Covid-19 e malattie ematologiche: l'esperienza italiana

Francesco Passamonti
Università degli Studi dell'Insubria, Varese

UK Coronavirus Cancer Monitoring Project (UKCCMP)

- 1044 cancers (March 18 to May 8, 2020), of whom 224 HM
- 319 (30·6%) of 1044 patients in the UKCCMP cohort died
- Patients with HM (AML, NHL, MM) had a more severe Covid-19 respect to patients with solid cancers
- After correction for age and sex, patients with HM who had chemotherapy within 1 months from Covid-19 had an increased risk of death during Covid-19 (OR 2·09, 95% CI 1·09–4·08)

Lennard Y W Lee Lancet Oncology 2020

HM diagnoses of 536 hospitalized patients with Covid-19

Myeloid neoplasms	175
Myeloproliferative neoplasms	83
Myelodysplastic syndromes	41
Acute myeloid leukemias	51
Acute lymphoblastic leukemia	16
Hodgkin Lymphomas	17
Non-Hodgkin Lymphomas	222
Aggressive	99
Indolent	54
Chronic lymphoproliferative disorders	69
Plasma cell neoplasms	106
Plasma cell myeloma	94

Passamonti F et al. Lancet Haematol. 2020 Aug 13

Covid-19 severity in HM in Italy and Spain

Clinical degree of Covid-19 severity

- severe & critical in 50% (ITA)
- severe & critical in 62% (SPA)

Associations with non-mild disease

- older age (ITA, SPA)
- higher Charlson Comorbidity Index (ITA), more comorbidity (SPA)
- more recent diagnosis of HM (ITA)

Covid-19 severity definition, by Chinese CDC:
Mild: non-pneumonia and mild pneumonia);
Severe: dyspnea, respiratory frequency ≥ 30/min, SpO2 ≤ 93%, PaO2)/fraction of inspired oxygen (FiO2) ≤ 300 mm Hg and/or lung infiltrates > 50%;
Critical (respiratory failure, septic shock, and/or multiple organ disfunction or failure)

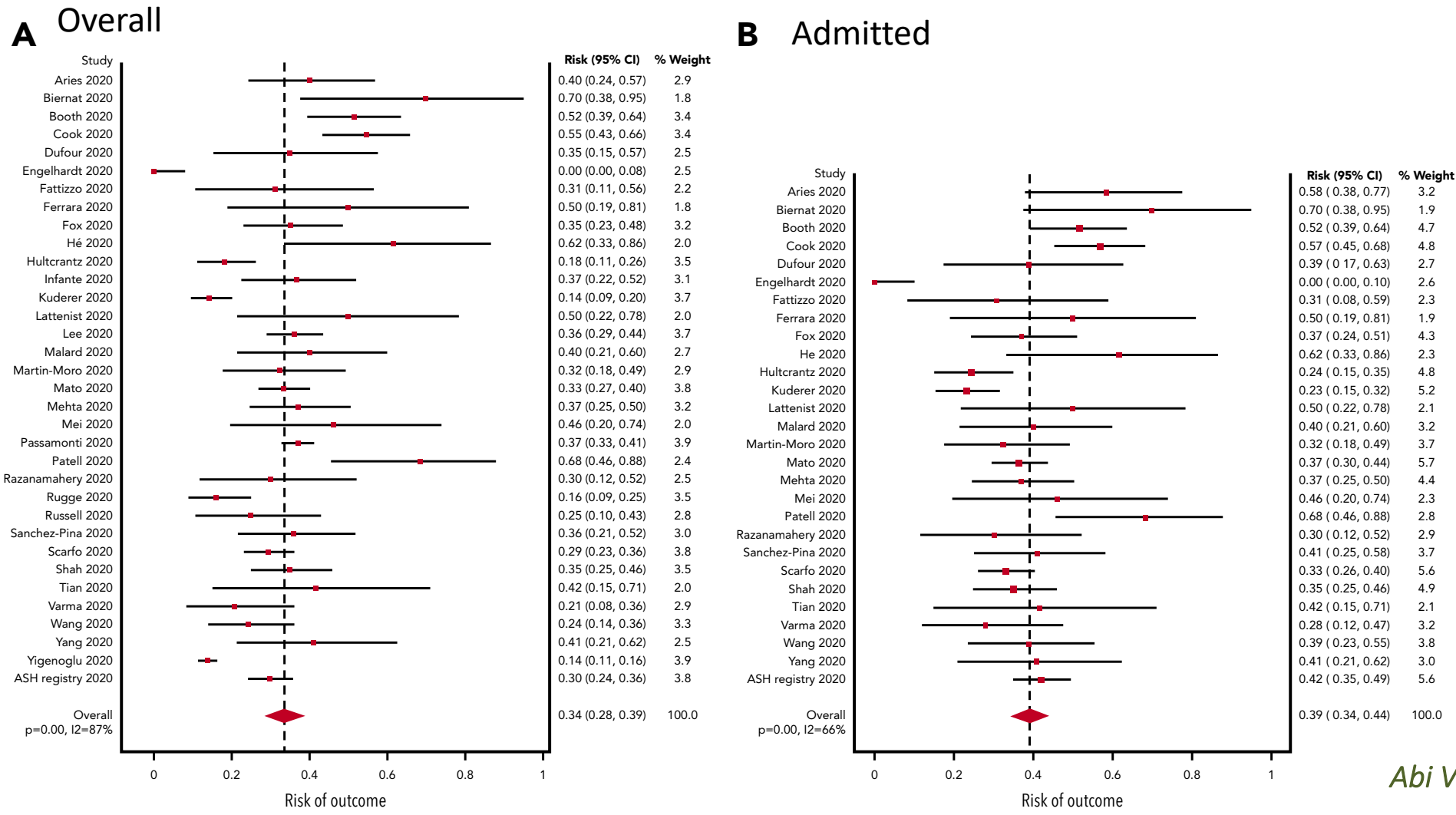
Passamonti F et al. Lancet Haematol. 2020 Aug 13; García-Suárez et al. J Hematol Oncol (2020) 13:133

Mortality rate in HM with Covid-19

- 198 of 536 (36.9%) patients had died
- Mortality rate: 153.2/10,000 person days
  - 169.2/10,000 person days (Feb 25 to Mar 30), 111.1 per 10,000 person days (Apr 1 to May 18): Wald Chi-square test, p=0·01
  - Concerning the level of care, mortality was 63.4% (52 of 82) among patients admitted to ICU and 32.2% (146 of 454) in non-ICU setting

Passamonti F et al. Lancet Haematol. 2020 Aug 13

Death of patients with HM and Covid-19: a meta-analysis of 3377 cases



Abi Vijenthira et al. Blood 2020

Standardized mortality rate (SMR) in HMs

SMR-1 to address mortality of HM *vs.* the Italian population with Covid-19 was:

