LATE EFFECTS
GUARIRE DAL LINFOMA E VIVERE BENE

FONDAZIONE ITALIANA LINFOMI

Impatto della pandemia da COVID-19 nel paziente con Linfoma e Leucemia Linfatica Cronica

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FONDAZIONE ITALIANA LINFOMI

Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
						Takeda	

Patients with hematologic malignancies are highly vulnerable to SARS-CoV-2 infection

Patients with hematologic malignancies are at risk for severe COVID-19

There is a higher incidence of COVID-19 infections in pts with lymphoprolipherative disorders (limphomas, CLL, MM)

Increased COVID-19 morbidity is related to pts age and comorbidities

Vaccinated patients with lymphoma often fail to develop a sufficient antiviral immune response

Liang W et al. *Lancet Oncol*. 2020
Wang Q, et al*Blood Rev*. 2022
Fendler A, et al *Nat Rev Clin Oncol*. 2022
Gurion R, et al *Haematologica*. 2022

Williamson et al*Nature*. 2020
WHO. Living Guidance for Clinical Management of COVID-19. Accessed 15 July 2022
Pagano et al *J Hematol Oncol (2021)*
Visco et al. Blood Advances 2021

Covid-19 and hematologic malignancies

TABLE 1 COVID-19 in patients with lymphoma and other hematologic malignancies

Study	Design	Demographic and clinical characteristics	Mortality rate	Predictors of mortality
Passamonti et al., 2020[6]	• Retrospective, multicenter study • Observation period: 3 m • To determine mortality and predictive factors of mortality • In-patients with HM, N = 536 (44% with lymphomas)	• Median age 68 (58–77) yr • 63% male • Median CCI 4 (3–6) • 50% with severe/critical COVID-19	• 37%	• Older age • Progressive HM (HR 2.10, 95% CI 1.41–3.12) • HM type (indolent lymphoma HR 2.19, 95% CI 1.07–4.48; aggressive lymphoma, HR 2.56, 95% CI 1.34–4.89) • Severe/critical COVID-19 (HR 4.08, 95% CI 2.73–6.09)
Yigenoglu et al., 2020[7]	• Retrospective analysis • To compare the outcomes of pts with HM, N = 740 (33.7% with lymphomas) versus pts with no cancer (N = 740)	• Median age: 56 versus 56 y • Male gender: 53.6% versus 54.1% • 28.7% versus 19.6% with severe/critical COVID-19	• CFR 13.8% versus 6.8%, $p = 0.0001$; 10.8% for NHL and 14.8% for HL • Significantly worse COVID-19 outcomes for HM pts versus pts with no cancer	NA
Garcia-Suarez et al., 2020[39]	• Prospective, registry study • To define mortality rate, prognostic factors • In- and out-patients with HM, N = 697 (69% with lymphoid malignancy)	• Median age 72 (IQR 60–79) yr • 60% male • 59% on active treatment for HM • 62% with severe/critical COVID-19	• 33%	• Age ≥60 yr • >2 comorbidities • AML versus NHL • Lymphoma treatment with mAb versus no treatment
Lamure et al., 2020[35]	• Retrospective, multicenter study • To characterize presentation and outcomes • Pts with lymphoma hospitalized for COVID-19, N = 89	• Median age, 67 (19–92) yr • 66% male • 72% with comorbidities • 44% with lymphoma complete remission	• 34% • 30-d OS, 71% (95% CI 62%–81%)	• Age ≥70 yr (HR 2.87, 95% CI 1.20–6.85, $p = 0.02$) • Relapsed/refractory lymphoma (HR 2.54, 95% CI 1.14–5.66, $p = 0.02$)
Regalado-Artamundi et al., 2021[36]	• Retrospective registry study • To define epidemiology and predictors of death • In- and out-patients with lymphoma, N = 177	• Median age 70 (IQR 56–77) yr • 55.9% male • >70% with comorbidities • 49.7% on active treatment for lymphoma • 86.3% hospitalized due to COVID-19	• 34.5%	• Age > 70 yr • Comorbidities • Active disease (vs. complete response, HR 2.770 [95% CI 1.143–6.712, $p = 0.024$])
Duléry et al., 2021[40]	• Retrospective, multicenter study • To examine prolonged length of stay in hospital and its determinants • 111 lymphoma in-pts	• Median age, 65 y • 71% treated for lymphoma within 1 yr • 12% with relapsed lymphoma	• 6-m survival 69%	• Recent anti-CD20 therapy was associated with prolonged stay in hospital and higher
Pagano et al., 2021[41]	• EPICOVIDHEA registry survey • To characterize epidemiology and predictors of mortality • Pts with HM, N = 3801; N = 1084 with NHL, N = 135 with HL	• Median age 65 (5 • 58.5% male • 30.8% with compl HM; 51.6% with a • 63.8% with severe		
Visco et al., 2022[37]	• Multicenter retrospective study and analysis of prospectively collected data • To identify predictors of death • In- and out-patients with lymphoma, N = 856[a] (N = 468 in-pts, N = 388 out-pts)	• Median age, 63 (19–94) yr • 59% male • 46% with complete remission of lymphoma • 59% of hospitalized pts had severe/critical COVID-19 versus 8% of out-pts	• Overall, 19.5% • 33.4% for in-pts • 3.8% for out-pts	• Age > 65 yr • Male gender • ALC < 650 × 10^9/L • Platelets < 100 × 10^9/L

Abbreviations: ALC, absolute lymphocyte count; CCI, Charlson Comorbidity Index; CFR, case fatality rate; HL, Hodgkin lymphoma; HM, hematologic malignancy; HR, hazard ratio; ICU, intensive care unit; NHL

Passamonti et al.
Review *Hematological Oncology*. 2022

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Licterature items

COVID 19 Epidemiology in HM

COVID 19 outcome in HM

Sequelae of COVID 19 infection in HM

COVID 19 antibody responce in HM

Managment of HM in the COVID 19 era

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COVID-19 infection in adult patients with hematological malignancies: a European Hematology Association Survey (EPICOVIDEHA)

Pagano *et al. J Hematol Oncol (2021)*

EPICOVIDEHA: Epidemiology of COVID-19 Infection in Patients with Hematological Malignancies

International open web-based registry for patients with HM infected with SARS-CoV-2

A prognostic model for patients with lymphoma and COVID-19: a multicentre cohort study

blood advances

Visco et al.

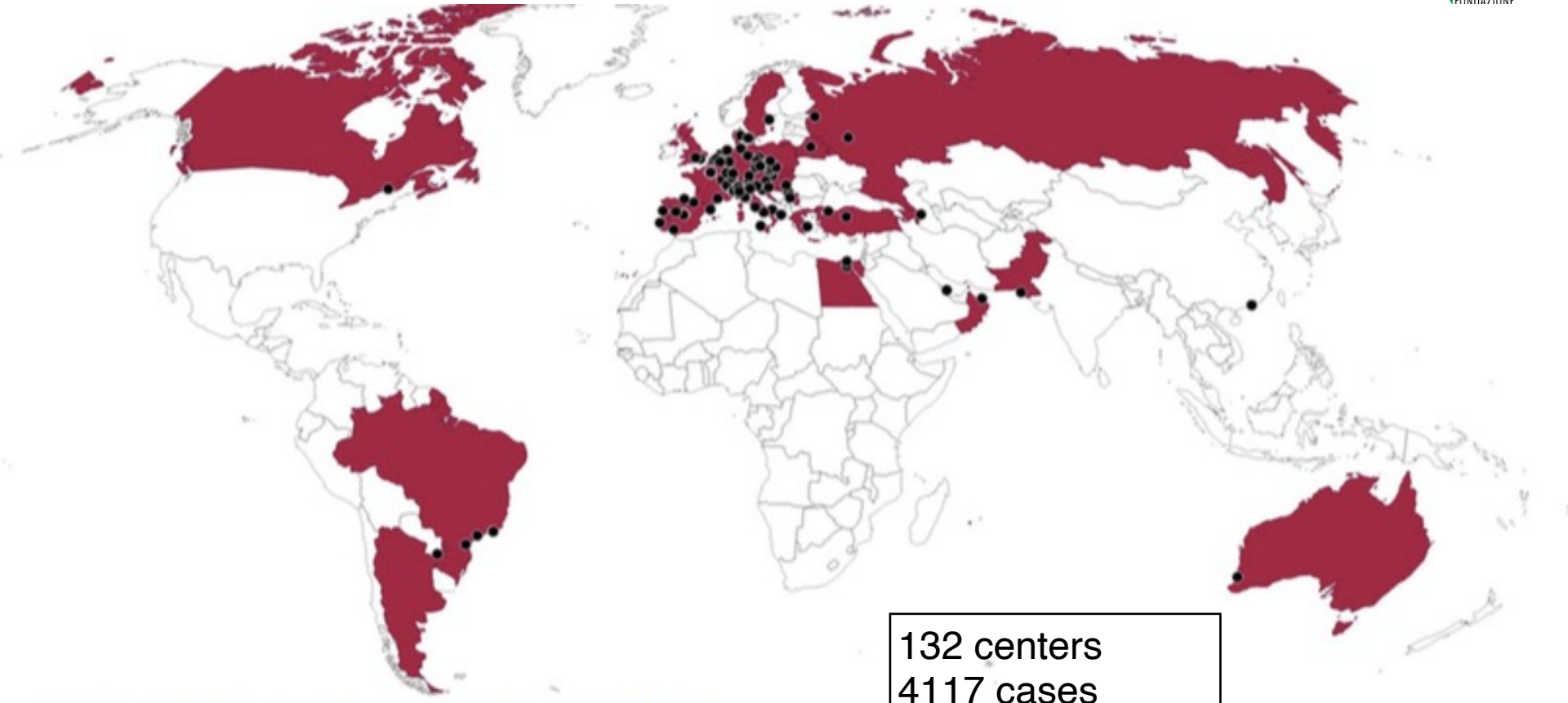
Italian Hematology Alliance on COVID-19 (ITA- HEMA-COV)

