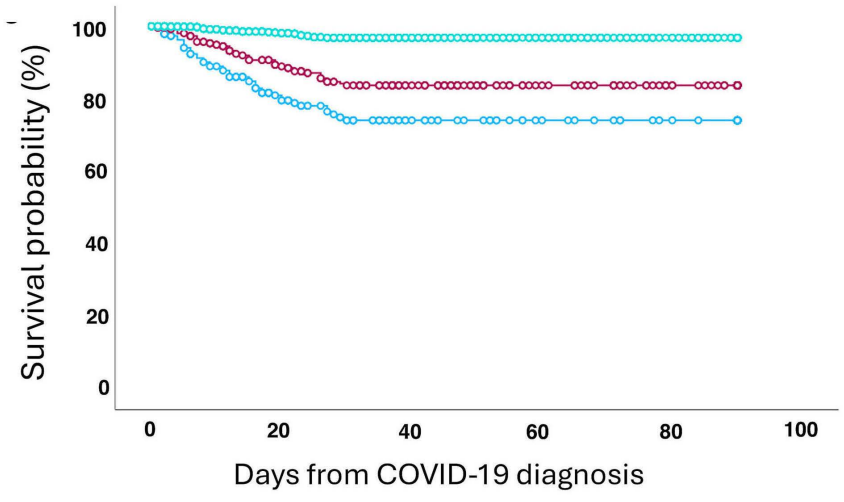
	Dexamethasone only	Dexamethasone plus antivirals
Dexamethasone plus antivirals	<0.001	
Antiviral strategy group	<0.001	<0.001

B



		Home			Hospital, no ICU			Hospital, ICU	
		Dexamethasone only	Antiviral strategy group	Dexamethasone plus antivirals	Dexamethasone Only	Antiviral strategy group	Dexamethasone plus antivirals	Dexamethasone Only	Antiviral strategy group
Home	Antiviral strategy group	0.155							
	Dexamethasone plus antivirals	0.603	0.016						
Hospital, no ICU	Dexamethasone only	0.006	<0.001	0.098					
	Antiviral strategy group	0.234	<0.001	0.677	<0.001				
	Dexamethasone plus antivirals	0.049	<0.001	0.291	<0.001	<0.001			
Hospital, ICU	Dexamethasone only	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001		
	Antiviral strategy group	<0.001	<0.001	0.004	<0.001	<0.001	<0.001	0.516	
	Dexamethasone plus antivirals	<0.001	<0.001	0.003	<0.001	<0.001	<0.001	0.162	0.677

C



	Dexamethasone only	Dexamethasone plus antivirals
Dexamethasone plus antivirals	0.011	
Antiviral strategy group	<0.001	<0.001

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 (%)	*P* dexamethasone only *versus* dexamethasone plus antivirals	Dexamethasone only N=500 N (%)	*P* 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)

Continued on following page.

Characteristics	Dexamethasone plus antivirals N=470 N (%)	*P* dexamethasone only *versus* dexamethasone plus antivirals	Dexamethasone only N=500 N (%)	*P* 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 ≥30 breaths per minute, SpO_2 ≤ 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.[3-5] 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.[4,6] 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.[7,8] Most factors associated with mortality identified in our study are well known.[9] 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.[10] 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			
	P	HR	Lower limit	Upper limit	*P*	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-δ (before May 2021)	-	-	-	-	-	-	-	-
δ (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 $0.5x10^9$/L during more than 7 days. Lymphopenia: absolute lymphocyte count of less than $0.2x10^9$/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.[11] 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.[12] 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.[13-15] 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.