- 2.04 in the whole population
- 3.72 in younger than 70 years
- 1.71 in older than 70 years

SMR-2 to address mortality of HM *vs.* the Italian population with HM without Covid-19 was

- 41.3

Mortality of HM (sex and age) and of Italian Covid-19

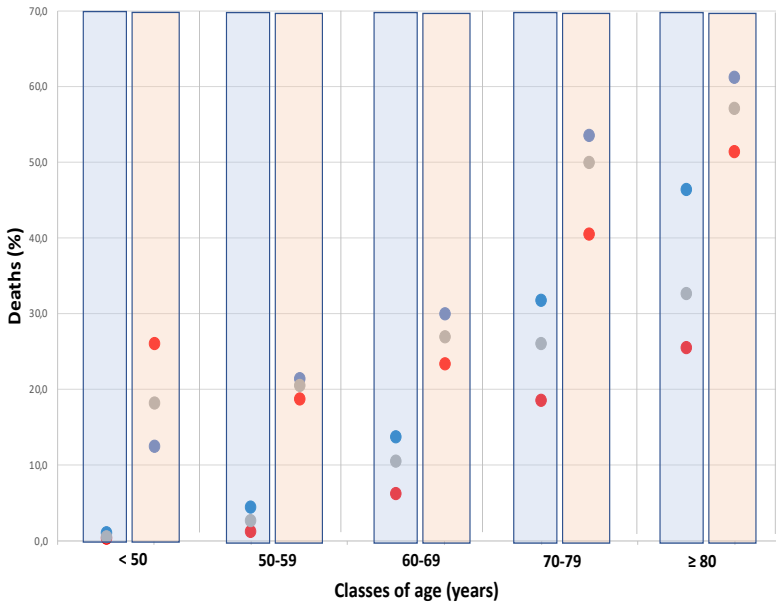


Figure 2

Blue column: COVID-19 from Italy. Yellow column: HM & COVID-19
Whole cohort (grey), Female (red), Males (blue)

Passamonti F et al. Lancet Haematol. 2020 Aug 13

2nd vs. 1st wave: has something changed for hospitalized patients?

30-day mortality

		OVERALL	1st WAVE	2nd WAVE
N		1452	647	805
Median follow-up (months)	Median (min-MAX)	1.6 (0.0-18.7)	2.3 (0.03-18.7)	1.4 (0.0-12.1)
Age -yr	mean (SD)	67.2 (13.1)	67.4 (13.2)	67.0 (13.0)
Sex- Female	n(%)	502 (34.6)	211 (32.6)	291 (36.2)
Myeloid neoplasm	n(%)	424 (29.3)	213 (32.9)	211 (26.3)
Myeloproliferative neoplasms	n(%)	184 (12.7)	103 (15.9)	81 (10.1)
Myelodysplastic syndromes	n(%)	92 (6.3)	46 (7.1)	46 (5.7)
Acute myeloid leukemias	n(%)	148 (10.2)	64 (9.9)	84 (10.4)
Acute lymphoblastic leukemias	n(%)	46 (3.2)	16 (2.5)	30 (3.7)
Hodgkin lymphomas	n(%)	37 (2.6)	18 (2.8)	19 (2.4)
Non Hodgkin Lymphomas	n(%)	642 (44.3)	273 (42.2)	369 (46.0)
Chronic lymphoproliferative NPLs	n(%)	231 (17.6)	95 (16.2)	136 (18.7)
Indolent lymphomas	n(%)	162 (12.3)	65 (11.1)	97 (13.3)
Aggressive lymphomas	n(%)	246 (18.7)	112 (19.1)	134 (18.4)
Plasma cell neoplasms	n(%)	300 (20.7)	127 (19.6)	173 (21.6)

The Italian Hematology Alliance on Covid-19 (ITA-HAEMA-COV), unpublished data

Risk factors for survival in HM with Covid-19

- Older age (HR, 1.03)
- Progressive disease status (HR, 2.10)
- Diagnosis of AML (HR, 3.49), of indolent NHL (HR, 2.19), of aggressive NHL (HR, 2.56), of plasma cell neoplasms (HR, 2.48)
- Severe/critical Covid-19 (HR, 4.08)
- Sex, Charlson Comorbidity Index, time from HM to Covid-19, time from last HM therapy to Covid-19, and HM therapy were neutral

Passamonti F et al. Lancet Haematol. 2020 Aug 13

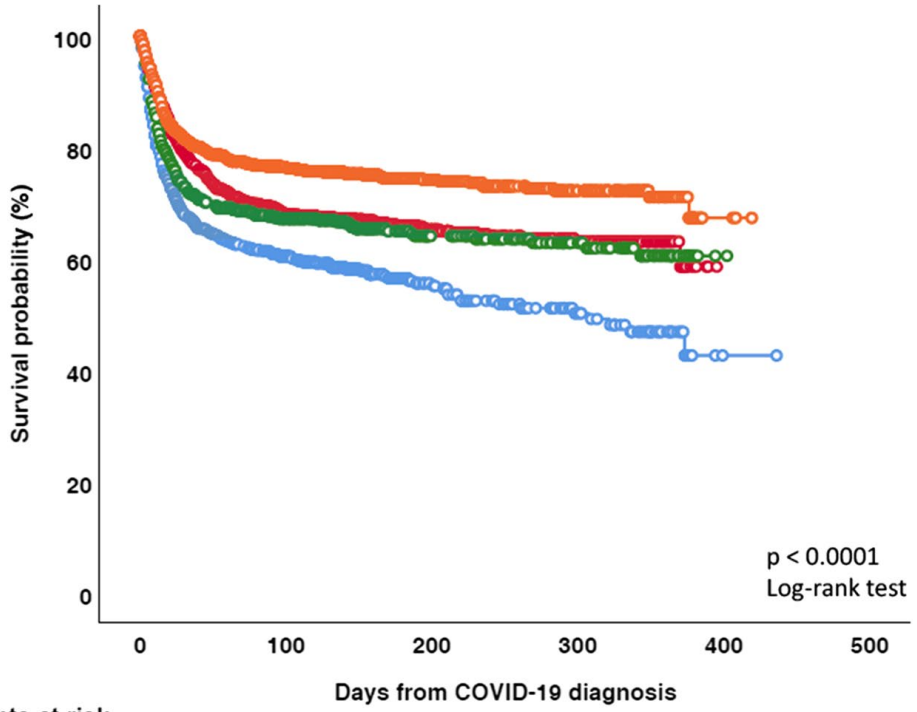
CML and Covid-19 (Campus CML network)

- 8665 CML patients followed at 46 centres, 217 had Covid-19
- 9·6% required hospitalization without respiratory assistance, 8.2% were hospitalized for respiratory assistance, 3.6% were admitted to ICU
- Mortality rate: 5.5%

- Imatinib role?
  - Early phases of infection, IMA prevents viral entry via Abl-mediated cytoskeletal modification
  - Later phases, IMA and DAS inhibit MERS-CoV replication through blocking of the Abl2 protein
  - BCR-Abl inhibitors also cause a decrease in B-cell numbers, Ab production, and Treg viability

Breccia et a. Br J Haematol. 2021 Oct 11; Sisk et al. J Gen Virol. 2018; 99(5):619-60. Rajala et al.J Cancer Res Clin Oncol. 2017;143(8):1543-54.