FONDAZIONE ITALIANA LINFOMI

COVID-19 infection in adult patients with hematological malignancies: a European Hematology Association Survey (EPICOVIDEHA)

Pagano *et al. J Hematol Oncol (2021)*

Multinational project aimed to collect COVID-19 cases occurring in HM patients in 2020
A survey was performed on behalf of the Scientific Working Group Infection in Hematology of the European Hematology Association (EHA) e objective was to assess epidemiology and outcomes of COVID-19 in HM patients



Geographical distribution of patient reported to EPICOVIDEHA

132 centers
4117 cases
1084 Lymphomas

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EPICOVIDEHA

Primary objective: to assess the epidemiology and the outcome of HM affected by COVID- 19

Secondary objectives: to estimate COVID disease severity
To evaluate hospitalization requires
Frequency of pre-existing comorbidities
Overall case-fatality rate
Treatment of the HM (off/on)
Type of therapy (i.e., chemotherapy, immunotherapy, targeted therapy, hematopoietic stem cell transplant [HSCT]).

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EPICOV
A total c
countrie
survey a
cases, 1

Baseline hematological malignancies		
Acute lymphoid leukemia	169	4.4
Chronic lymphoid leukemia	474	12.5
Acute myeloid leukemia	497	13.1
Chronic myeloid leukemia	161	4.2
Myelodysplastic syndrome	279	7.3
Low-intermediate risk	138	3.6
High risk	48	1.3
Not stated	93	2.4
Hairy cell leukemia	23	0.6
Hodgkin lymphoma	135	3.6
Non-Hodgkin lymphoma	1084	28.5
Indolent	497	13.1
Aggressive	516	13.6
Not stated	71	1.9
Essential thrombocythemia	69	1.8
Myelofibrosis	122	3.2
Polycythemia vera	70	1.8
Systemic mastocytosis	6	0.2
Multiple myeloma	6	
Amyloidosis	8	
Aplastic anemia	2	

	n	%
Sex		
Female	1579	41.5
Male	2222	58.5
Age, median (IQR) [range]	65 (54–74), [18–95]	
Comorbidities		
Chronic cardiopathy	1146	30.1
Chronic pulmonary disease	614	16.2
Diabetes mellitus	620	16.3
Liver disease	167	4.4
Obesity	345	9.1
Renal impairment	325	8.6
		12.5
		38.5

Demograph
of enrolled patients at COVID-19 diagnosis

Status[a]		
Controlled disease	1760	46.3
Complete remission	1170	30.8
Partial remission	590	15.5
Activedisease	1963	51.6
Onset	888	23.4
Refractory/Resistant	473	12.4

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Treatments for Hematological Malignancies at the onset of COVID-19

	n	%
Last/ongoing treatment strategy before COVID-19		
Immunochemotherapy	857	22.5
Targeted therapy[a]	607	16.0
Conventional chemotherapy	597	15.7
No treatment	538	14.1
Palliative/supportive measures	226	6.0
Immunomodulators	218	5.7
Allogeneic HSCT	173	4.6
Anagrelide/Hydroxyurea	145	3.8
Hypomethylating agents	141	3.7
Immunotherapy only	125	3.3
Autologous HSCT	74	1.9
Unknown	41	1.1
Other	28	0.7
CAR-T	21	0.6
Radiotherapy	10	0.3
Summary of received treatment[b]		
Chemotherapy	3178	83.6
In the last month	1979	52.1
In the last 3 months	523	13.8
Treatment ended > 3 months	631	16.6
Not stated	45	1.2
Radiotherapy	186	4.9
Allogeneic HSCT	265	7.0
Autologous HSCT	292	7.7
CAR-T	24	0.6
Other strategies	150	3.9
No treatment	538	14.2

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Clinical features of COVID-19 in our patient cohort

	n	%
COVID-19 infection		
Asymptomatic	675	17.8
Mild	658	17.3
Severe	1736	45.7
Critical	689	18.1
Unknown	43	1.1
COVID-19 test sample[a]		
BAL	60	1.6
SARS-CoV-2 nasopharyngeal swab	3700	97.3
SARS-CoV-2 serology	86	2.3
Reason for COVID-19 test[a]		
Pulmonary symptoms	1454	38.3
Pulmonary + extrapulmonary symptoms	831	21.9
Extrapulmonary symptoms	742	19.5
Screening	727	19.1
Unknown	47	1.2
Neutrophils level at COVID-19 diagnosis[b]		
$\leq 0.5 \times 10^9/mm^3$	280	7.4
$0.501–0.999 \times 10^9/mm^3$	217	5.7
$\geq 1 \times 10^9/mm^3$	2738	72.0
Lymphocytes level at COVID-19 diagnosis[b]		
$\leq 0.2 \times 10^9/mm^3$	344	9.1
$0.201–0.499 \times 10^9/mm^3$	538	14.2
$\geq 0.5 \times 10^9/mm^3$	2367	62.3
Stay during COVID-19		
Admitted to hospital	2778	73.1
Length of hospital stay, median (IQR) [range]	15 (8–27), [1–235]	–
ICU	689	18.1
Length of ICU stay, median (IQR) [range]	11 (5–20), [1–111]	–
Invasive MV	449	11.8
Non-invasive MV	221	5.8
Clinical outcome of COVID-19		
Death	1185	31.2
Observation time, median (IQR) [range]	89 (21–172), [0–436]	–
Reason for death[a]		
Not related to COVID-19	125	3.3
Contributable by COVID-19	155	4.1
Attributable to COVID-19	843	22.2
Attributable to HM	328	8.6
Death due to other reasons	123	3.2
Death due to unknown reasons	78	2.1

COVID disease was:
Severe in 45%
Critic in 18%
Mild 17%
Asimptomatic 17%

73% have been hospedalised

31% death:
for Covid 58%
HM 15%
Both 13%

Overall mortality rate by disease and treatment received

	Overall mortality	
	Survived *n* (%)	Died *n* (%)
Baseline hematological malignancies		
Acute lymphoid leukemia	125 (74)	44 (26)
Chronic lymphoid leukemia	340 (71.7)	[illegible]
Acute myeloid leukemia	298 (60)	199 (40)
Chronic myeloid leukemia	144 (89.5)	[illegible]
Myelodysplastic syndrome	161 (57.7)	118 (42.3)
Low-intermediate risk	77 (55.8)	[illegible]
High risk	26 (54.2)	22 (45.8)
Not stated	58 (62.4)	35 (37.6)
Hairy cell leukemia	15 (65.2)	8 (34.8)
Hodgkin lymphoma	120 (88.9)	15 (11.1)
Non-Hodgkin lymphoma	739 (68.2)	345 (31.8)
Indolent	354 (71.3)	143 (28.7)
Aggressive	337 (65.3)	179 (34.7)
Not stated	48 (67.6)	23 (32.4)
Essential thrombocythemia	57 (82.6)	12 (17.4)
Myelofibrosis	77 (63.1)	45 (36.9)
Polycythemia vera	56 (80)	14 (20)
Systemic mastocytosis	5 (83.4)	1 (16.6)
Multiple Myeloma	458 (67)	226 (33)
Amyloidosis	7 (87.5)	1 (12.5)
Aplastic anemia	14 (70)	6 (30)
Last/ongoing treatment strategy before COVID-19		
Anagrelide/Hydroxyurea	106 (73.1)	39 (26.9)
Conventional chemotherapy	423 (70.9)	174 (29.1)
Hypomethylating agents	58 (41.2)	83 (58.8)
Immunotherapy only	89 (71.2)	36 (28.8)
Immunochemotherapy	595 (69.4)	262 (30.6)
Immunomodulators	139 (63.8)	79 (36.2)
Targeted therapy[a]	453 (74.6)	154 (25.4)
Allogeneic HSCT	130 (75.2)	43 (24.8)
Autologous HSCT	54 (73)	20 (27)
CAR-T	11 (52.4)	10 (47.6)
Radiotherapy	9 (90)	1 (10)
Palliative/supportive measures	122(56)	104 (46)
Other	17 (60.7)	11 (39.3)
Unknown	[illegible]	[illegible]
No treatment	382 (71)	156 (29)