Authors

Tommaso Francesco Aiello,[1*] Jon Salmanton-García,[2*] Francesco Marchesi,[3] Barbora Weinbergerová,[4] Andreas Glenthøj,[5] Jens Van Praet,[6] Francesca Farina,[7] Julio Dávila-Valls,[8] Sonia Martín-Pérez,[8] Shaimaa El-Ashwah,[9] Martin Schönlein,[10] Iker Falces-Romero,[11-12] Jorge Labrador,[13] Uluhan Sili,[14] Caterina Buquicchio,[15] Antonio Vena,[16] Gaëtan Plantefeve,[17] Verena Petzer,[18] Monika M. Biernat,[19] Tobias Lahmer,[20] Ildefonso Espigado,[21] Jaap Van Doesum,[22] Ola Blennow,[23] Klára Piukovics,[24] Carlo Tascini,[25] Michail Samarkos,[26] Yavuz M. Bilgin,[27] Luana Fianchi,[28] Federico Itri,[29] Toni Valković,[30-31] Nicola S. Fracchiolla,[32] Michelina Dargenio,[33] Moraima Jiménez,[34-35] Ferenc Magyari,[36] Alberto López-García,[37] Lucia Prezioso,[38] Natasha Čolović,[39] Evgenii Shumilov,[40] Ghaith Abu-Zeinah,[41] Carolin Krekeler,[42] Esperanza Lavilla-Rubira,[43] Mario Virgilio Papa,[44] Tomás José González-López,[45] László Imre Pinczés,[46] Fatih Demirkan,[47] Natasha Ali,[48] Caroline Besson,[49] Guillemette Fouquet,[50] Alessandra Romano,[51] José-Ángel Hernández-Rivas,[52] Maria Ilaria Del Principe,[53] Avinash Aujayeb,[54] Maria Merelli,[55] Sylvain Lamure,[56] Joyce Marques De Almeida,[57] Maria Gomes Da Silva,[58] Noha Eisa,[59] Joseph Meletiadis,[60] Ikhwan Rinaldi,[61] Olimpia Finizio,[62] Ozren Jaksic,[63] Mario Delia,[64] Summiya Nizamuddin,[65] Monia Marchetti,[66] Marriyam Ijaz,[65] Marina Machado,[67] Rebeca Bailén-Almorox,[68] Martin Čerňan,[69] Nicola Coppola,[70] Eleni Gavriilaki,[71] Chiara Cattaneo,[72] Ana Groh,[73] Zlate Stojanoski,[74] Nurettin Erben,[75] Nikola Pantic,[39] Gustavo-Adolfo Méndez,[76] Roberta Di Blasi,[77] Stef Meers,[78,79] Cristina De Ramón,[80-81] Nathan C. Bahr,[82] Ziad Emarah,[83] Gina Varricchio,[44] Milche Cvetanoski,[74] Ramón García-Sanz,[80] Mirjana Mitrovic,[39] Raphaël Liévin,[84] Michaela Hanakova,[85] Zdeněk Ráčil,[85] Maria Vehreschild,[73] Athanasios Tragiannidis,[86] Raquel Nunes Rodrigues,[87] Daniel García-Bordallo,[43] Raul Cordoba,[37] Alba Cabirta,[34] Anna Nordlander,[23] Emanuele Ammatuna,[22] Elena Arellano,[21] Dominik Wolf,[18] Romane Prin,[17] Alessandro Limongelli,[16] Martina Bavastro,[16] Gökçe Melis Çolak,[14] Stefanie Gräfe,[2] Ditte Stampe Hersby,[5] Laman Rahimli,[2] Oliver A. Cornely,[2] Carolina Garcia-Vidal[1,12#] and Livio Pagano[28#]

**TFA and JS-G contributed equally as first authors.*

#CG-V and LP contributed equally as senior authors.

[1]Infectious Diseases Department, Hospital Clinic of Barcelona-IDIBAPS, Universitat de Barcelona, Barcelona, Spain; [2]University of Cologne, Faculty of Medicine and University Hospital Cologne, Translational Research, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), Cologne, Germany; [3]Hematology and Stem Cell Transplant Unit, IRCCS Regina Elena National Cancer Institute, Rome, Italy; [4]Department of Internal Medicine - Hematology and Oncology, Masaryk University Hospital Brno, Brno, Czech Republic; [5]Department of Hematology, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark; [6]Department of Nephrology and Infectious diseases, AZ Sint-Jan Brugge-Oostende AV, Brugge, Belgium; [7]IRCCS Ospedale San Raffaele, Milan, Italy; [8]Hospital Nuestra Señora de Sonsoles, Ávila, Spain; [9]Oncology Center, Mansoura University, Mansoura, Egypt; [10]Department of Oncology, Hematology and Bone Marrow Transplantation with Section of Pneumology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [11]La Paz University Hospital, Madrid, Spain; [12]CIBERINFEC, Instituto de Salud Carlos III, Madrid, Spain; [13]Department of Hematology, Research Unit, Hospital Universitario de Burgos, Burgos, Spain; [14]Department of Infectious Diseases and Clinical Microbiology, School of Medicine, Marmara University, Istanbul, Turkey; [15]Hematology Department, Dimiccoli Hospital, Barletta, Italy; [16]Ospedale San Martino, Genova, Italy; [17]Centre Hospitalier d'Argenteuil, Argenteuil, France; [18]Department of Hematology and Oncology, Medical University of Innsbruck, Innsbruck, Austria; [19]Department of Hematology, Blood Neoplasms, and Bone Marrow Transplantation, Wroclaw Medical University, Wroclaw, Poland; [20]Medizinische Klinik II, Klinikum rechts der Isar, TU