Survey of the EHA-WG on Infection in Hematology: the EPICOVIDEHA



Number of patients at risk

AML + MDS	**774**	301	113	52	1	0
NHL	**1080**	525	250	112	0	0
MM	**682**	304	130	73	1	0
Other malignancies	**1254**	625	299	136	3	0

- 3801 cases
  - NHL: 1084; MM: 684; CLL: 474; AML: 497; MDS: 279
- 63.8% had severe/critical Covid-19
- 31.2% died

Pagano et al. J Hematol Oncol (2021) 14:168

Acute myeloid leukemia and Covid-19 (Pethema data)

- 108 AML (52% active, 70.4% under therapeutic schedules for AML)
- Mortality rate was 43.5%; MVA showed that dyspnoea, severe Covid-19, ICU admission, NEU <1000/mcL, and D-dimer levels >500 ng/mL were associated with higher mortality

Type of AML treatment at SARS-CoV-2 diagnosis				
AML therapy administered at SARS-CoV-2 diagnosis (NA = 8)	Yes	35 (49.3)	36 (50.7)	.301
	No	11 (37.9)	18 (62.1)	
Induction chemotherapy (NA = 17)	Yes	13 (56.5)	10 (43.5)	.231
	No	26 (41.9)	36 (58.1)	
Consolidation chemotherapy (NA = 16)	Yes	5 (35.7)	9 (64.3)	.429
	No	34 (47.2)	38 (52.8)	
Maintenance (NA = 17)	Yes	0 (0)	1 (100)	.354
	No	39 (46.4)	45 (53.6)	
Hypomethylating agents (NA = 16)	Yes	7 (43.8)	9 (56.2)	.887
	No	32 (45.7)	38 (54.3)	
FLT3 inhibitors (NA = 17)	Yes	2 (50.0)	2 (50.0)	.827
	No	36 (44.4)	45 (55.6)	
Venetoclax (NA = 16)	Yes	0 (0)	3 (100)	.117
	No	38 (45.8)	45 (54.2)	
Clinical trial (NA = 17)	Yes	8 (53.3)	7 (46.7)	.459
	No	30 (42.9)	40 (57.1)	
High intensity regimen (NA = 16)	Yes	16 (50.0)	16 (50.0)	.505
	No	23 (42.6)	31 (57.4)	

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

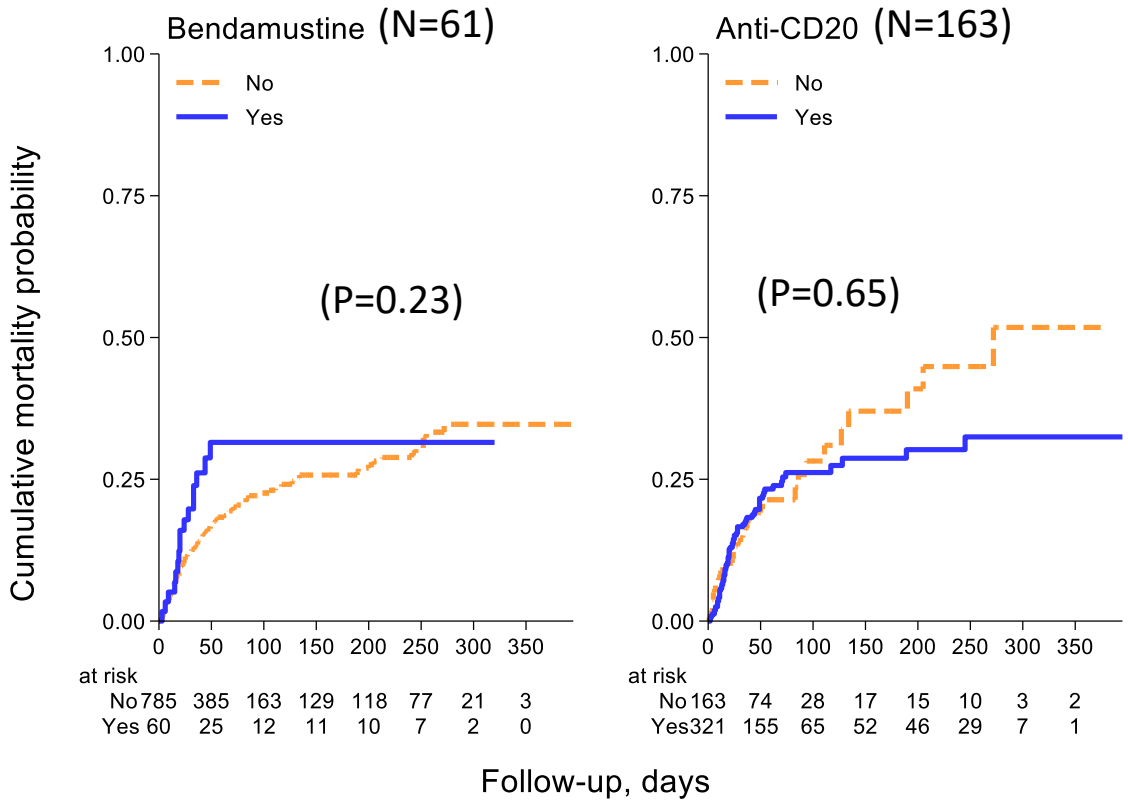
Chronic lymphocitic leukemia and Covid-19 (US, UK, Spain data)

- N= 198 patients diagnosed with symptomatic Covid-19
- Case fatality rate was 33% (25% still admitted)
- Watch and wait (39%) and treated cohorts (BTKi; n=68/90, 76%) had similar rates of admission (89% vs. 90%), ICU admission (35% vs. 36%), intubation (33% vs. 25%), and mortality (37% vs. 32%)
- BTKi did not impact survival (case fatality rate: 34% vs. 35%)

Mato et al Blood. 2020 Jul 20

Lymphoma and Covid-19

- N=856 (outpatient=388; hosp.=468)
- Case fatality of admitted vs. not admitted was 33.4% and 3.8%
- Predictors of worse survival: age >65 years-old, male gender, LYN< 650 $x10^9$/L, and PLT <100 $x10^9$/L
- The longer the time between diagnosis and Covid-19, the better the survival



Visco et al. Blood Adv. 2021 Oct 13:bloodadvances.2021005691.

