9th EUROPEAN CONFERENCE on INFECTIONS in LEUKAEMIA

COVID Group

Epidemiology and risk factors

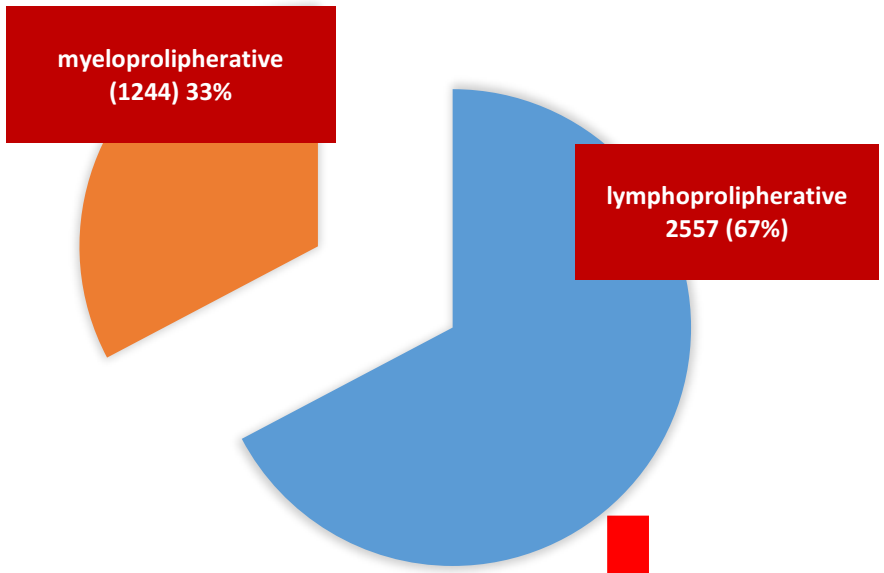
▶ VIRTUAL CONFERENCE
From September
16th to 17th 2021