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Overall mortality predictors in COVID-19 HM patients

	Univariable			Multivariable		
	p value	HR	95% CI	*p* value	HR	95% CI
Sex						
Female	–	–	–	–	–	–
Male	**0.059**	1.119	0.095–1.258	0.376	1.065	0.927–1.223
Age	**<0.0001**	1.036	1.031–1.041	**<0.0001**	1.032	1.026–1.039
Malignancy status						
Controlled disease	–	–	–	–	–	–
Active disease	**<0.0001**	2.107	1.863–2.383	**<0.0001**	1.860	1.615–2.141
Unknown	**<0.0001**	2.293	1.607–3.274	**<0.0001**	2.353	1.538–3.601
Hematological malignancy						
Hodgkin lymphoma	–	–	–	–	–	–
Chronic lymphoid leukemia	**<0.0001**	2.789	1.635–4.757	0.763	1.093	0.614–1.947
Acute myeloid leukemia	**<0.0001**	4.364	2.581–7.376	**0.011**	2.046	1.176–3.557
Chronic myeloid leukemia	0.915	0.963	0.481–1.928	0.086	0.513	0.239–1.099
Acute lymphoblastic leukemia	**0.002**	2.530	1.405–4.553	0.250	1.457	0.767–2.768
Non-Hodgkin lymphoma	**<0.0001**	3.041	1.814–5.100	0.569	1.171	0.68–2.015
Aplastic anemia	**0.040**	2.695	1.045–6.948	0.179	2.022	0.724–5.645
Essential thrombocythemia	0.234	1.585	0.742–3.387	0.332	0.667	0.295–1.511
Multiple myeloma	**<0.0001**	3.355	1.989–5.658	0.630	1.145	0.661–1.984
Myelodysplastic syndrome	**<0.0001**	4.627	2.704–7.919	0.072	1.706	0.953–3.056
Myelofibrosis	**<0.0001**	3.786	2.110–6.791	0.185	1.540	0.813–2.915
Polycythemia vera	0.059	2.016	0.973–4.176	0.985	0.992	0.456–2.158
Amyloidosis	0.893	1.150	0.152–8.705	0.932	-	-
Hairy cell leukemia	**0.019**	2.936	1.197–7.202	0.301	1.806	0.589–5.533
Systemic mastocytosis	**0.715**	1.457	0.192–11.031	0.968	0.959	0.126–7.323
COVID-19 infection						
Asymptomatic	–	–	–	–	–	–
Mild infection	0.545	1.087	0.830–1.422	0.653	1.074	0.786–1.467
Severe infection	**<0.0001**	2.127	1.722–2.628	**<0.0001**	1.682	1.312–2.157
Critical infection	**<0.0001**	5.333	4.300–6.613	**<0.0001**	4.230	3.294–5.432
Unknown	0.623	1.229	0.540–2.800	0.928	–	–
Chronic cardiopathy	**<0.0001**	2.011	1.792–2.257	**<0.0001**	1.406	1.218–1.624
Liver disease	**0.008**	1.394	1.091–1.781	**0.020**	1.388	1.052–1.831
Chronic pulmonary disease	**<0.0001**	1.516	1.320–1.740	0.926	1.008	0.85–1.195
Diabetes mellitus	**<0.0001**	1.352	1.172–1.560	0.439	1.070	0.901–1.272
Obesity	0.796	0.974	0.796–1.191	–	–	–
Renal impairment	**<0.0001**	1.883	1.589–2.232	**<0.0001**	1.404	1.143–1.724
Smoking history	**0.013**	1.224	1.043–1.436	**0.031**	1.223	1.019–1.469
Neutrophils, cells/mm³						
≤ 0.5 × 10^9/mm³	–	–	–	–	–	–
0.501-0.999 × 10^9/mm³	**<0.0001**	0.594	0.450–0.785	0.272	0.845	0.626–1.141
≥ 1 × 10^9/mm³	**<0.0001**	0.514	0.431–0.614	0.184	0.862	0.693–1.073
Lymphocytes, cells/mm³						
≤ 0.2 × 10^9/mm³	–	–	–	–	–	–
0.201-0.499 × 10^9/mm³	**0.004**	0.746	0.611–0.912	**0.021**	0.779	0.629–0.963
≥ 0.5 × 10^9/mm³	**<0.0001**	0.499	0.422–0.590	**<0.0001**	0.601	0.499–0.722
Last chemotherapy						
>3 months before COVID-19	–	–	–	–	–	–
In the last 3 months	**<0.0001**	1.531	1.226–1.912	0.081	1.236	0.974–1.568
In the last month	**<0.0001**	1.688	1.408–2.024	0.657	1.047	0.854–1.284
Unknown	0.103	1.578	0.911–2.734	0.998	0.999	0.537–1.86

In the **multivariable analysis**
Mortality impact factors : age, active disease, chronic cardiopathy, liver disease, renal impairment, smoking history, and ICU stay
Among HM, AML is the malignancy associated with a significantly high mortality

Neutrophil count > 0.5×109/mm3
lymphocyte count > 0.2 × 109/mm3 were protective

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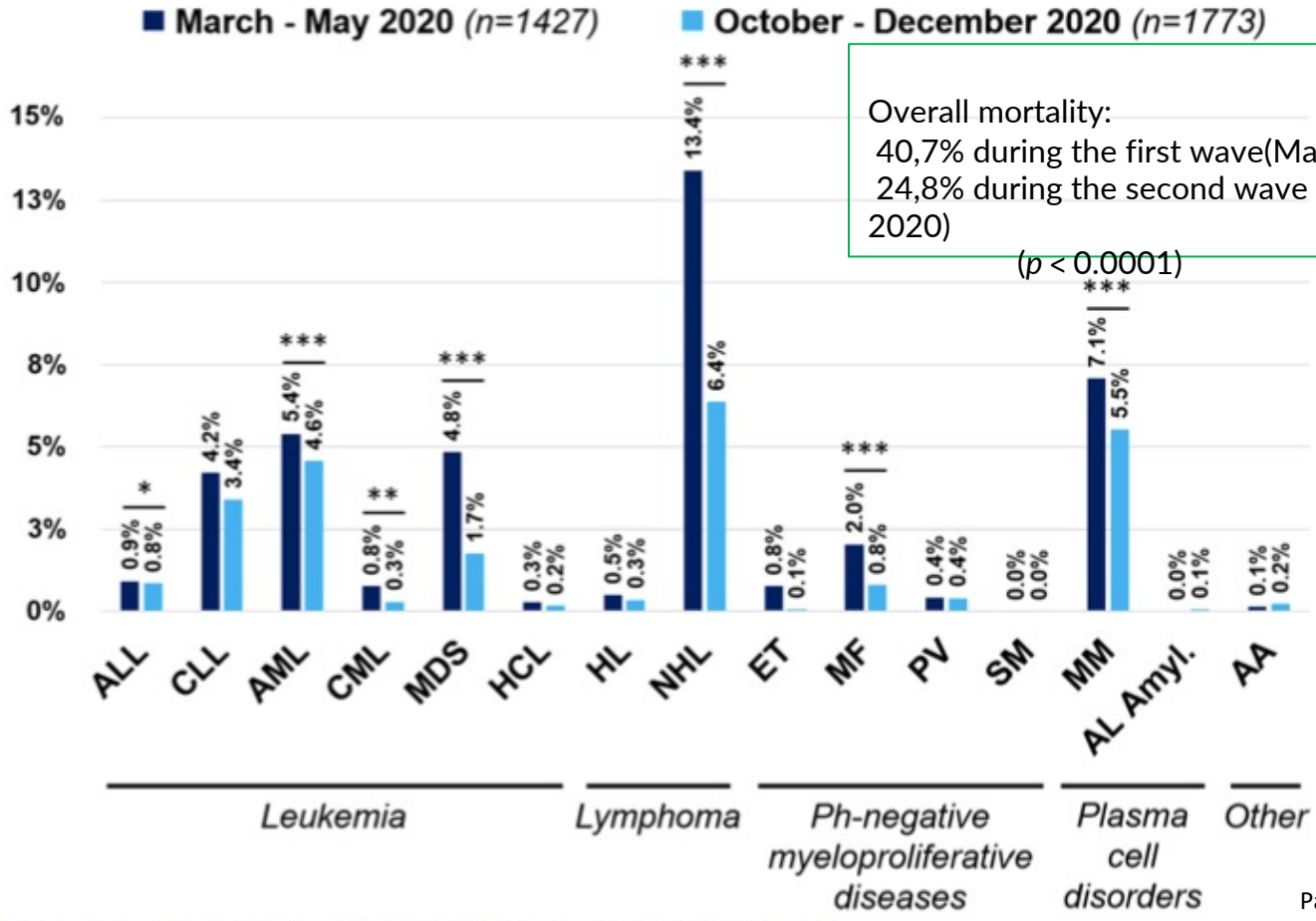