Multiple myeloma and Covid-19 (IMM Society Data)

- N=650
- All hospitalized MM patients [36% recently diagnosed (2019-2020)]; 54% were receiving first-line therapy
- 33% have died
- In univariate, neither history of SCT (anytime), nor other anti-MM treatments were associated with outcomes
- Multivariate analysis found that only age, high-risk MM, renal disease, and suboptimal MM control remained independent predictors of adverse outcome with Covid-19 infection

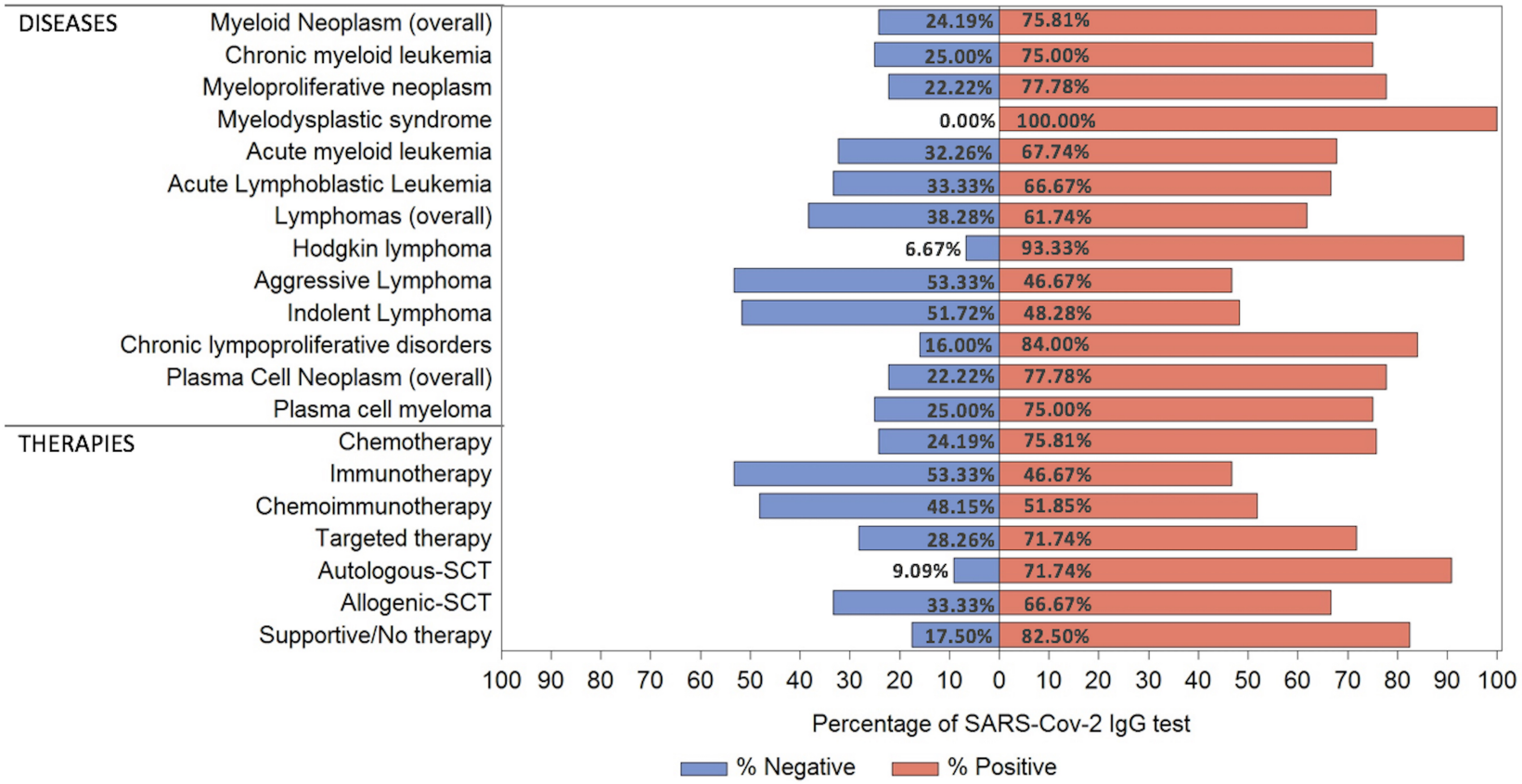
Chari et al, Blood 2020 Nov 6

Stem cell transplant and Covid-19 (CIBMTR data)

- N= 318
- Median time from HSCT to Covid-19 was 17/23 months for allo/auto HSCT
- 18% of allo-HSCT were on immunosuppression within 6 months
- Mild in 49%; severe with mechanical ventilation in 15%-13% of allo/auto
- 30d overall survival was 68% for allo-HSCT and 67% for auto-HSCT
- Age >50 years, male sex, development of Covid-19 within 12 months of HSCT were associated with a higher risk of mortality among allo-HSCT
- Disease indication of lymphoma was associated with a higher risk of mortality compared with plasma cell disorder or myeloma in auto-HSCT

Sharma et al. Lancet Haematology 2021

Patterns of seroconversion for SARS-CoV-2 IgG after Covid-19 in HM



Sweden study on 17 CLL

- T cell immunity against SARS-CoV-2 by IFN-gamma ELISpot assay
- 14 (82%) were positive
- Positive T cell assay was paralleled by seroconversion

Passamonti et al. Br J Haematol. 2021 Jul 16:10.1111/bjh.17704. Blixt et al. Leukemia. 2021 Sep 25 : 1–6.

Antibody response to Covid-19 vaccination in HM: a systematic review and meta-analysis (I)

- 43 studies comprising 10416 adult patients with HMs
- The pooled response for HM was 65% (95% CI, 60-70%), *vs.* 95% (95% CI, 0.92-0.97) for solid cancers and 98% (95% CI, 96-99%) for healthy controls
- The pooled response was:
  - 51% (95% CI, 41-61%) for CLL
  - 65% (95% CI, 49-78%) for aggressive NHL
  - 65% (95% CI, 49-79%) for indolent NHL
  - 76% (95% CI, 65-83%) for MM
  - 78% (95% CI, 60-89%) for MPNs
  - 94% (95% CI, 86-98%) for HL