Final revised slide set
post-ECIL meeting

COVID-19 in Hematological Malignancies. Epidemiology and risk factors

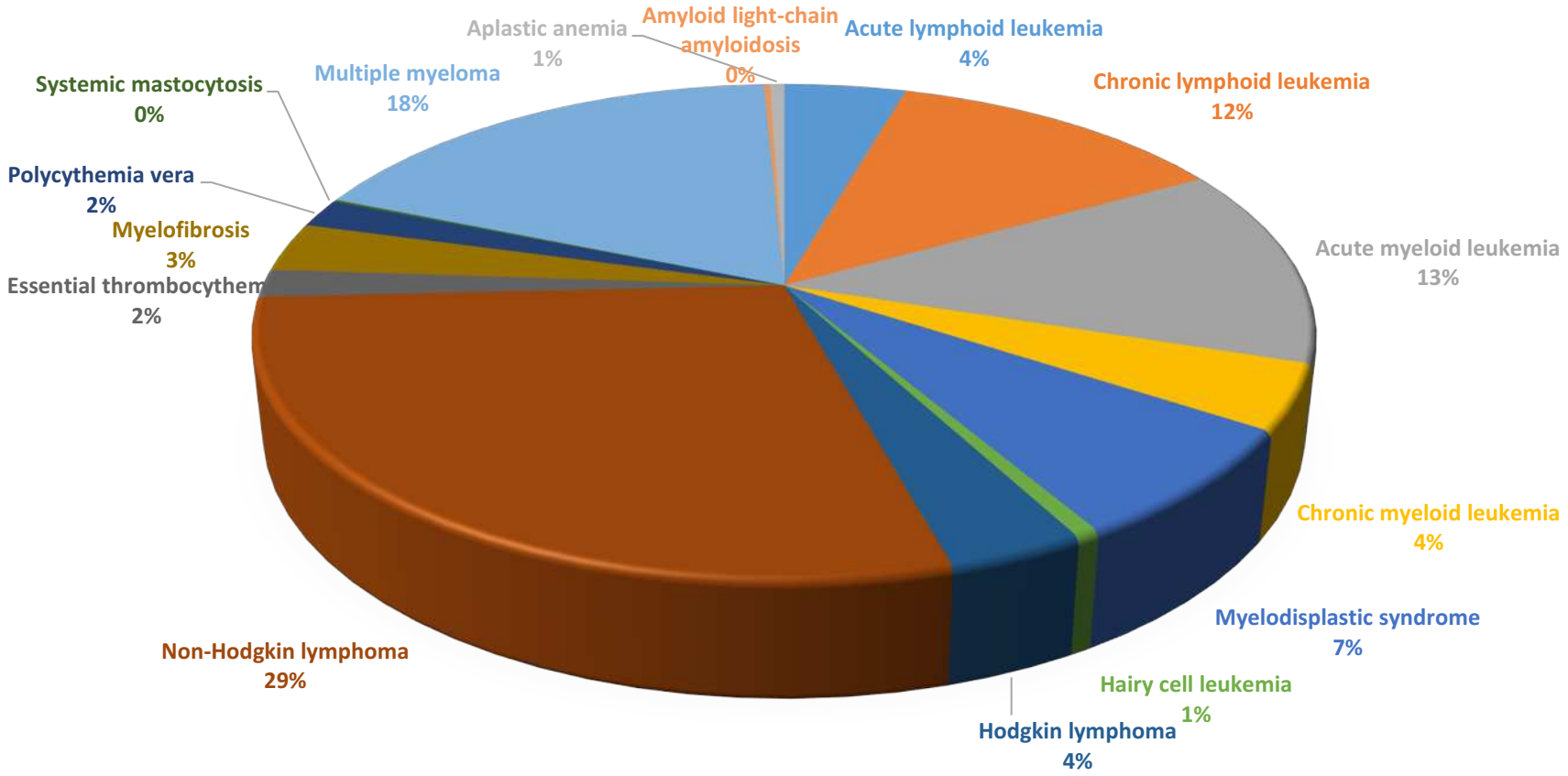
- **Livio Pagano** (Italy, chair)
- **Simone Cesaro** (Italy, co-chair) (pediatric subset)
- **Raul Cordoba**(Spain) (Myeloprolipherative, acute and chronic)
- **Caroline Besson** (France)(Lymphoproliferative)
- **Varun Mehra** (UK)(auto, allo HSCT and CAR-T)

Distribution of COVID-19 among Hematological Malignancy patients EPICOVIDEHA Survey (Pagano et al, JHON 2021)