München, Munich, Germany; [21]Department of Hematology, University Hospital Virgen Macarena - University Hospital Virgen del Rocío, Instituto de Biomedicina de Sevilla (IBIS/CSIC), Universidad de Sevilla, Seville, Spain; [22]University Medical Center Groningen, Groningen, the Netherlands; [23]Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden; [24]Department of Internal Medicine, South Division Faculty of Medicine University of Szeged, Szeged, Hungary; [25]Azienda Sanitaria Universitaria del Friuli Centrale, Udine, Italy; [26]Laikon Hospital, Athens, Greece; [27]Department of Internal Medicine, ADRZ, Goes, the Netherlands; [28]Hematology Unit, Fondazione Policlinico Universitario Agostino Gemelli - IRCCS, Rome, Italy; [29]San Luigi Gonzaga Hospital - Orbassano, Orbassano, Italy; [30]University Hospital Centre Rijeka, Rijeka, Croatia; [31]Croatian Cooperative Group for Hematological Diseases (CROHEM), Faculty of Medicine and Faculty of Health Studies University of Rijeka, Rijeka, Croatia; [32]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [33]Hematology and Stem Cell Transplant Unit, Vito Fazzi, Lecce; [34]Department of Hematology, Vall d'Hebron Hospital Universitari, Experimental Hematology, Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; [35]Departament de Medicina, Universitat Autònoma de Barcelona, Bellaterra, Spain; [36]Division of Hematology, Institution of Internal Medicine, Faculty of Medicine, University of Debrecen, Debrecen, Hungary; [37]Fundación Jimenez Diaz University Hospital, Health Research Institute IIS-FJD, Madrid, Spain; [38]Hospital University of Parma - Hematology and Bone Marrow Unit, Parma, Italy; [39]University Clinical Center Serbia, Medical Faculty University Belgrade, Belgrade, Serbia; [40]UK Münster, Münster, Germany; [41]Division of Hematology and Oncology, Weill Cornell Medicine, New York, NY, USA; [42]Department of Medicine A, Hematology, Oncology and Pneumology, University Hospital Münster (UKM), Münster, Germany; [43]Hospital Lucus Augusti, Lugo, Spain; [44]Azienda Ospedaliera Sant'Anna e San Sebastiano, Caserta, Italy; [45]Department of Hematology, Hospital Universitario de Burgos, Burgos, Spain; [46]Division of Hematology, Department of Internal Medicine, Faculty of Medicine, University of Debrecen, Debrecen, Hungary; [47]Dokuz Eylul University, Division of Hematology, Izmir, Turkey; [48]Aga Khan University, Karachi, Pakistan; [49]Centre Hospitalier de Versailles, Le Chesnay and Université Paris-Saclay, UVSQ, INSERM, Équipe "Exposome et Hérédité", CESP, Villejuif, France; [50]Department of Hematology, CH Sud Francilien, Corbeil Essonnes, France; [51]Divisione Clinicizzata di Ematologia, Ospedale Ferrarotto, Catania, Italy; [52]Hospital Universitario Infanta Leonor, Madrid, Spain; [53]Hematology, Department of Biomedicine and Prevention, University of Rome Tor Vergata, Rome, Italy; [54]Northumbria Healthcare, Newcastle, UK; [55]Azienda Sanitaria Universitaria del Friuli Centrale, Udine, Italy; [56]Department of Clinical Hematology, Montpellier University Hospital, IGMM UMR5535 CNRS, University of Montpellier, Montpellier, France; [57]Istituto Oncologico della Svizzera Italiana, Bellinzona, Switzerland; [58]Portuguese Institute of Oncology, Lisbon, Portugal; [59]Aseer Central Hospital, Abha, Saudi Arabia; [60]Clinical Microbiology Laboratory, Medical School, "Attikon" University General Hospital, National and Kapodistrian University of Athens, Athens, Greece; [61]Division of Hematology and Medical Oncology, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia; [62]UOC Hematology, AORN Cardarelli, Naples, Italy; [63]Department of Hematology, University Hospital Dubrava, Zagreb, Croatia; [64]Hematology and Stem Cell Transplantation Unit, AOUC Policlinico, Bari, Italy; [65]Memorial Cancer Hospital and Research Center, Lahore, Pakistan; [66]Azienda Ospedaliera Nazionale SS. Antonio e Biagio e Cesare Arrigo, Alessandria, Italy; [67]Clinical Microbiology and Infectious Diseases Department, Hospital General Universitario Gregorio Marañón, Madrid, Spain; [68]Hematology Department, Hospital General Universitario Gregorio Marañón, Madrid, Spain; [69]Department of Hemato-Oncology, Faculty of Medicine and Dentistry, Palacky University and University Hospital Olomouc, Olomouc, Czech Republic; [70]Department of Mental Health and Public Medicine, University of Campania, Naples, Italy; [71]General Hospital of Thessaloniki "George Papanikolaou", Thessaloniki, Greece; [72]Hematology Unit, ASST-Ospedali Civili, Brescia, Italy; [73]Infektiologie, Universitätsklinikum Frankfurt am Main, Frankfurt am Main, Germany; [74]University Clinic of Hematology, Skopje, North Macedonia; [75]Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine Eskisehir Osmangazi University, Eskisehir, Turkey; [76]Hospital Escuela de Agudos Dr. Ramón Madariaga, Posadas, Argentina; [77]Service d'Hematologie-Oncologie, Hopital St Louis, Assistance Publique - Hopitaux de Paris, Université de Paris Diderot, Paris, France; [78]AZ KLINA, Brasschaat, Belgium; [79]IBSAL, Centro de Investigación del Cáncer-IBMCC (USAL-CSIC), Salamanca, Spain; [80]Hematology Department, Hospital Universitario de Salamanca, Salamanca, Spain; [81]IBSAL, Centro de Investigación del Cáncer-IBMCC (USAL-CSIC), Salamanca, Spain; [82]University of Kansas Medical Center, Kansas City, MO, USA; [83]Oncology Center, Mansoura University, Mansoura, Egypt; [84]Hospital St Louis, Paris, France; [85]Institute of Hematology and Blood Transfusion, Prague, Czech Republic; [86]Aristotle University of Thessaloniki, Thessaloniki, Greece and [87]Portuguese Institute of Oncology, Lisbon, Portugal