Overall mortality:
40,7% during the first wave(March–May 2020)
24,8% during the second wave (October-December 2020)

($p < 0.0001$)

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Overall survival in the different HMS by time distribution (first vs. the second wave)

Italian Hematology Alliance on COVID-19 (ITA-HEMA-COV)

The ITA-HEMA-COV worked on behalf of all Italian societies dealing with hematology: Società Italiana di Ematologia, Società Italiana di Ematologia Sperimentale, Gruppo Italiano Trapianto Midollo Osseo, Sorveglianza Epidemiologica Infezioni nelle Emopatie, and Fondazione Italiana Linfomi.

A prognostic model for patients with lymphoma and COVID-19: a multicentre cohort study

blood advances

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Table 1. Baseline patients' characteristics by hospital admission

Status	Overall n (%)	Admitted n (%)	Not-admitted n (%)	*P*-value
	856 (100)	468 (55)	388 (45)	
Median age (range)	63	67	57	<.001
	(19-94)	(20-92)	(19-94)	
Gender				<.001
Male	504 (59)	305 (65)	199 (51)	
Charlson Index				<.001
>6	166 (20)	123 (28)	43 (11)	
Anemia				<.001
<12 g/dL	122 (16)	95 (22)	27 (8)	
Total lymphocytes				
<650/mmc	140 (22)	105 (28)	35 (12)	<.001
Histology				
DLBCL	251 (29)	147 (31)	104 (27)	.152
FL	183 (21)	111 (24)	72 (19)	.078
HG-NOS, DHL	55 (6)	34 (7)	21 (5)	.327
MZL	72 (8)	48 (10)	24 (6)	.036
LPL	61 (7)	32 (7)	29 (7)	.790
MCL	60 (7)	34 (7)	26 (7)	.789
T-cell	47 (5)	28 (6)	19 (5)	.530
cHL	115 (13)	28 (6)	87 (22)	<.001
LP-HL	11 (1)	6 (1)	5 (1)	1.00
Smoker				.008
Never	429 (70)	199 (66)	230 (75)	
Former	128 (21)	79 (26)	49 (16)	
Current	53 (9)	24 (8)	29 (9)	
COVID-19 severity				<.001
Mild	505 (63)	184 (40)	321 (92)	
Severe	230 (29)	206 (45)	24 (7)	
Critical	68 (8)	66 (14)	2 (1)	
line treatment				.428
1	345 (69)	189 (72)	156 (66)	
2	87 (17)	41 (16)	46 (19)	
3	39 (8)	18 (7)	21 (9)	
4+	32 (6)	15 (6)	17 (87)	
Time to COVID-19				<.001
≤3 mo	138 (16)	99 (21)	39 (10)	
3-12 mo	188 (22)	113 (24)	75 (19)	
12-24 mo	133 (16)	68 (15)	65 (17)	
24-36 mo	73 (9)	46 (10)	27 (7)	
36-48 mo	58 (7)	17 (4)	41 (11)	
>48 mo	259 (31)	119 (25)	140 (36)	
Status at COVID-19				<.001
CR	374 (46)	159 (36)	215 (57)	
PR	137 (17)	89 (20)	48 (13)	
SD	98 (12)	64 (15)	34 (9)	
PD	120 (15)	82 (19)	38 (10)	
W&W	83 (10)	44 (10)	39 (10)	

E

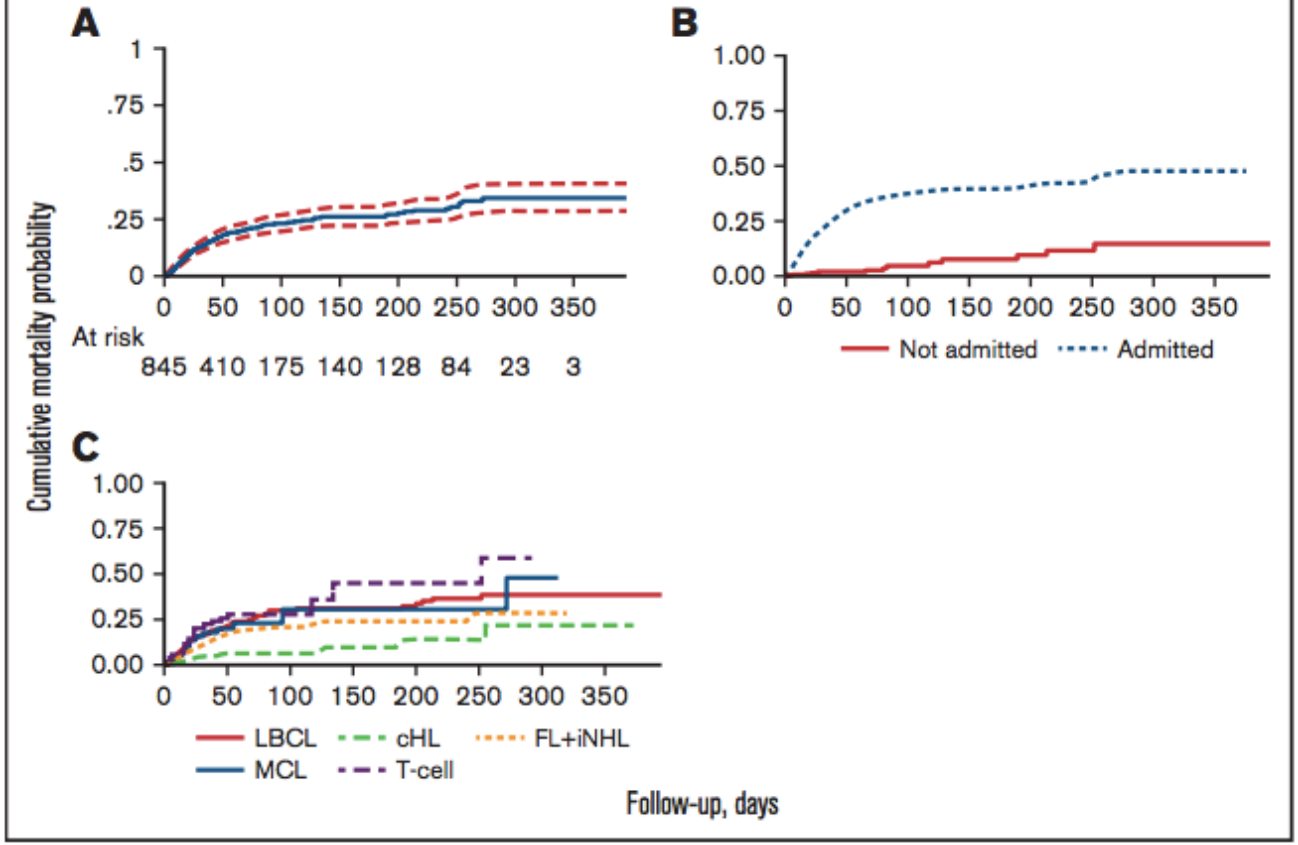
Covariate	n (%)	100-d Death % (95%CI)	HR (95%)	*P*-value
COVID-19 severity				
Mild	500 (63)	9 (6-13)	1.00	
Severe	227 (29)	38 (31-46)	4.67 (3.16-6.90)	<.001
Critical	67 (8)	75 (61-87)	12.1 (7.82-18.6)	<.001
Hospital admission				
No	382 (45)	5 (2-10)	1.00	
Yes	463 (55)	37 (32-43)	8.82 (5.18-15.0)	<.001
Lymphoma status at COVID-19				
CR	368 (46)	16 (11-21)	1.00	
PR	135 (17)	22 (19-31)	1.96 (1.24-3.10)	.004
SD	98 (12)	26 (17-39)	1.92 (1.15-3.20)	.013
PD	119 (15)	41 (30-53)	3.37 (2.21-5.14)	<.001
W&W	81 (10)	22 (13-35)	1.52 (0.85-2.73)	.162
CR/W&W	449 (56)	17 (13-22)	1.00	
PR/SD	233 (29)	23 (18-30)	1.77 (1.22-2.57)	.003
PD	119 (15)	41 (30-53)	3.08 (2.07-4.58)	<.001

856 pts with lymphoma and Covid in 64 centres
from february to june 2020: retrospective cohort (237)
From june 2020 to february 2021: prospective cohort (619)

Objectives:
To assess mortality rate
To identify predictors of mortality

Visco et al. Blood Advances 2021

Overall survival for enrolled patients. Kaplan-Meyer curves for overall survival in all enrolled patients (A), and according to admission to the hospital (B), lymphoma histotype (C).