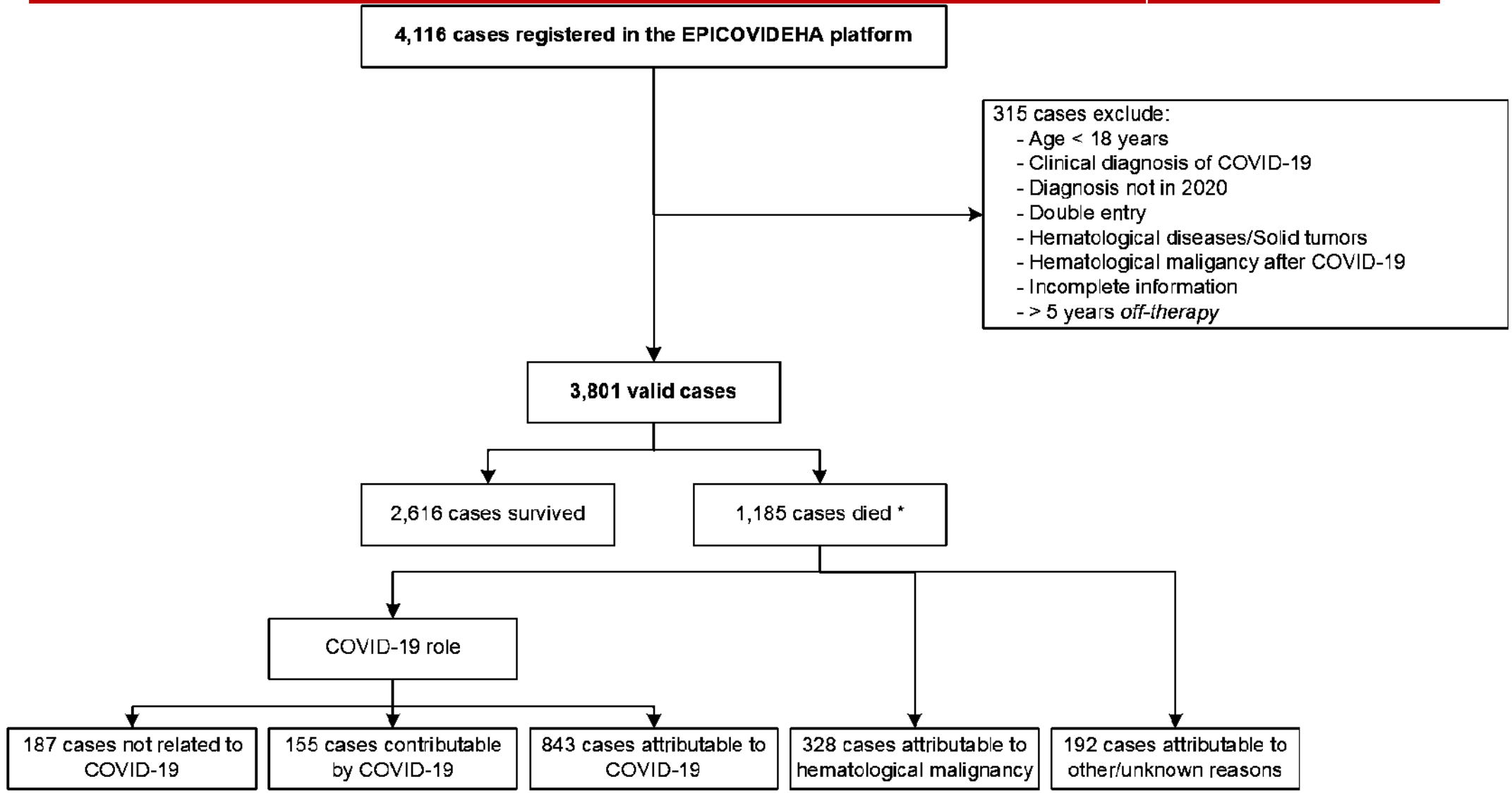
MALIGNANCY	CASES
Acute lymphoid leukemia	169
Chronic lymphoid leukemia	474
Acute myeloid leukemia	497
Chronic myeloid leukemia	161
Myelodisplastic syndrome	279
• Low - intermediate risk	138
• High risk	48
• Not stated	93
Hairy cell leukemia	23
Hodgkin lymphoma	135
Non-Hodgkin lymphoma	1084
• Indolent	497
• Aggressive	516
• Not stated	71
Essential thrombocythemia	69
Myelofibrosis	122
Polycythemia vera	70
Systemic mastocytosis	6
Multiple myeloma	684
Amyloid light-chain amyloidosis	8
Aplastic anemia	20

3801 adult patients



VIRTUAL

Overall crude mortality rate *	**1185 (31.2%)**
Attributable to COVID-19	**843 (22.2%)**
Contributable to COVID-19	**155 (4.1%)**
Attributable to HM	**328 (8.6%)**



** The mortality in certain patients might be attributable to more than 1 factor*

Characteristics, clinical outcomes, and risk factors of SARS-COV-2 infection in adult acute myeloid leukemia patients: experience of the PETHEMA group

Table 4. Significant associations between mortality and baseline AML characteristics after logistic regression.

