



9<sup>th</sup> EUROPEAN  
CONFERENCE on  
INFECTIONS in  
LEUKAEMIA

**COVID Group**  
Epidemiology and risk factors



► **VIRTUAL CONFERENCE**  
From September  
16<sup>th</sup> to 17<sup>th</sup> 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) (Myeloproliferative, acute and chronic)
- **Caroline Besson** (France)(Lymphoproliferative)
- **Varun Mehra** (UK)( auto, allo HSCT and CAR-T)



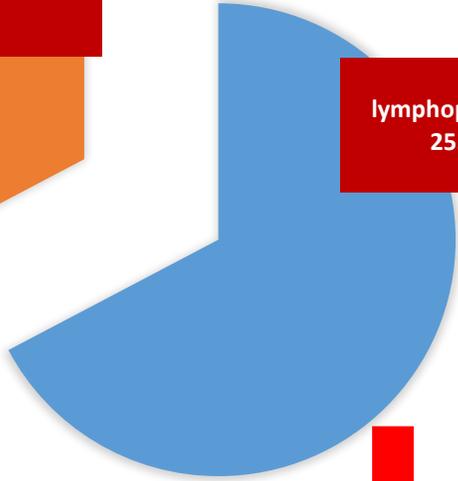
# Distribution of COVID-19 among Hematological Malignancy patients

## EPICOVIDEHA Survey (Pagano et al, JHON 2021)

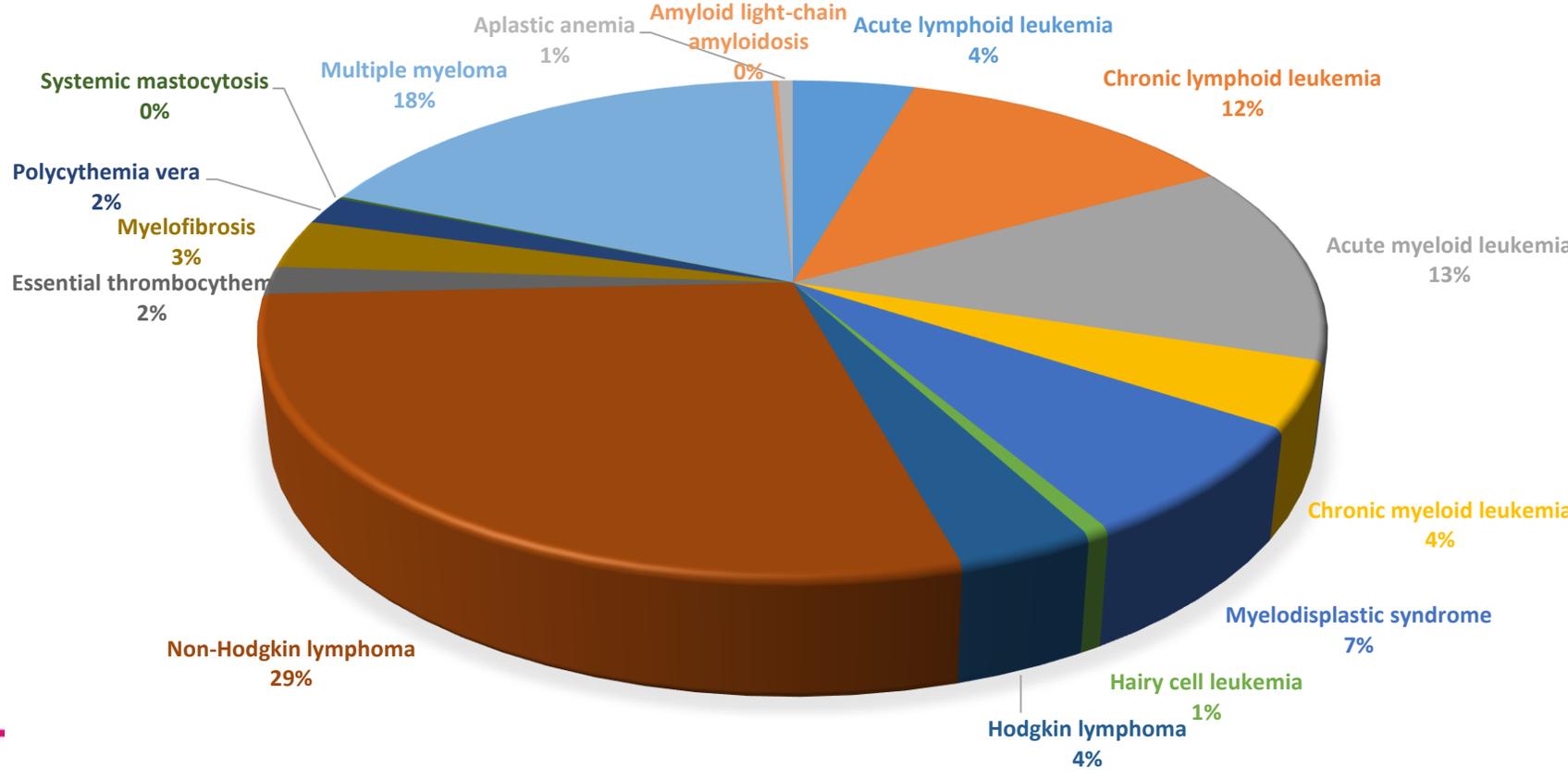
3801 adult patients

myeloproliferative  
(1244) 33%

lymphoproliferative  
2557 (67%)