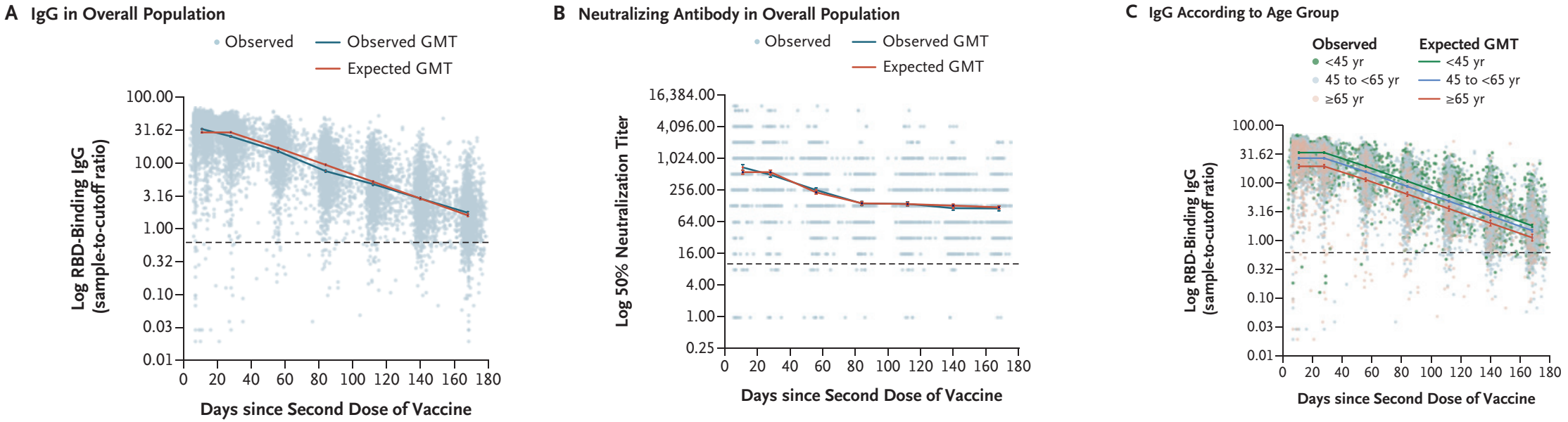
Gagelmann et al., submitted 2021

Antibody response to Covid-19 vaccination in HM: a systematic review and meta-analysis (II)

- Patients in remission and with Covid-19 before vaccination showed significantly higher responses
- Markedly low pooled response was identified for
  - Active treatment (35%)
  - Anti-CD20 therapy ≤1 year (15%)
  - Bruton kinase inhibition (23%)
  - Venetoclax (26%)
  - Ruxolitinib (41%)
  - Chimeric antigen receptor T-cell therapy (47%)
  - Allo and auto HSCT (82% and 83%)

Gagelmann et al., submitted 2021

Waning immune humoral response to BNT162b2 Covid-19 vaccine

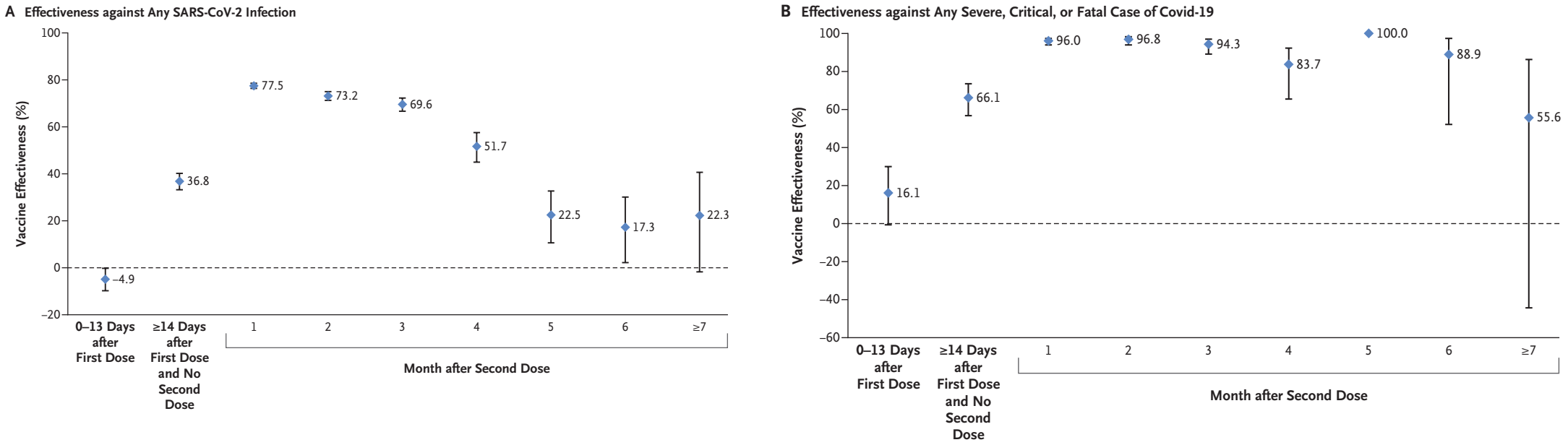


- Patients on immunosuppression had decreases in the IgG and neutralizing Ab levels of 65% and 70%, respectively, vs. immunocompetent ones