Variable	Classification	Death, *n* (%)	Alive, *n* (%)	OR (95%CI)	*p* value	Significant covariates	OR (95%CI); *p* value
Age	≤60 years	11 (39.3)	17 (60.7)	1		Gender	0.4 (0.1–0.98); *p*=.047
	>60 years	36 (49.3)	37 (50.7)	4.4 (1.1–17.3)	.036		
Gender	Male	32 (56.1)	25 (43.9)	1		Age	4.4 (1.1–17.3); *p*=.036
	Female	15 (34.1)	29 (65.9)	0.4 (0.1–0.98)	.047		
AML status	Complete remission	10 (27.8)	26 (72.2)	1		Age	4.9 (1.2–20.1); *p*=.027
	Active disease	32 (60.4)	21 (39.6)	4.1 (1.3–12.8)	.014		
	Partial remission	1 (20.0)	4 (80.0)	ND	NS		

AML: acute myeloid leukemia; CI: confidence interval; ND: not determined; NS: non-significant; OR: odds ratio.

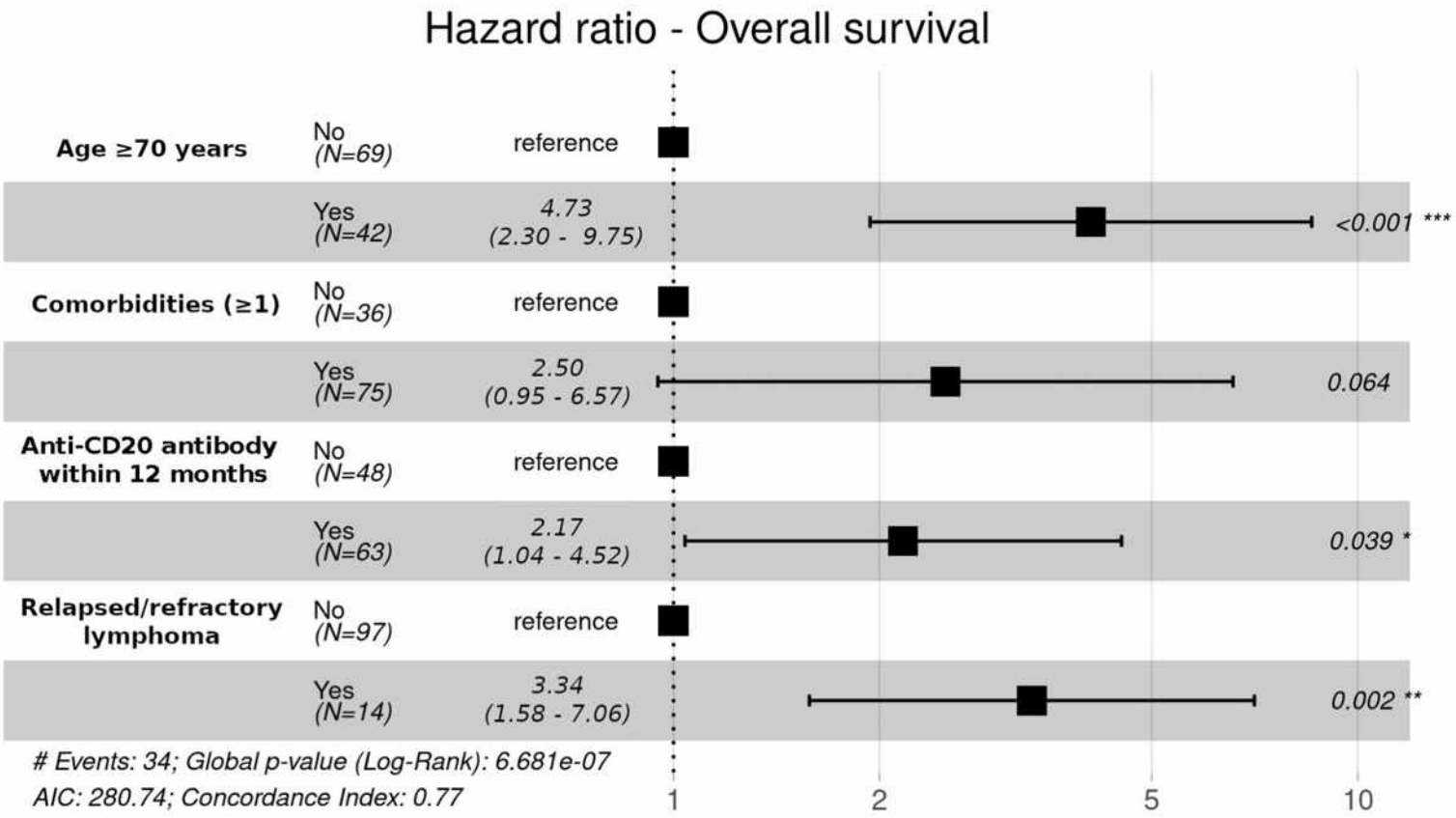
Palanques-Pastor et al. Leuk Lymphoma. 2021 Jul 22;1-11.