MALIGNANCY	CASES
Acute lymphoid leukemia	169
Chronic lymphoid leukemia	474
Acute myeloid leukemia	497
Chronic myeloid leukemia	161
Myelodysplastic 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



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# Overall crude mortality rate \*

Attributable to COVID-19

Contributable to COVID-19

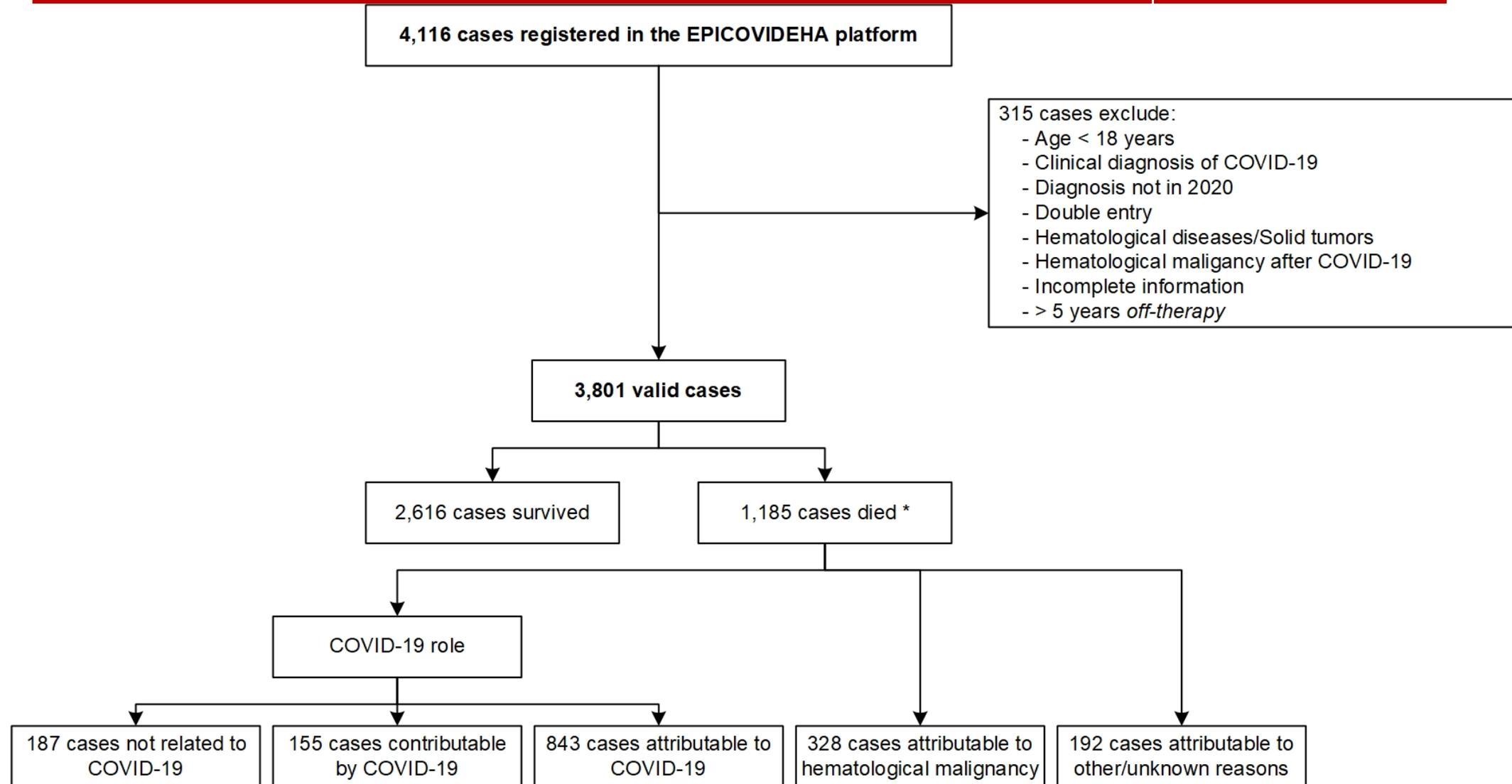
Attributable to HM

**1185 (31.2%)**

**843 (22.2%)**

**155 (4.1%)**

**328 (8.6%)**



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

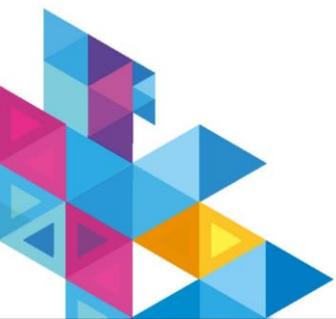


# Characteristics, clinical outcomes, and risk factors of SARS-COV-2 infection in adult acute myeloid leukemia patients: experience of the PETHEMA group