- 165 (19%) pts died after a median FU of 66 days (range 1-395)
- 30- and 100-days mortality was 13% and 23%
- 91% were due to COVID-19 infection
- Patients admitted to the hospital had significantly worse OS than patients not admitted (35% vs 4%) (P=0.001)

cHL was associated with significantly better OS (P=0,001)
FL / i-NHL were borderline (P= 0.049)

Overall Survival

Visco et al. Blood Advances 2021

474 pts were treated for lymphoma:
- 33% were on treatment at the time of the COVID-19diagnosis
- 24% had completed therapy more than 6 months

Patients who had received antilymphoma treatment had worse OS than patients that were never treated

Time interval between lymphoma diagnosis and COVID-19 infection was inversely related to mortality, with 36 months as cutoff

Pts that had received bendamustine had no significant difference in terms of OS

No negative impact on OS has been demostrated by anti-CD20 immunotherapy

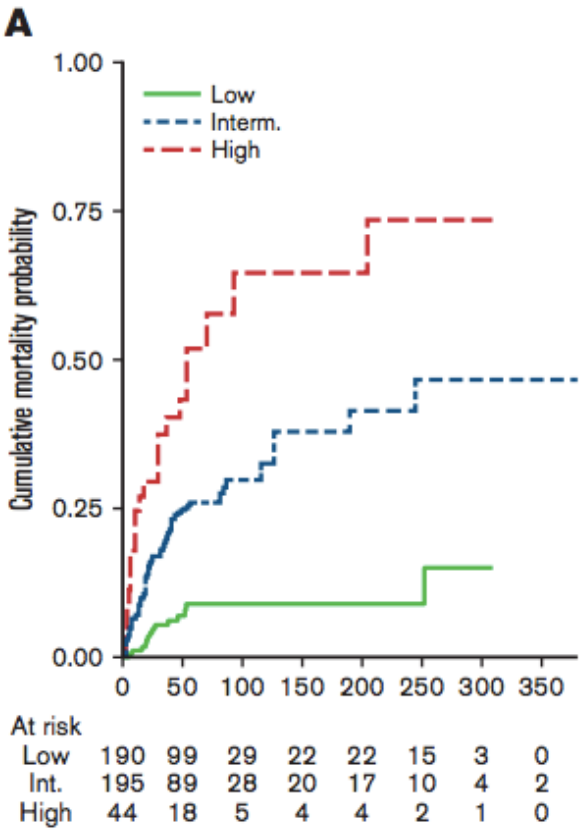
Table 4. **Prognostic model**

Complete cases (n=429) Score	N (%)	100-d Death % (95% CI)	HR (95% CI)	*P*-value
Low 0-1	190 (44)	9 (5-15)	1.00	
Intermediate 2-3	195 (45)	30 (22-39)	3.79 (2.09-6.85)	<.001
High 4-5	44 (10)	65 (46-83)	8.85 (4.55-17.2)	<.001
Overall	429	25 (20-31)	–	–
Incomplete cases (n=193)				
Score	**N (%)**	**100-d Death % (95% CI)**	**HR (95% CI)**	***P*-value**
Low 0-1	79 (36)	7 (3-17)	1.00	
Intermediate 2-3	106 (48)	26 (17-38)	3.93 (1.50-10.3)	.010
High 4-5	37 (17)	43 (26-63)	7.63 (2.77-21.0)	<.001
Overall	193	22 (17-27)	–	–

Score ranging from 0 to 5
2 for age
1 for male gender, lymphopenia, thrombocytopenia a was obtained

3 risk categories by Kaplan-Meier curves: low (0-1), interme- diate (2-3), and high (4-5)

100-days mortality was:
8% for low risk
29% for intermediate risk
54% for high risk



Visco et al. Blood Advances 2021

FONDAZIONE ITALIANA LINFOMI

Prevalence and impact of COVID-19 sequelae on treatment and survival of patients with cancer who recovered from SARS-CoV-2 infection: evidence from the OnCovid retrospective, multicentre registry study

Sequelae

D. Pinato et al. Lancet Oncol 2021;

European registry study enrolling 2795 consecutive pts with solid or haematological malignancy and with diagnosis of RT-PCR SARS-CoV-2 infection

Primary endpoint: To describe the prevalence of COVID-19 sequelae and their impact on recovery from COVID-19 and outcome of neoplastic disease

Long-term sequelae of COVID-19 infection

D. Pinato et al. Lancet Oncol 2021;

Respiratory symptoms
Residual fatigue
Weight loss
Neurocognitive symptoms

Negative impact on:

- Recovery from COVID-19
- Oncologic outcomes

COVID-19 long-term sequelae were associated with shorter survival and higher incidence of therapy discontinuation

FONDAZIONE ITALIANA LINFOMI

bjh short report

COVID-19 elicits an impaired antibody response against SARS-CoV-2 in patients with haematological malignancies

Passamonti et al.

Antibody response

The ITA-HEMA-COV project investigated seroconversion for SARS-CoV-2 IgG in 237 patients with HMs and SARS-CoV-2 PCR-positive

In multivariable logistic regression:
Chemoimmunotherapy was associated with a lower rate of seroconversion

54 (22%) plasma cell neoplasms
69% of pts had detectable IgG SARS-CoV-2 serum antibodies

Consequently a low rate of seroconversion after vaccination is expexted

chemotherapy 26%
chemoimmunotherapy in 22 %
immunotherapy only 6 3%
targeted therapies in 19 4%
autologous and allogeneic HSCT 4 6% and 4% respectively
56% were on active therapy at the time of COVID-19.

FONDAZIONE ITALIANA LINFOMI

Antibody response after vaccination against SARS-CoV-2 in adults with hematological malignancies: a systematic review and meta-analysis

Gagelmann N et al

Preferred Reporting Items for Systematic Reviews and Meta-analyses **(PRISMA)** reporting guideline and the Meta-analysis of Observational Studies in Epidemiology **(MOOSE**) checklist.

Review and meta-analysis of 49 studies
Primary endpoint: to assess antibody response, efficacy, and safety
after vaccination against SARS-CoV-2 in patients with hematological malignancies.

Studies published from 1 July 2020 to spt 2021 on adults with hematological malignancies (myeloid, lymphoid, or plasma cell dyscrasias) after one or two doses of vaccine were considered for inclusion.

Antibody response after vaccination against SARS-CoV-2 in adults with hematological malignancies: a systematic review and meta-analysis

ENE

Gagelmann N et al.

A significant difference was identified between hematological malignancies, solid cancer, and healthy controls (*P*<0.001). Global response was:
37% for hematological malignancies
62% for solid cancer
78% for healthy controls

Antibody response according to the type of hematologic disease
chronic lymphocytic leukemia 50%
multiple myeloma 76%
myeloproliferative neoplasms 83%
indolent lymphoma 58%
aggressive lymphoma 61%
Hodgkin lymphoma 91%

A significant difference was found for pts in remission compared (72%) with patients with stable or progressive disease (48%) at time of vaccination (*P*=0.014)

Table 1. Pooled antibody response rates across subgroups.

Subgroups	N	Pooled response	95% CI	I^2	*P*
Hematopoietic cell transplant					
Allogeneic	697	82%	77-87	64%	0.60
Autologous	547	83%	73-90	83%	
CAR-T therapy	92	42%	27-60	54%	
Treatment					
Active	1,228	35%	25-47	93%	<0.001
No	1,034	76%	68-82	83%	
Anti-CD20 therapy					
>1 year	388	59%	46-72	87%	<0.001
≤1 year	321	15%	9-		
Anti-CD38	351	55%	40		
Chemotherapy	443	69%	54		
Bruton kinase inhibition	636	23%	14-35	85%	
Venetoclax	155	26%	20-34	0%	
Disease status					
Remission	835	72%	64-79	80%	0.014
Stable or progressive disease	590	48%	31-		
Prior COVID-19					
Yes	107	87%	75-		
No	2,654	66%	57-		
Risk of bias					
Low	5,904	64%	58-70	94%	0.91
Moderate	612	63%	52-72	82%	
mRNA vaccine					
BNT162b2	4,224	63%	57-69	93%	0.43
mRNA-1273	1,058	72%	52-86	96%	

Response was significantly affected by the timing of anti-CD20 therapy (*P*<0.001)
15%≤1 year prior to vaccination
59%>1 year prior to vaccination

Reduced response rates for pts receiving allogeneic transplantation <6 months prior to vaccination

Bruton kinase inhibitor therapy: response was 23%
venetoclax therapy: response was 26%

Gagelmann N et al.