Mortality rate in COVID-19 patients with myeloproliferative neoplasms

- Observational retrospective study (MPN-COVID) was promoted by ELN and had the endorsement of the European Haematology Association, GEMFIN Spanish network on MPN and HARMONY platform.
- 175 patients with myeloproliferative neoplasms (MPN) and COVID-19, diagnosed between February and June 2020.
- Prognostic factors for worse survival (univariate analysis): age, diagnosis of myelofibrosis, discontinuation of ruxolitinib after COVID-19 onset, comorbidities (chronic dialysis/kidney disease, chronic heart failure, diabetes mellitus) neutrophils/lymphocytes ratio, O_2 saturation, need of respiratory support, need of ICU

Barbui Tet al. Leukemia 35, 485–493 (2021).

Lymphoma : Multivariate analysis of factors associated with overall mortality



Dulery et al, Am J Hematol. 2021 Aug 1;96(8):934-944

CLL: worse outcomes in patients without treatment, protective effect of Ibrutinib versus immunochemotherapy

Hospitalization rate for severe COVID-19 was lower ($p < 0.05$) for patients on ibrutinib versus those on other regimens or off treatment: 27/1729 (1.6%) on ibrutinib were hospitalized, 8/442 (1.8%) on venetoclax and 18/428 (4.2%) on combined immunotherapy.

In CLL, (1) COVID-19 severity increases with age; (2) antileukemic treatment (particularly BTK inhibitors) appears to exert a protective effect; (3) age and comorbidities did not impact on mortality.

Table 3 Patients' disposition based on COVID-19 severity.

Variable	Severe COVID-19 ($n = 151$)	Nonsevere COVID-19 ($n = 39$)	p
Age			
≥65 years (%)	112 (74.2)	17 (43.6)	**<0.05**
<65 years (%)	39 (25.8)	22 (56.4)	
Gender			
Male (%)	98 (64.9)	28 (71.8)	n.s.
Female (%)	53 (35.1)	11 (28.2)	
Median time between CLL diagnosis and COVID-19	88	71	n.s.
Treatment for CLL			
Untreated (%)	64 (42.7)	9 (23.1)	**<0.05**
Treated (%)	86 (57.3)	30 (76.9)	

Scarfò et al, Leukemia 2020 Sep;34(9):2354-2363

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Multiple myeloma : worse outcome in patients with renal insufficiency

Table 4 Prognostic factors of inpatient mortality in multiple myeloma (MM) patients hospitalized with COVID-19.

Prognostic factors[a]	N	Inpatient mortality, no. (%)	Unadjusted analysis[b]		Adjusted analysis[c]		GoF P value	c-statistic (95% CI)
			Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value		
All patients	167	56 (34)						
Age > 65 years	112	47 (42)	3.7 (1.6–8.3)	0.002	3. (1.4–8.4)	0.006	NA	NA
Males	95	39 (41)	2.3 (1.1–4.4)	0.018	3.8 (1.7–8.4)	0.001	NA	NA
MM comorbidities and status at hospital admission for COVID-19								
Renal disease	32	19 (59)	3.9 (1.7–8.7)	<0.001	4.6 (1.9–11.3)	<0.001	NA	NA
Hypertension	67	28 (42)	1.8 (0.96–3.5)	0.065	1.7 (0.8–3.5)	0.18	NA	NA
Active disease or progression	43	21 (49)	2.4 (1.2–4.9)	0.015	2.7 (1.2–6.0)	0.017	NA	NA
Reference model:	0.7	0.79 (0.72–0.86)						
MM features at diagnosis and treatment								
Monoclonal component, immunoglobulin G	83	22 (27)	0.5 (0.3–1.0)	0.05	0.6 (0.3–1.3)	0.18	0.6	0.80 (0.73–0.87)
Renal disease at diagnosis	45	23 (51)	2.8 (1.4–5.7)	0.004	1.3 (0.4–3.7)	0.6	0.8	0.79 (0.72–0.86)
Diagnosis in 2020 (time since diagnosis ≤ 3 months)	25	12 (48)	2.0 (0.9–4.9)	0.10	2.7 (0.7–5.8)	0.19	0.5	0.79 (0.72–0.86)
Prior stem cell transplantation	51	9 (17)	0.3 (0.1–0.7)	0.004	0.6 (0.2–1.7)	0.4	0.4	0.79 (0.71–0.86)