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

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

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

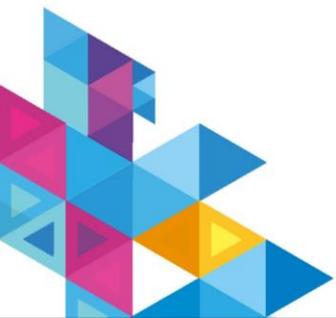
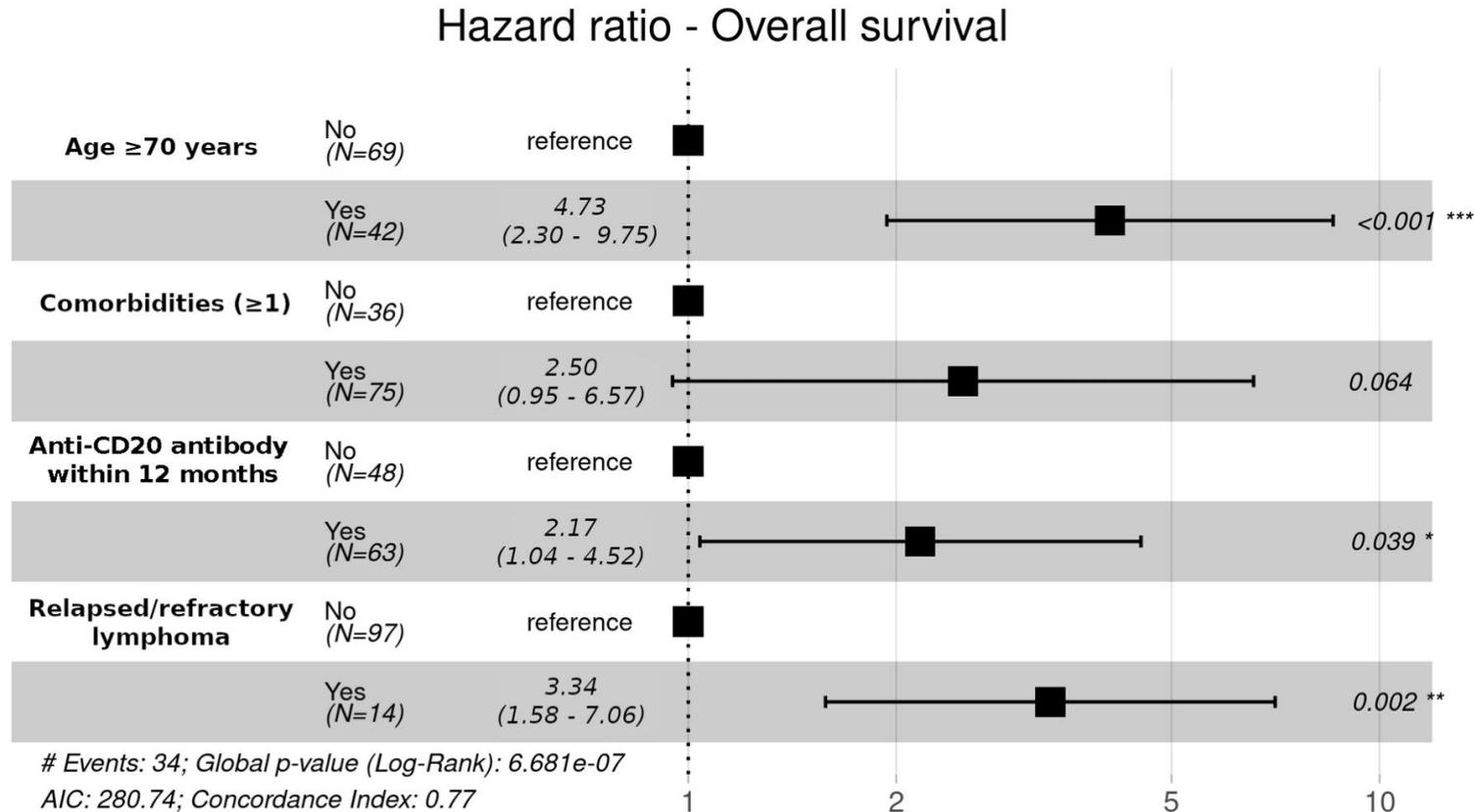