Levin et al. N Engl J Med. 2021 Oct 6;NEJMoa2114583

Effectiveness of the BNT162b2 vaccine over time

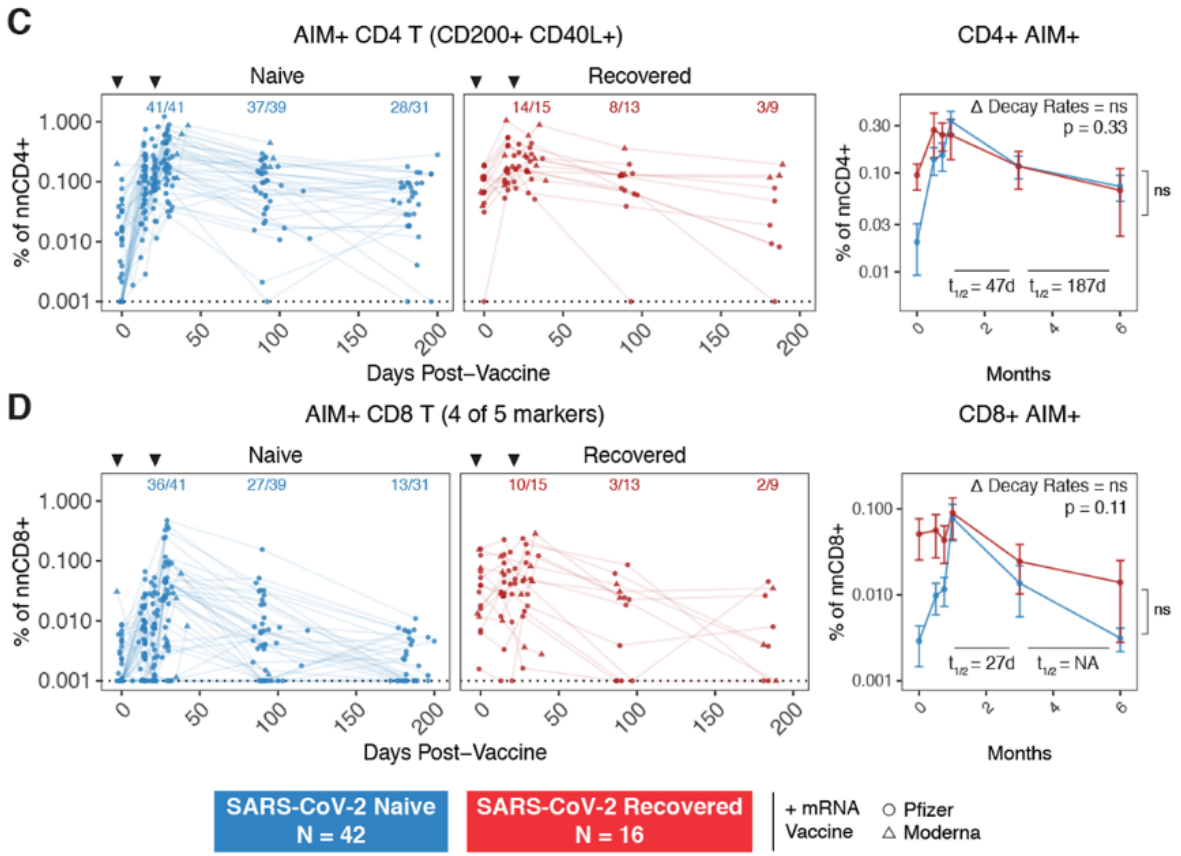
Qatar nationwide, digital health information platform, 907,763 completed the two-dose regimen



- Unlike effectiveness against infection, effectiveness against hospitalization and death did not decline over time

Chemaitelly et al N Engl J Med. 2021 Oct 6:NEJMoa2114114.

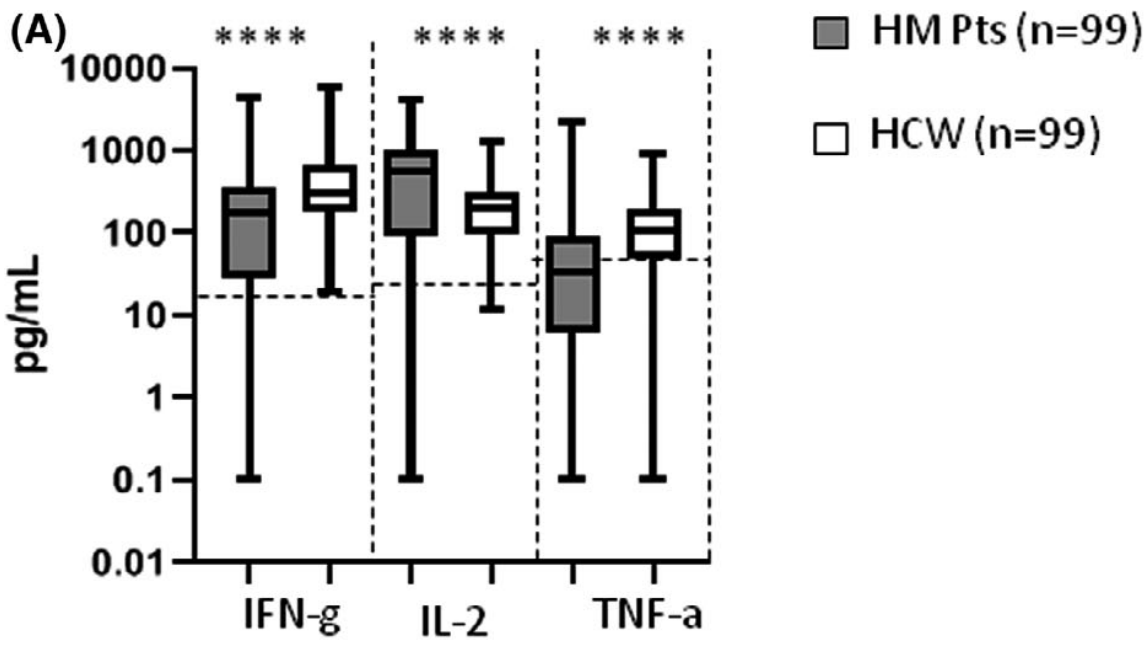
Durable immune memory to SARS-CoV-2 by mRNA vaccines



- Vaccines generated functional memory B cells that increased from 3-6 months post-vaccination, with the majority of these cells cross-binding the Alpha, Beta, and Delta variants
- Recall responses to vaccination in individuals with pre-existing immunity primarily increased antibody levels without substantially altering antibody decay rates

Goel et al. Science. 2021 Oct 14;eabm0829.

T-cell-mediated immune response in 99 lymphoid neoplasms



- 49% were seropositive after vaccination
- T-cell immune response was detectable in 98% and 74% of seropositive and seronegative patients, respectively.
- 13% were defined as “double negative”

Marasco et al. Br J Haematol. 2021 Oct 14.

Effectiveness of the BNT162b2mRNA Covid-19 vaccine in HMs

- 32,156 individuals with HM, followed from D7 to D43 post 2nd vaccine dose
- Vaccinated HM vs. vaccinated controls had a higher incidence of :
  - Documented Covid-19 infections (RR, 1.60): 106 (0.3% of total HM) *vs.* 54
  - Symptomatic disease (RR, 1.72)
  - Covid-19-related hospital admissions (RR, 3.13)
  - Severe Covid-19 (RR, 2.27)
  - Covid-19-related death (RR, 1.66, n.s.): 23 (21%) *vs.* 16
- Restriction of the analysis to those with actively treated HMs increased the RR

Mittelman et al. Blood. 2021 Oct 18:blood.2021013768.