FONDAZIONE ITALIANA LINFOMI

Antibody response to COVID-19 vaccination in patients with lymphoma

Kentaro Narita[1] · So Nakaji[2] · Rikako Tabata[1] · Toshiki Terao[1] · Ayumi Kuzume[1] · Takafumi Tsushima[1] · Daisuke Ikeda[1] · Ami Fukumoto[1] · Daisuke Miura[1] · Masami Takeuchi[1] · Masahiro Doi[3] · Yuka Umezawa[3] · Yoshihito Otsuka[3] · Hiroyuki Takamatsu[4] · Kosei Matsue[1]

Prospective observational study (between June and October 2021) to monitor the antibody response in 500 patients with lymphoma after SARS-CoV-2 vaccination

Primary objective
to evaluate the serological response to the SARS-CoV-2 vaccine
to investigate the clinical variables related to vaccine responses in patients with lymphomas and CLL

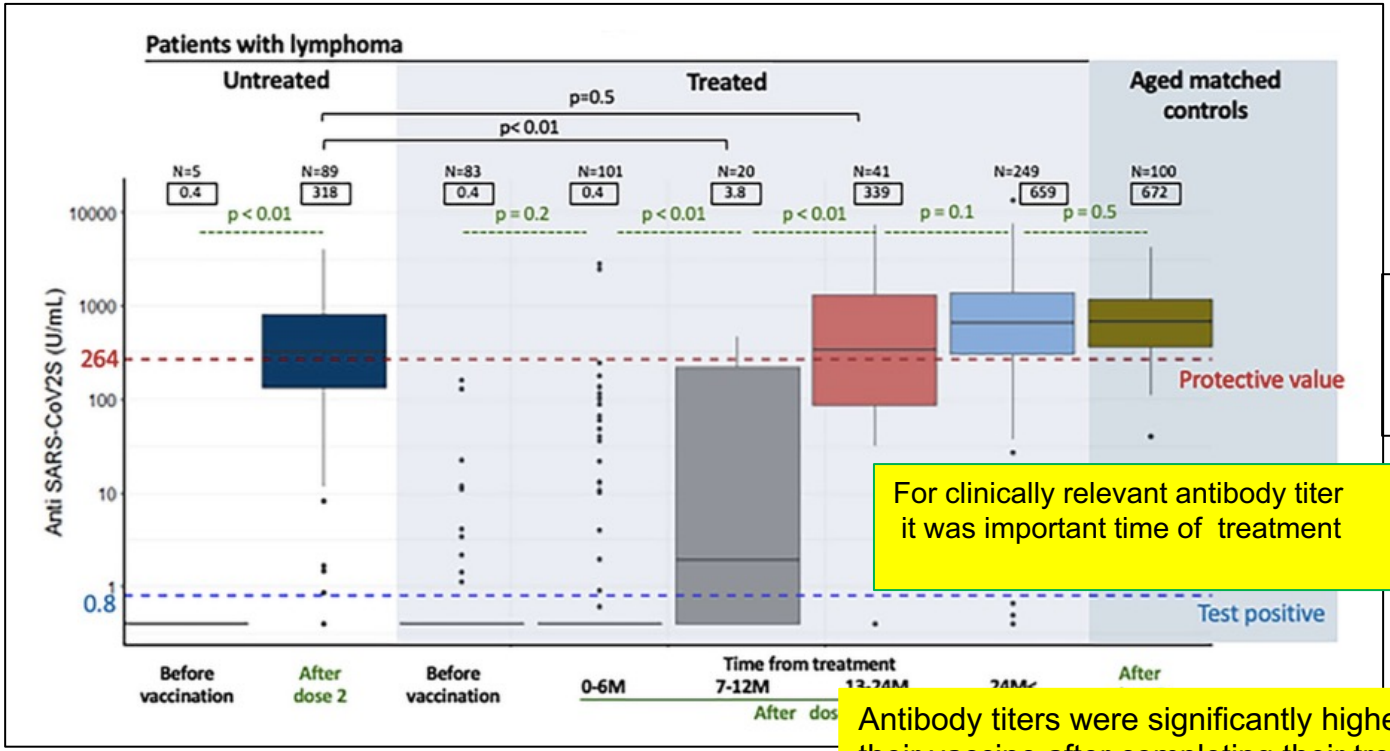
FONDAZIONE ITALIANA LINFOMI

Table 1 Clinical characteristics of patients according to the SARS-CoV-2 antibody titer

Variables	All patients	Anti-S <0.8 U/mL	Anti-S ≥0.8 U/mL	Anti-S <264 U/mL	Anti-S ≥264 U/mL
Number of patients (%)	500	109 (21.8)	391 (78.2)	236 (47.2)	264 (52.8)
Age, median (range)	73 (18–92)	74 (54–92)	71 (18–92)	75 (39–92)	70 (18–91)
Sex, *n* (%)					
Male sex (%)	260 (52.1)	60 (11.1)	196 (39.2)	94 (20.7)	141 (31.1)
Lymphoma subtype, *n*, (%)					
DLBCL	212 (42.4)	44 (8.8)	168 (33.6)	93 (18.6)	119 (23.8)
Other aggressive BCL	15 (3.0)	8 (1.6)	7 (1.4)	12 (2.4)	3 (0.6)
FL	134 (26.8)	29 (5.8)	105 (21.0)	60 (12.0)	74 (14.8)
Other indolent BCL	83 (16.6)	24 (4.8)	59 (11.8)	45 (9.0)	38 (7.6)
HD	20 (4.0)	1 (0.2)	19 (3.8)	5 (1.0)	15 (3.0)
TCL	36 (7.2)	3 (0.6)	33 (6.6)	21 (4.2)	15 (3.0)
Treatment, *n* (%)					
CD20 ± chemo-Tx	327 (65.4)	85 (17.0)	242 (48.4)	153 (30.6)	174 (34.8)
BTKi	14 (2.8)	9 (1.8)	5 (1.0)	13 (2.6)	1 (0.2)
Combination chemotherapy	45 (9.0)	3 (0.6)	42 (8.4)	20 (4.0)	25 (5.0)
CAR-T	1 (0.2)	1 (0.2)	0	1 (0.2)	0
ASCT	26 (5.2)	5 (1.0)	21 (4.2)	11 (2.2)	15 (3.3)
Allo-SCT	11 (2.2)	2 (0.4)	9 (1.8)	5 (1.0)	6 (1.2)
Active treatment	101 (20.2)	78 (15.6)	23 (4.6)	99 (19.8)	2 (0.4)
Untreated	89 (17.8)	5 (1.0)	84 (16.8)	40 (8.0)	49 (9.8)
Time from last Tx, median (range) [month]	40 (0–271)	3 (0–169)	56 (0–271)	6 (0–169)	66 (1–271)
Blood test, median (range)					
WBC [$\times 10^3/\mu L$]	5.3 (4.9–74.5)	4.6 (3.9–74.5)	5.4 (4.9–50.9)	5.1 (3.9–74.5)	5.4 (4.9–16.9)
Lymphocyte [%]	30 (2–97)	24 (4–97)	31 (2–94)	26 (2–97)	32 (8–64)
CD3 [%]	61 (2–98)	74 (2–94)	59 (3–98)	69 (2–98)	58 (23–98)
CD4 [%]	28 (1–67)	26 (1–53)	28 (2–67)	26 (1–62)	30 (2–67)
CD8 [%]	26 (1–80)	40 (1–80)	24 (1–73)	34 (1–80)	23 (6–67)
CD19 [%]	11 (0–97)	0 (0–97)	14 (0–96)	3 (0–97)	16 (0–69)
IgG [mg/dL]	1116 (55–5887)	779 (55–2278)	1175 (71–5887)	1018 (55–5887)	1211 (71–2597)
IgA [mg/dL]	189 (3–1369)	112 (3–549)	216 (3–1369)	143 (3–1052)	230 (3–1369)
IgM [mg/dL]	62 (1–5362)	29 (1–3815)	70 (8–5362)	45 (1–5362)	73 (8–2980)
sIL2R [U/mL]	519 (147–9453)	564 (147–5153)	504 (178–9453)	612 (147–9453)	468 (178–5918)

K. Narita et al.

K. Narita et al.



Relationship between anti-S antibody levels before vaccination and after two doses