# Mortality rate in COVID-19 patients with myeloproliferative neoplasms

- 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<sub>2</sub> saturation, need of respiratory support, need of ICU



# Lymphoma : Multivariate analysis of factors associated with overall mortality



# 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
<b>Age</b>			
≥65 years (%)	112 (74.2)	17 (43.6)	<b>&lt;0.05</b>
<65 years (%)	39 (25.8)	22 (56.4)	
<b>Gender</b>			
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.
<b>Treatment for CLL</b>			
Untreated (%)	64 (42.7)	9 (23.1)	<b>&lt;0.05</b>
Treated (%)	86 (57.3)	30 (76.9)	



# 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 <sup>a</sup>	N	Inpatient mortality, no. (%)	Unadjusted analysis <sup>b</sup>		Adjusted analysis <sup>c</sup>		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
<i>MM comorbidities and status at hospital admission for COVID-19</i>								
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)					
<i>MM features at diagnosis and treatment</i>								
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.

<sup>a</sup>Predefined set of well-established prognostic factors assessed before admission; all variables were dichotomized according to standard categories.

<sup>b</sup>Crude odds ratio and 95% confidence interval.

<sup>c</sup>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  
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# 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)



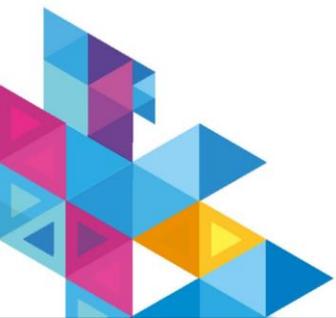
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*Sharma et al. Lancet Haematol. 2021;8:e185–e193*  
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# Epidemiology in HSCT- EBMT/GETH study

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%.



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

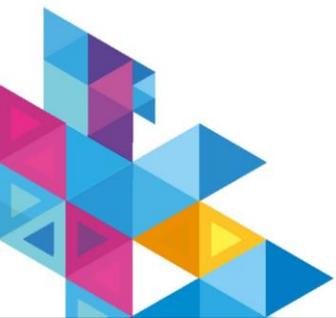
### Risk factors:

- Lymphoma > Myeloma
- Absolute lymphocyte count of  $0.3 \times 10^9$  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  $\geq 50$  yrs
2. Male gender
3.  $\leq 12$  months post allo-HSCT



# 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 ( $\leq 12$  months)

## Additional factors to consider

- Male gender\*
- Low ALC/CRP ratio
- Low BMI  $\leq 20$
- 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 $\geq$ 1	Yes 17.1%
Intensive treatment	31.9%



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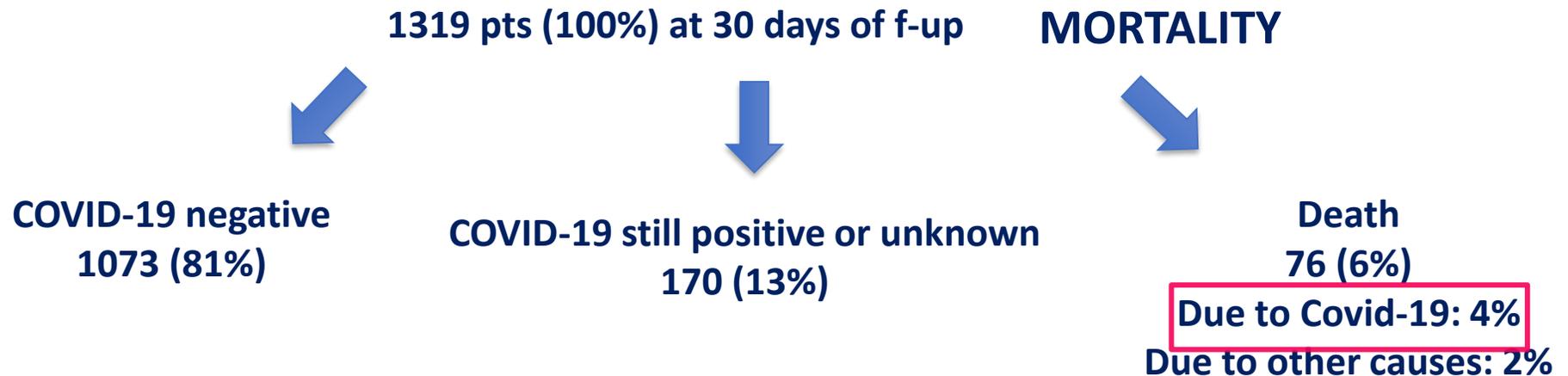
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Risk factors for COVID-19 severity	
Income group	Low-middle income
Age	15-18 yrs
ALC	= or < 300
ANC	= or < 500
Comorbidities	yes
Intensive treatment	yes

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



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# 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 insufficiency 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