CI confidence interval, *COVID-19* coronavirus disease 2019, *GoF* goodness-of-fit, *NA* not applicable.
[a]Predefined set of well-established prognostic factors assessed before admission; all variables were dichotomized according to standard categories.
[b]Crude odds ratio and 95% confidence interval.
[c]Each logistic model included age, sex, myeloma status, comorbidities (hypertension, renal disease) at diagnosis of COVID-19 (reference model), and one variable from the "Multiple myeloma at diagnosis and treatment" set. Calibration and discrimination of the models were assessed with the Hosmer–Lemeshow goodness-of-fit test (GoF *P* value) and the c-statistic.

Martinez-Lopez et al , Blood Cancer J 2020 Oct 19;10(10):103

Outcomes in HSCT with COVID-19- CIBMTR study

318 HSCT Patients diagnosed with COVID-19 reported between Mar and Aug 2020.

Covid-19 & HSCT	Auto	Allo
Median time from HSCT to Covid-19	23 months	17 months
Median duration of Infection	19 days (IQR 11-31)	14 days (IQR 7-31)
Moderate disease	20 % (27/134)	27 % (49/184)
Severe disease	13% (17/134)	15% (28/184)
Covid-19 as primary cause of death	73% (19/26)	93% (36/40)
probability of survival at 30 days	67% (55–78)	68% (95% CI 58–77)

Sharma et al. Lancet Haematol. 2021;8:e185–e193

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Epidemiology in HSCT- EBMT/GETH study

382 patients- 236 Allo, 146 Auto (incl Paediatrics- n: 38); 22 countries

- 84% had LRTI. 22.5% were admitted to an ICU
- COVID-19 was a severe complication in HSCT recipients with an attributable mortality of 25%
- **Overall survival at 6 weeks from diagnosis was 77.9% and 72.1% in allogeneic and autologous recipients, respectively**. Children had a survival of 93.4%.

Ljungman et al, Leukemia (2021). https://doi.org/10.1038/s41375-021-01302-5

Autologous HSCT Risk factors for Mortality post COVID-19: CIBMTR

Risk factors:

- Lymphoma > Myeloma
- Absolute lymphocyte count of 0·3 × 10^9 cells/L or less at COVID-19 diagnosis was associated with worse survival (56% [95% CI 34–76] *vs* 85% [78–90]; p=0·003)

Allogeneic HSCT Risk factors for Mortality post COVID-19: CIBMTR

Risk Factors:

1. Age≥50yrs
2. Male gender
3. ≤12 months post allo-HSCT

Sharma et al. Lancet Haematol. 2021;8:e185–e193

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Summary: Prognostic Risk factors for survival

Prognostic Risk factors for poor survival

- **Older Age**
- **Poor performance status**
- **ISI score intermediate + high vs. low**
- **Time from HSCT to COVID-19 (≤12 months)**

Additional factors to consider
- Male gender*
- Low ALC/CRP ratio
- Low BMI≤20
- Number of comorbidities

*Gender risk factor differences between EBMT and CIBMTR series

- Lower 10.9% mortality among female allogeneic HCT recipients in CIBMTR, compared to 27.2% in EBMT series
- Male mortality were 33.7% vs. 28.5% in the CIBMTR and EBMT series, respectively