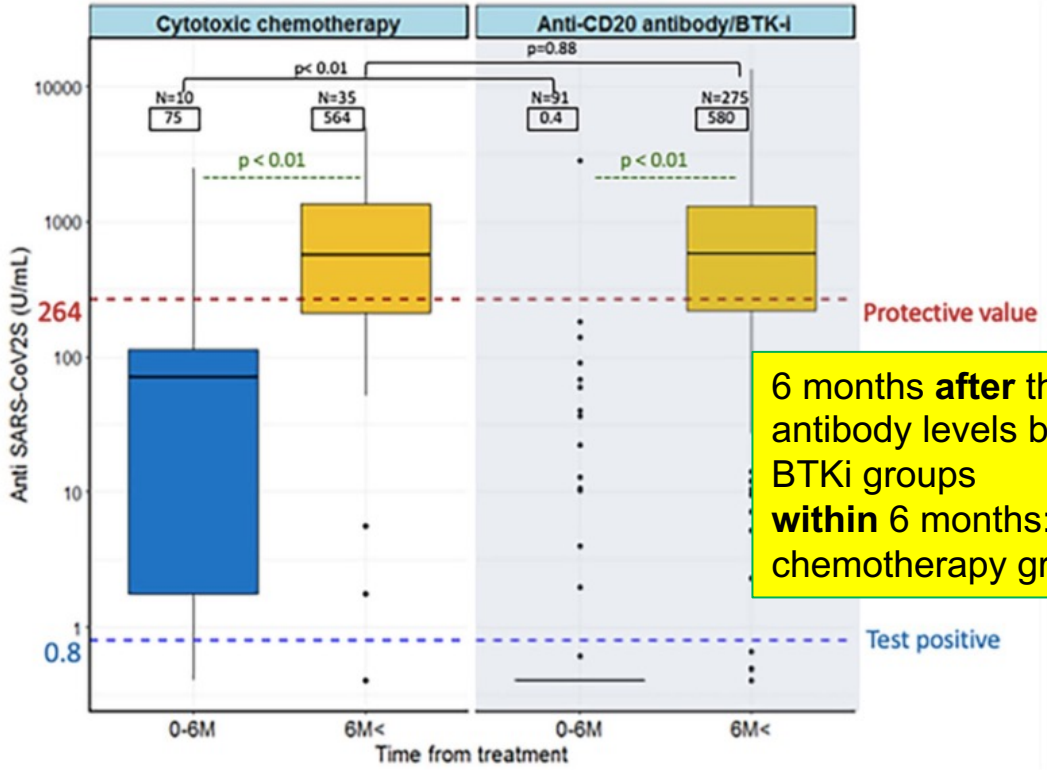
anti-S ≥ 264 U/mL:
clinically protective level of antibody titer
for SARS-CoV-2 virus infection

For clinically relevant antibody titer it was important time of treatment

Antibody titers were significantly higher in patients who received their vaccine after completing their treatment more than 12 months

antibody titers after 2 doses vaccine in untreated and treated ly
treated groups are divided into 0–6 months, 7–12 months, 13–24 months, and 24 months since last treatment. Median values for each group are shown in squares

K. Narita et al.

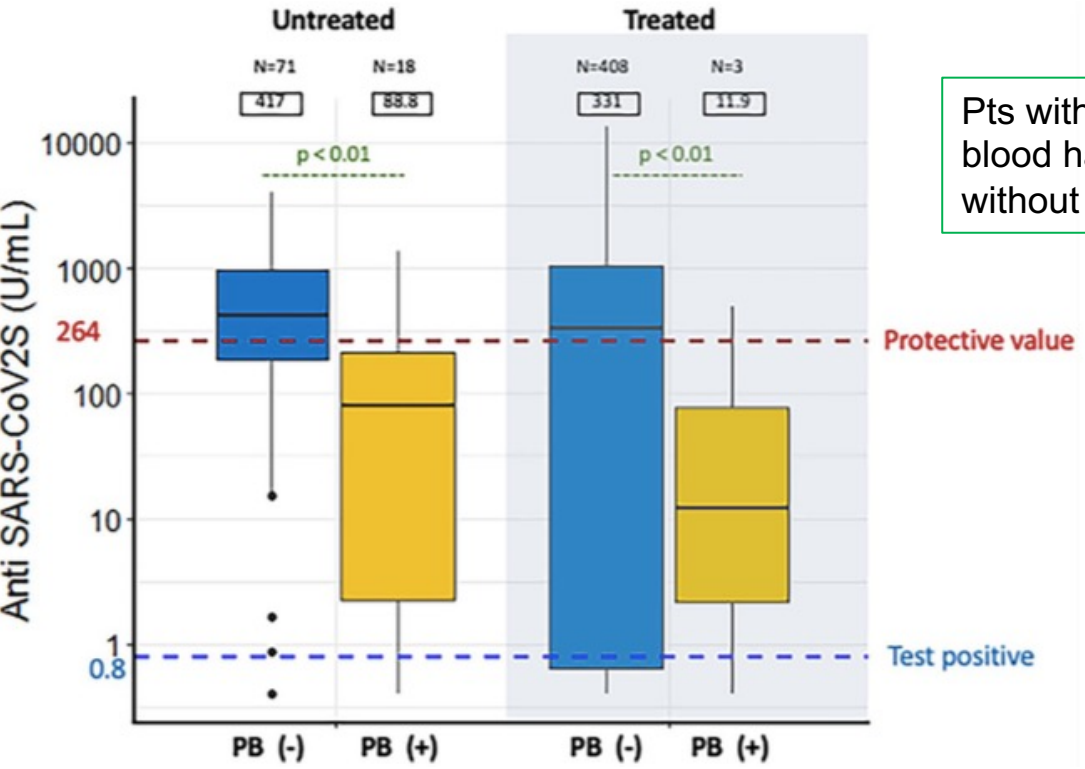


6 months **after** the end of treatment: no difference in antibody levels between chemotherapy and CD20/ BTKi groups
within 6 months: significantly higher anti-S levels for chemotherapy group ($p < 0.01$).

Antibody titers in patients treated with chemotherapy with or without CD20 antibodies or BTKi within 6 months of last treatment and thereafter

Antibody titers in untreated and treated patients with and without lymphoma cell infiltration in the peripheral blood

K. Narita et al.



Pts with lymphoma cell infiltration in the peripheral blood had significantly lower anti-S levels than those without in both the treated and untreated groups

Multivariate analysis of variables associated with achievement of anti-S≧264 U/mL

K. Narita et al.

Variable	OR	95%CI	P
Age ≧73 yr	0.61	0.37–0.98	0.04
WBC ≧5.1 ×10^3/μL	1.68	1.04–2.73	0.03
Lymphocyte ≧ 30%	2	1.24–3.25	
CD19 ≧ 10%	4.23	2.54–7.14	
CD3 ≧ 66%	1	0.57–1.79	
CD4 ≧ 27%	1.84	1.12–3.05	0.01
IgG ≧ 1090 mg/dL	1.45	0.88–2.39	0.13
IgA ≧ 195 mg/dL	1.9	1.14–3.16	0.01
IgM ≧ 50 mg/dL	2.47	1.51–4.06	<0.01
sIL2-R ≧ 600 U/mL	0.43	0.26–0.70	<0.01
PB involvement (+)	0.11	0.02–0.38	<0.01

Age, lymphocyte, CD19, CD4, IgG, IgA, IgM, time from treatment, sIL2-R, PB lymphoma cell infiltration are significantly associated with anti-S ≥ 264 U/mL

Booster vaccination

Lymphoma pts who did not achieve seroconversion after complete vaccination **may benefit from an additional dose of vaccine**

Third dose of vaccine (booster) enhances SARS-CoV-2 neutralizing antibodies also in pts who demonstrated a waning response after vaccination

Benefits are variable across lymphoma histotypes (lower in patients with B-cell lymphomas)

Improve response against SarsCOV2 variants

Persistent SARS-CoV-2 infections in immunocompromised patients can trigger high number of viral genome mutations

Greenberger et al. *Blood*. 2021
Salvini Met al. *Am J Hematol*. 2022
Gressens SB, et al. *Clin Microbiol Infect*. 2022
Gagelmann N . review and meta-analysis *Haematologica2022*
Jimenez M et al *Blood Adv*. 2022
Shapiro LC et al *Cancer Cell*. 2022
Fendler A, et al *Lancet*. 2022 (CAPTURE)
Fendler A, et al *Cancer Cell*. 2022 (CAPTURE)
Borges V et al. mSphere 2021

FONDAZIONE ITALIANA LINFOMI

Managing hematological cancer patients during the COVID-19 pandemic: an ESMO-EHA Interdisciplinary Expert Consensus