Correspondence:
C. GARCIA-VIDAL - cgarciav@clinic.cat
J. SALMANTON-GARCIA - jon.salmanton-garcia@uk-koeln.de

https://doi.org/10.3324/haematol.2023.284678

Received: December 12, 2023.
Accepted: March 22, 2024.
Early view: April 4, 2024.

©2024 Ferrata Storti Foundation
Published under a CC BY-NC license

Disclosures

CG-V has received honoraria for talks on behalf of Gilead Science, MSD, Pfizer, Janssen, Novartis, Basilea, GSK, Shionogi, AbbVie and Advanz Pharma; and a grant support from Gilead Science, Pfizer, GSK, MSD and Pharmamar.

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,

ES, GAZ, CK, ELR, MP, TGL, LP, FD, NA, CB, GF, AR, JHR, MDP, AA, MM, SL, JMDA, MGDS, NE, JM, IR, OF, OJ, MD, SN, MM, MI, MM, RBA, MC, NC, EG, CC, AG, ZS, NE, NP, GM, RDB, SM, CDR, NB, ZE, GV, MC, RGS, MM, RL, MH, ZR, MV, A.T, RNR, DGB, RC, AC, AN, EA, EA, DW, RP, AL, MB, GC, SG, DH and LR. Formal analysis by CGV and JSG. Project administration by CGV, JSG and TFA. Writing of the original draft by CGV, TFA and JSG. Reviewing and editing of the manuscript by CGV, TFA, JSG, OAC, LP. 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, ES, GAZ, CK, ELR, MP, TGL, LP, FD, NA, CB, GF, AR, JHR, MDP, AA, MM, SL, JMDA, MGDS, NE, JM, IR, OF, OJ, MD, SN, MM, MI, MM, RBA, MC, NC, EG, CC, AG, ZS, NE, NP, GM, RDB, SM, CDR, NB, ZE, GV, MC, RGS, MM, RL, MH, ZR, MV, AT, RNR, DGB, RC, AC, AN, EA, DW, RP, AL, MB, GC, SG, DH and LR.

Acknowledgments

Acknowledged are the following collaborative group members: M. Mladenović, C. Flasshove, B. Mišković, J-M Ribera-Santa Susana, M. Hoenigl, J. Prattes, M. Mikulska, A. Cuccaro, E. Bekirova, J. Batinić, N. De Jonge, T. Adžić-Vukičević, L. Drgoňa, H. M. Orth, F. Reizine, M. Piedimonte, J. Schubert, A. Soto-Silva, J. Loureiro-Amigo, L. Serrano, L. Lorenzo De La Peña, A. Guidetti, I. Ormazabal-Vélez, S. Malak, M. Calbacho, N. Fernández, R. F. Duarte, E. De Kort, G. Cengiz Seval, L. Verga, R. Bergantim, M-J. Jiménez-Lorenzo, J. Maertens, N. Khanna, M. Egger, O-F. Coronel-Ayala, P. Zdziarski, A. Busca, E. Busch, C. B. Poulsen, F. Danion, T. Cushion, S. Pinzón, Y. Gonzaga, A. Kulasekararaj, H. Zarrinfar, B. Hoell-Neugebauer, C. S. Kho, R. Duléry, M. Kolditz, M. Fung and A. D. Tanase.