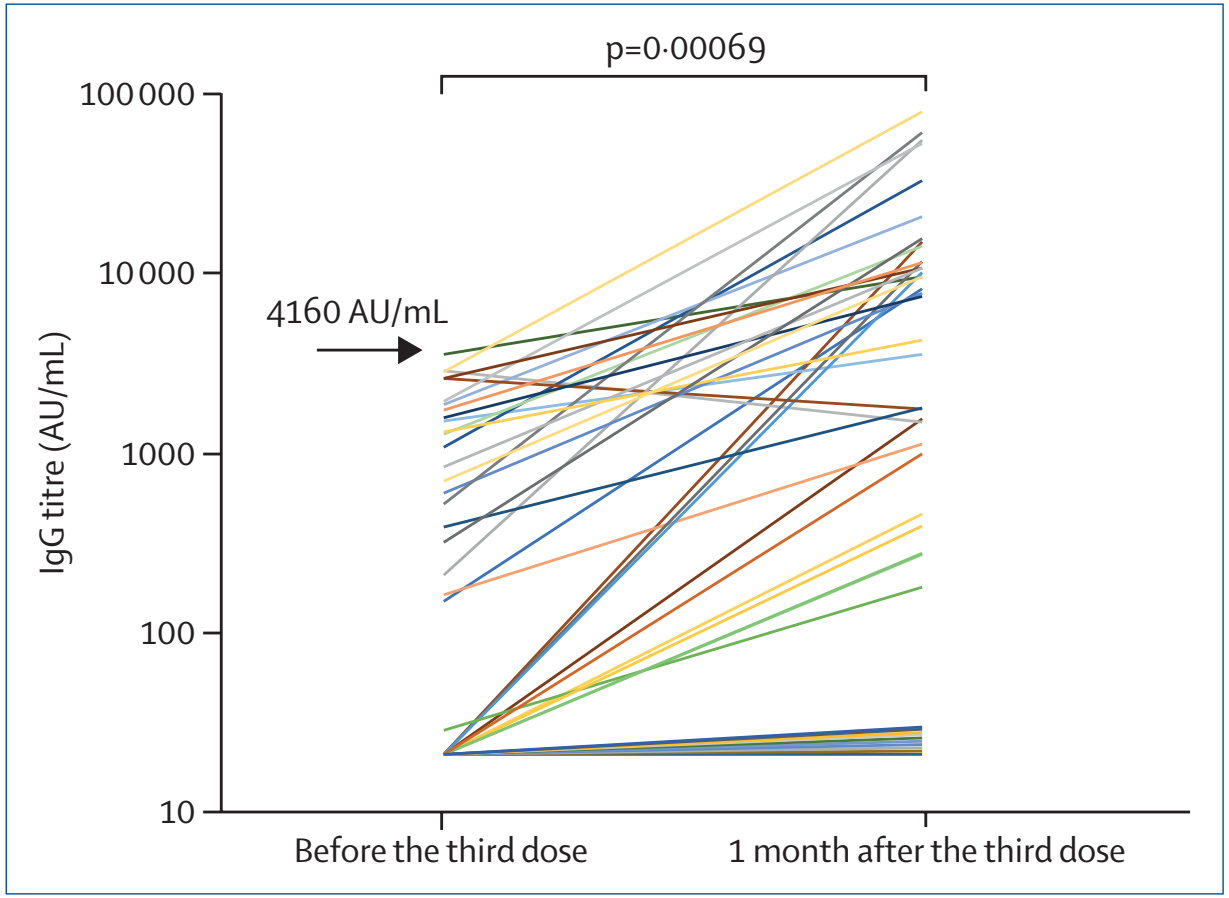
Covid-19 post vaccine in the EPICOVIDEHA project

- 113 Covid-19 among partially or completely vaccinated patients with HM
- 70% received an mRNA vaccine
- 79 (60.4%) patients had a severe or critical infection
- The overall mortality rate was 12.4%
- In 40 with post-vaccine IgG levels against SARS-CoV-2 spike protein tested, 13 (32.5%) presented an antibody response to vaccine, whereas the remaining 27 (67.5%) were considered no responders

Pagano et al, Blood, accepted for pub

Antibody response after booster BNT162b2 dose in HSCT recipients

- N=42 patients, vaccinated in the first year after HSCT 52%
- The third dose led to a significant increase in anti-SARS-CoV-2 antibodies with IgG (S-RBD) increasing from 737 AU/mL to 11.099 AU/mL
- Factors favoring high response after the third dose: circulating B-cell count >0·25 g/L and high IgG after second dose



Redjoul et al, Lancet Haematol. 2021 Sep 3

Booster dose in lymphoid neoplasms

- 49 fully vaccinated B cell neoplasms, 38 seronegative before booster
  - 21 seroconverted after booster
- Anti-CD 20 treated
  - Among 21 patients who completed, 7 seroconverted
  - Most of those ongoing failed to seroconvert
- BTKi treated
  - 4 seroconverted: (2 discontinued, 1 dose reduced, 1 ongoing)

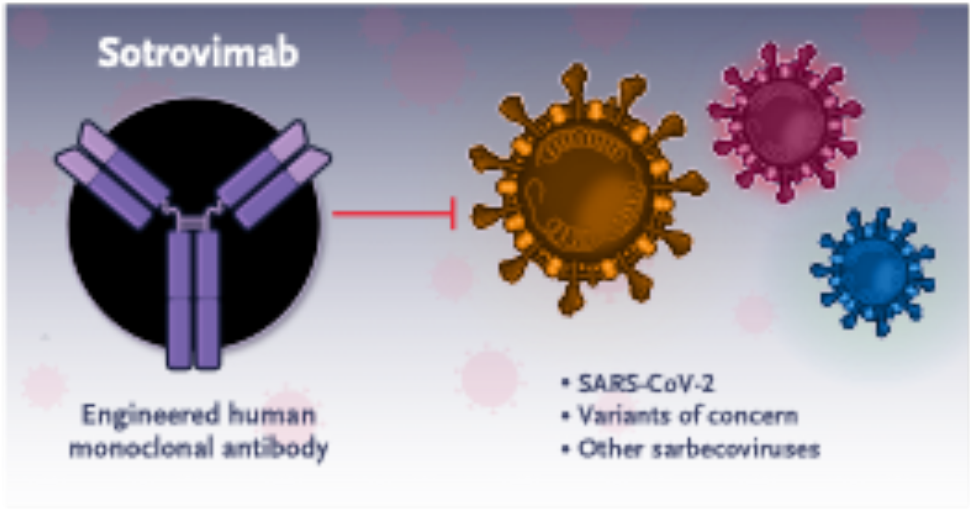
Greenberger et al. Cancer Cell. 2021 Oct 11;39(10):1297-1299.