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

C. Buske[1*], M. Dreyling[2], A. Alvarez-Larrán[3], J. Apperley[4], L. Arcaini[5,6], C. Besson[7,8], L. Bullinger[9,10], P. Corradini[11], M. Giovanni Della Porta[12,13], M. Dimopoulos[14], S. D'Sa[15], H. T. Eich[16], R. Foà[17], P. Ghia[18], M. G. da Silva[19], J. Gribben[20], R. Hajek[21], C. Harrison[22], M. Heuser[23], B. Kiesewetter[24], J. J. Kiladjian[25], N. Kröger[26], P. Moreau[27], J. R. Passweg[28], F. Peyvandi[29,30], D. Rea[31], J.-M. Ribera[32], T. Robak[33], J. F. San-Miguel[34], V. Santini[35], G. Sanz[36,37], P. Sonneveld[38], M. von Lilienfeld-Toal[39,40], C. Wendtner[41], G. Pentheroudakis[42] & F. Passamonti[43*]

ESMO/EHA recommendations for lymphomas and CLL management in the COVID-19 pandemic

COVID-19 diagnosis, treatment, and mitigation strategies (Coordinator: M. von Liliefeld-Toal)	What are efficient strategies to prevent SARS-CoV-2 infection?	STATEMENT 1: Patients, persons in their close relationship, and caregivers must apply common preventive strategies such as: hygiene measures, physical distancing, wearing facial masks, and staying, if possible, in single bedrooms. Efforts in the reorganization of hematology units with telehealth to reduce clinic visits, regular SARS-CoV-2 swab testing and vaccination of health care personnel, of persons in close relationship to patients and caregivers are to be favored.
	Are anti-COVID-19 vaccines indicated in HM patients to prevent SARS-CoV-2 infection?	STATEMENT 2: Vaccination is strongly recommended. Whenever possible, vaccination should be proposed before initiation of treatment. If this is not possible, vaccines can be administered any time during disease course or any therapy in principle. In the case an urgent treatment is required, withholding the planned therapy for receiving vaccines is not justified. To note, immune response might be severely reduced in those receiving B-cell depleting agents.
	Are current available vaccines safe in HMs?	STATEMENT 3: The benefits of vaccination far outweigh the risks of vaccine-related adverse events and given the greater severity of the disease and higher risk of death, HM patients are considered a high-priority subgroup for SARS-CoV-2 vaccination.
	Who should be tested for SARS-CoV-2 at what time?	STATEMENT 4: Diagnostic testing is mandatory at presentation of any COVID-19 symptoms and after COVID-19 diagnosis until receiving two negative results, even after receiving vaccination against SARS-CoV-2. We recommend screening all asymptomatic patients for SARS-CoV-2 at admission for in-hospital stay, 2-3 days later, and then following local policy. Concerning outpatient clinic visits, we encourage developing local policies according to local risk and recommend testing in the case of high SARS-CoV-2 incidence in the community.
	What type of test should be used with which material?	STATEMENT 5: NAT (nucleic acid amplification technique) testing is preferred, usually using RT-PCR as the most sensitive method. Material from the respiratory tract should be used, swabs are preferred but spit tests, throat gargles, sputum and nasopharyngeal aspirates are also under investigation. The evaluation of serum neutralizing antibodies for detecting immune response after exposure to SARS-CoV-2 is encouraged, when feasible.

FONDAZIONE ITALIANA LINFOMI

When should we initiate lymphoma treatment in the COVID-19 pandemic?

Should we modify lymphoma treatment in the COVID-19 pandemic?

In **indolent lymphomas and CLL** :
'watch and wait' for asymptomatic patients with low tumor burden.
When treatment is indicated, in unvaccinated patients,treatment deferral after anti-SARS-CoV-2 vaccination in the absence of an urgent treatment indication.
If treatment is necessary in indolent lymphoma, less immunosuppressive therapies [e.g. therapies avoiding anti-CD20 antibodies in CLL and anti-CD20 maintenance in follicular lymphoma (FL)]

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

FONDAZIONE ITALIANA LINFOMI

When should we initiate lymphoma treatment in the COVID-19 pandemic?

Should we modify lymphoma treatment in the COVID-19 pandemic?

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

In **aggressive lymphoma** a delay of treatment initiation is not recommended.
In unvaccinated pts, however, in the absence of urgent treatment indication, an individual treatment deferral after anti-SARS-CoV-2 vaccination (at least one injection) may be considered.
In the absence of an urgent treatment indication, a congruous interval (up to 4 weeks) before an anti-CD20 antibody-containing regimen should be respected.
If treatment options are equivalent, less immunosuppressive therapies and treatment with less need for hospital stays are recommended.

FONDAZIONE ITALIANA LINFOMI

In relapsed aggressive lymphoma (DLBCL, MCL, PTCL) and HL? Should autologous, allogeneic SCT or CAR-T cell therapy be postponed in the pandemic?

Patients with refractory and/or relapsed DLBCL, PTCL, and HL who are eligible to autologous, allogeneic SCT or chimeric antigen receptor T-cell (CAR-T cell) therapy should first receive salvage regimens.
HDT/ASCT or CAR-T cell therapy should be considered in eligible patients with DLBCL and MCL.
Delaying (or omitting) consolidative autologous SCT in PTCL patients in complete remission following induction therapy may be considered, as its role is still controversial

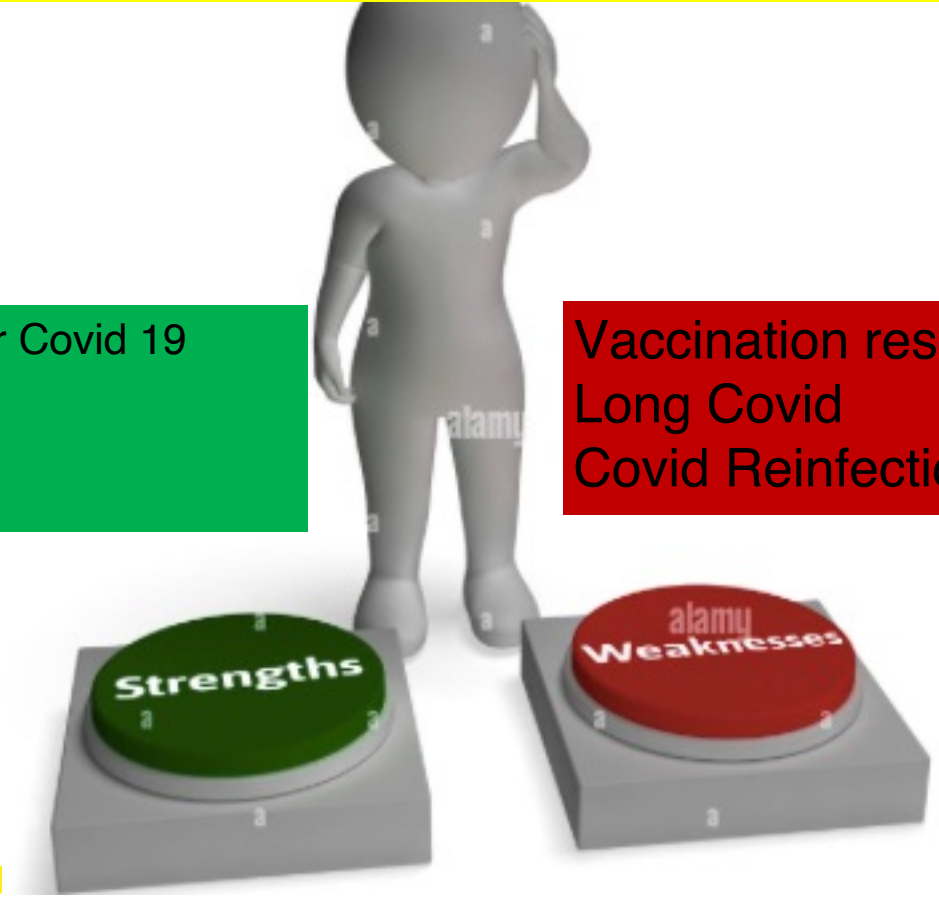
FONDAZIONE ITALIANA LINFOMI

How to treat lymphoma in the case of SARS-CoV-2 positive asymptomatic or oligosymptomatic patients? All histological types, at diagnosis, or during therapy

All positive cases should be investigated with lung CT scan.
In indolent lymphomas, if possible, defer commencement of treatment until nasopharyngeal swab negativity and resolution of clinical symptoms.
If already on treatment the decision to continue or stop treatment should be based on the nature of the treatment and the severity of COVID-19.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Managment of lymphoma pts in Covid-19 era: Today



Treatments strategies for Covid 19
Vaccines
Antiviral drugs
Mo Ab

Vaccination response
Long Covid
Covid Reinfections


Thank
You