Funding

This study has been co-funded by the European Regional Development Fund (EDRD). CG-V [FIS PI21/01640] have received research grants from the Ministerio de Sanidad y Consumo, Instituto de Salud Carlos III. The Project PI21/01640 has been funded by Instituto de Salud Carlos III (ISCIII) and co-funded by the European Union. No funding bodies had any role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. This work was co-funded by a research grant (SGR 01324 Q5856414G) from the AGAUR (Agencia de Gestión de Ayudas Universitarias y de Investigación) of Catalunya. A-TF has received a pre-doctoral grant supported by the Ministerio de Sanidad y Consumo, Instituto de Salud Carlos III [RH RH042953].

Data-sharing statement

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

References

1. Cesaro S, Ljungman P, Mikulska M, et al. Recommendations for the management of COVID-19 in patients with haematological malignancies or haematopoietic cell transplantation, from the 2021 European Conference on Infections in Leukaemia (ECIL 9). Leukemia. 2022;36(6):1467-1480.
2. Pan H, Peto R, Henao-Restrepo AM, et al. Repurposed antiviral drugs for Covid-19 - Interim WHO Solidarity Trial Results. N Engl J Med. 2021;384(6):497-511.
3. Aiello TF, Puerta-Alcalde P, Chumbita M, et al. Infection with the Omicron variant of SARS-CoV-2 is associated with less severe disease in hospitalized patients with COVID-19. J Infect. 2022;85(5):e152-e154.
4. Garcia-Vidal C, Moreno-García E, Hernández-Meneses M, et al. Personalized therapy approach for hospitalized patients with coronavirus disease 2019. Clin Infect Dis. 2022;74(1):127-159.
5. Hedberg P, Karlsson Valik J, Van Der Werff S, et al. Clinical phenotypes and outcomes of SARS-CoV-2, influenza, RSV and seven other respiratory viruses: a retrospective study using complete hospital data. Thorax 2022;77(2):1-10.
6. Garcia-Vidal C, Alonso R, Camon AM, et al. Impact of remdesivir according to the pre-admission symptom duration in patients with COVID-19. Journal of Antimicrobial Chemotherapy 2021;76(12):3296-3302.
7. Blennow O, Salmanton-García J, Nowak P, et al. Outcome of infection with omicron SARS-CoV-2 variant in patients with hematological malignancies: an EPICOVIDEHA survey report. Am J Hematol. 2002;97(8):E312-E317.
8. Vijenthira A, Gong IY, Fox TA, et al. Outcomes of patients with hematologic malignancies and COVID-19: a systematic review and meta-analysis of 3377 patients. Blood. 2020;136(25)2881-2892.
9. Sharma A, Bhatt NS, St Martin A, et al. Clinical characteristics and outcomes of COVID-19 in haematopoietic stem-cell transplantation recipients: an observational cohort study. Lancet Haematol. 2021;8(3):e185-e193.
10. Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 2021;384(8):693-704.
11. Abani O, Abbas A, Abbas F, et al. Higher dose corticosteroids in patients admitted to hospital with COVID-19 who are hypoxic but not requiring ventilatory support (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2023;401(10387):1499-1507.
12. Camon AM, Alonso R, Muñoz FJ, et al. C-reactive protein cut-off for early tocilizumab and dexamethasone prescription in hospitalized patients with COVID-19. Sci Rep 2022;12(1):5250.
13. Aiello T-F, Puerta-Alcalde P, Chumbita M, et al. Current outcomes of SARS-CoV-2 Omicron variant infection in high-risk haematological patients treated early with antivirals. J Antimicrob Chemother. 2023;78(6):1454-1459.
14. Mikulska M, Sepulcri C, Dentone C, et al. Triple combination therapy with 2 antivirals and monoclonal antibodies for persistent or relapsed severe acute respiratory syndrome coronavirus 2 infection in immunocompromised patients. Clin Infect Dis. 2023;77(2):280-286.
15. Salmanton-García J, Marchesi F, Gomes da Silva M, et al. Nirmatrelvir/ritonavir in COVID-19 patients with haematological malignancies: a report from the EPICOVIDEHA registry. EClinicalMedicine. 2023;58:101939.