MonoAb treatments of Covid-19: network meta-analysis

- Random effects bayesian meta-analysis, by GRADE approach
- Pts with non-severe Covid-19 receiving MonoAb had lower risk of hospitalization vs. PBO
  - casirivimab-imdevimab OR 0.29; RD −4.2% (moderate certainty)
  - bamlanivimab OR 0.24; RD −4.1% (low certainty)
  - bamlanivimab-etesevimab OR 0.31; RD −3.8% (low certainty)
  - sotrovimab (OR 0.17 (0.04 to 0.57); RD −4.8% (low certainty)
- No other intervention had any meaningful effect on mortality, mechanical ventilation, time to symptom resolution, time to/viral clearance at 7 days
- No intervention, including antiviral antibodies, had an important impact on any outcome in patients with severe or critical covid-19

Siemieniuk et a. BMJ 2021;374:n2231

Early treatment for covid-19 with SARS-Cov-2 neutralizing antibody Sotrovimab in high risk patients



Among high-risk outpatients with mild-to-moderate Covid-19, a single infusion of the monoclonal antibody sotrovimab lowered the risk of disease progression without an increase in adverse events

Primary Outcome: Hospitalization for >24 Hours or Death		
Outcome	Sotrovimab N=291	Placebo N=292
Hospitalization for any cause through day 29	3	21
Death from any cause through day 29	0	1

Adverse Events (Safety Analysis Population)		
Event	Sotrovimab N=430	Placebo N=438
Any adverse event	73	85
Any serious adverse event	7	26
Any infusion-related reaction	6	5

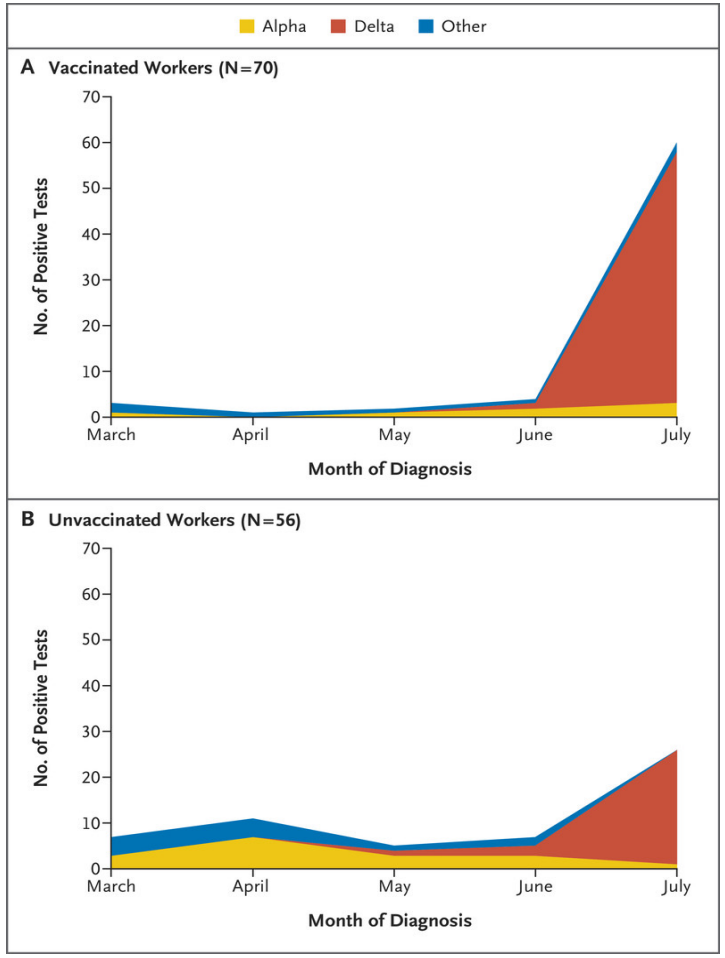
Gupta et al NEJM, this morning

Molnupiravir is effective in suppressing replication of SARS-CoV-2: Double-blind, randomized, placebo-controlled, Phase 2 study on 175 patients

- Participants were randomized if they had signs or symptoms of Covid-19 within 7 days, and a positive SARS-CoV-2 RT-PCR within 4 days of enrolment
- Nasopharyngeal swabs at enrolment, day 3, and day 5 for SARS-CoV-2 infectivity
- 67 had a positive SARS-CoV-2 culture at enrolment (52 on active and 26 on placebo)
- Among these:
  - DAY 3 positive viral culture was 20% on molnupiravir and 28% on placebo ($p = 0.56$)
  - DAY 5 positive viral culture was 0% on molnupiravir and 24% on placebo ($p = 0.001$)

Painter et a. Conference on Retroviruses and Opportunistic Infections, March 6, 2021:777

Resurgence of SARS-CoV-2 infection in a highly vaccinated cohort



The dramatic change in vaccine effectiveness from June to July is likely to be due to both:

- the emergence of the delta variant and waning immunity over time
- the end of masking requirements in California and the resulting greater risk of exposure in the community

Keehner et al, N Engl J Med. 2021 Sep 30;385(14):1330-1332

Conclusions

- Mortality of hospitalized patients with HM and symptomatic Covid-19 was 37%, 42-fold higher than HM mortality without Covid-19
- Older age, progressive disease status, AML, indolent and aggressive NHL, plasma cell neoplasms diagnosis and severe/critical Covid-19 were predictors of mortality
- Withholding specific effective treatments during the pandemic is not justified, especially as immunosuppressive effect of the treatments is long lasting: do not compromise HM care due to Covid-19 pandemic
- The humoral immune response to anti-SARS-CoV-2 vaccines in patients with HMs is heterogeneous, overall estimated at 65%; booster is suggested
- Proceed with available monoclonal antibodies in the case of Covid-19
- Continue practicing social distancing, wearing masks, handwashing

The ITA-HEMA-COV Investigators

Chiara Cattaneo
Luca Arcaini
Riccardo Bruna
Michele Cavo
Francesco Merli
Emanuele Angelucci
Mauro Krampera
Roberto Cairoli
Matteo Giovanni Della Porta
Nicola Fracchiolla
Marco Ladetto
Carlo Gambacorti Passerini
Marco Salvini
Monia Marchetti
Roberto Lemoli
Alfredo Molteni
Alessandro Busca
Antonio Cuneo
Alessandra Romano
Nicola Giuliani

Sara Galimberti
Alessandro Corso
Alessandro Morotti
Brunangelo Falini
Atto Billio
Filippo Gherlinzoni
Giuseppe Visani
Maria Chiara Tisi
Agostino Tafuri
Patrizia Tosi
Francesco Lanza
Massimo Massaia
Mauro Turrini
Felicetto Ferrara
Carmela Gurrieri
Daniele Vallisa
Maurizio Martelli
Enrico Derenzini
Attilio Guarini
Annarita Conconi
Annarosa Cuccaro

Laura Cudillo
Domenico Russo
Fabrizio Ciambelli
Anna Maria Scattolin
Mario Luppi
Carmine Selleri
Elettra Ortu La Barbera
Celestino Ferrandina
Nicola Di Renzo
Attilio Olivieri
Monica Bocchia
Massimo Gentile
Francesco Marchesi
Pellegrino Musto
Augusto Bramante Federici
Anna Candoni
Adriano Venditti
Carmen Fava
Antonio Pinto
Piero Gallieni

Luigi Rigacci
Daniele Armiento
Fabrizio Pane
Margherita Oberti
Patrizia Zappasodi
Patrizia Zappasodi
Carlo Visco
Matteo Franchi
Paolo Antonio Grossi
Lorenza Bertù
Giovanni Corrao
Livio Pagano
Paolo Corradini