Epidemiology and Survival

- **Limited community prevalence data (small studies; HSCT- 9.4%, CART-4.8%)**
- **Moderate-Severe disease incidence range 32-45%**
- **Survival similar between autografts and allo-HSCTs**
- **OS ranges between 68-72% at D30-42 in HSCTs with Covid-19.**
- **COVID-19 attributable mortality in severe disease - 24% in HSCT and 43% in CART population**

Global registry of COVID-19 in Childhood Cancer

Mukkada et al. Lancet Oncol 2021 Aug 26:S1470-2045(21)00454-X

Period April 2020-January 2021

1500 pts (1319 with 30 days of f-up), 45 countries, 131 Institutions

Demographic and clinical characteristics	
Male sex	59.4%
Median age	8 yrs
Diagnosis	ALL/LHN-LH 49.1% Solid T. 24.2% CNS T. 8.4% Other 0.5%
HSCT	5.4%
Radiotherapy	10.7%
Chemotherapy	Active 80.9% Completed 8.5% Palliative 3.5% Other 5.1%

COVID 19 characteristics	
Symptoms	Asymptomatic 35.1% Mild/Moderate 45% Severe/Critical 19.9%
ANC < 500	30.9%
ALC < 300	23%
Hospitalization	Yes, ward, 49.9% Yes, higher level of care: 17.5% No 32.6%
Treatment modification	Yes 55.8% (chemo withheld 45%)
Comorbidity ≥ 1	Yes 17.1%
Intensive treatment	31.9%

Global registry of COVID-19 in Childhood Cancer

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1319 pts (100%) at 30 days of f-up

COVID-19 negative
1073 (81%)

COVID-19 still positive or unknown
170 (13%)

MORTALITY

Death
76 (6%)
Due to Covid-19: 4%
Due to other causes: 2%

Global registry of COVID-19 in Childhood Cancer

Mukkada et al. Lancet Oncol 2021 Aug 26:S1470-2045(21)00454-X

Period April 2020-January 2021

1500 pts (1319 with 30 days of f-up), 45 countries, 131 Institutions

Risk factors for COVID-19 severity	
Income group	Low-middle income
Age	15-18 yrs
ALC	= or < 300
ANC	= or < 500
Comorbidities	yes
Intensive treatment	yes

Risk factors for treatment modification	
Income group	Low-middle income
Diagnosis	ALL/LNH
ALC	= or < 300
Comorbidities	yes
Covid-19 symptoms	yes

COVID-19 in Hematological Malignancies. Epidemiology and risk factors Consideration I

- No data on the real incidence in hema malignancy patients, but we retain that it is higher than in normal population
- With regard to the prevalence by number, lymphoproliferative diseases (i.e. NHL, CLL and MM) are those characterized by a higher number of cases (but they are also the most frequent hematological malignancies)
- Acute leukemias and high risk-myelodysplastic syndromes are instead characterized by a higher mortality rate
- Patients receiving CAR-T therapy have a worse prognosis with a high mortality rate
- In all subset of patients, advanced age, comorbidities and uncontrolled malignancy represent the main risk factors for mortality in all population

COVID-19 in Hematological Malignancies. Epidemiology and risk factors Consideration II

- In MPN Ruxolitinib discontinuation is characterized by a worst prognosis
- Administration of anti-CD20 therapy within the last 12 months is one of the main risk factors for longer hospitalization and death from Covid-19 among patients with lymphomas
- In CLL, Ibrutinib seems to be protective against severe Covid; combined immunochemotherapy being associated with worse outcomes
- In MM, renal insufficency is associated with a higher mortality

COVID-19 in Hematological Malignancies. Epidemiology and risk factors Pediatric subset

- Few epidemiological data in children and adolescent, also for the lower incidence than in adults
- Milder outcome than in adult hematological population with 4-5% of mortality rate
- Beyond the clinical and demographic factors, the country socioeconomic level was associated to higher mortality rate in pediatric patients
- Overall, COVID 19 associated mortality was higher in the pediatric hematology oncology population than the general pediatric population