COVID19 and Vaccines: Considerations for Patient Care and Clinical Trials

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Disclosures

Elizabeth Brem, MD

Consultancy: TG Therapeutics

Speakers Bureau: Pharmacyclics/Janssen, SeaGen, Morphosys/Incyte

Advisory Boards: Celgene, Karyopharm, Morphosys, Bayer, Sanofi, KiTE

I will not be discussing off label or investigational use.

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Are things getting better?

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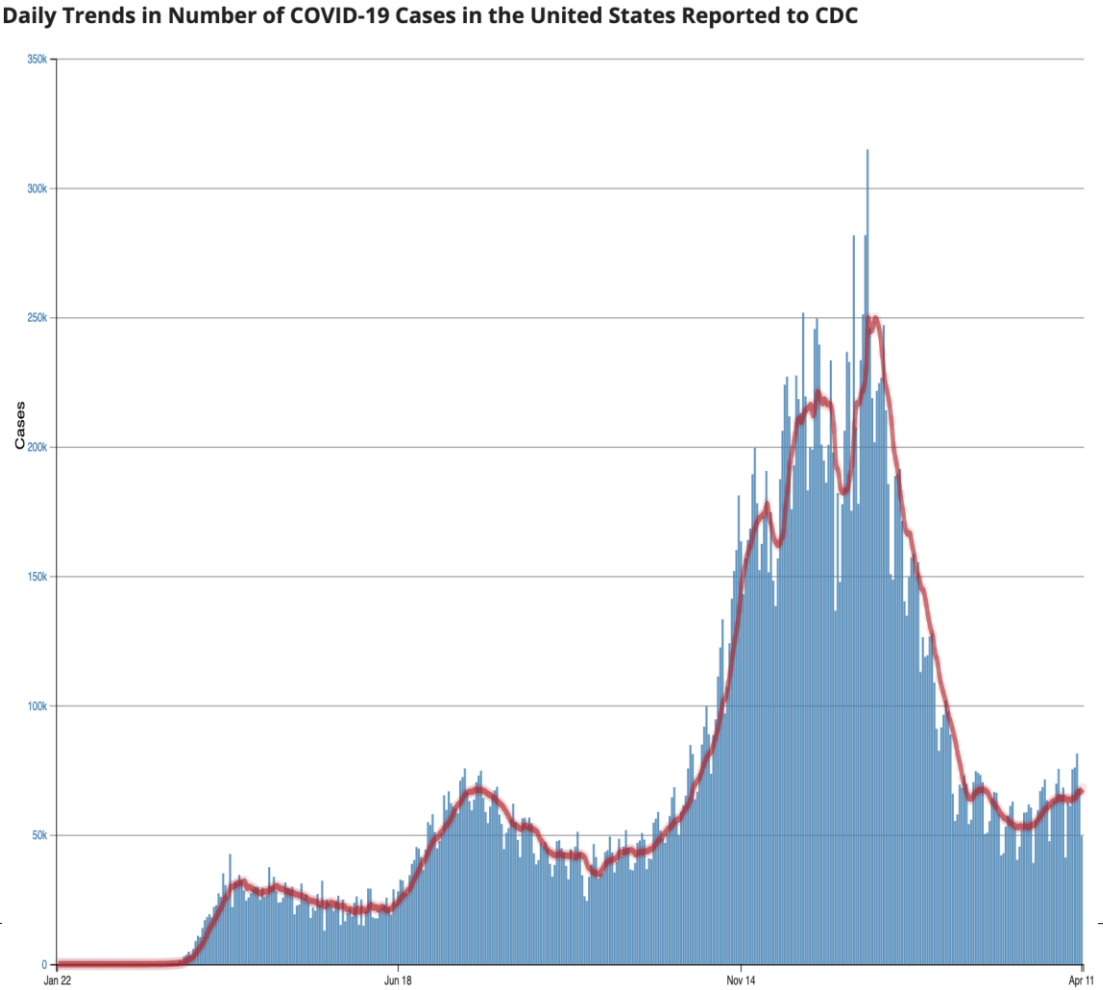
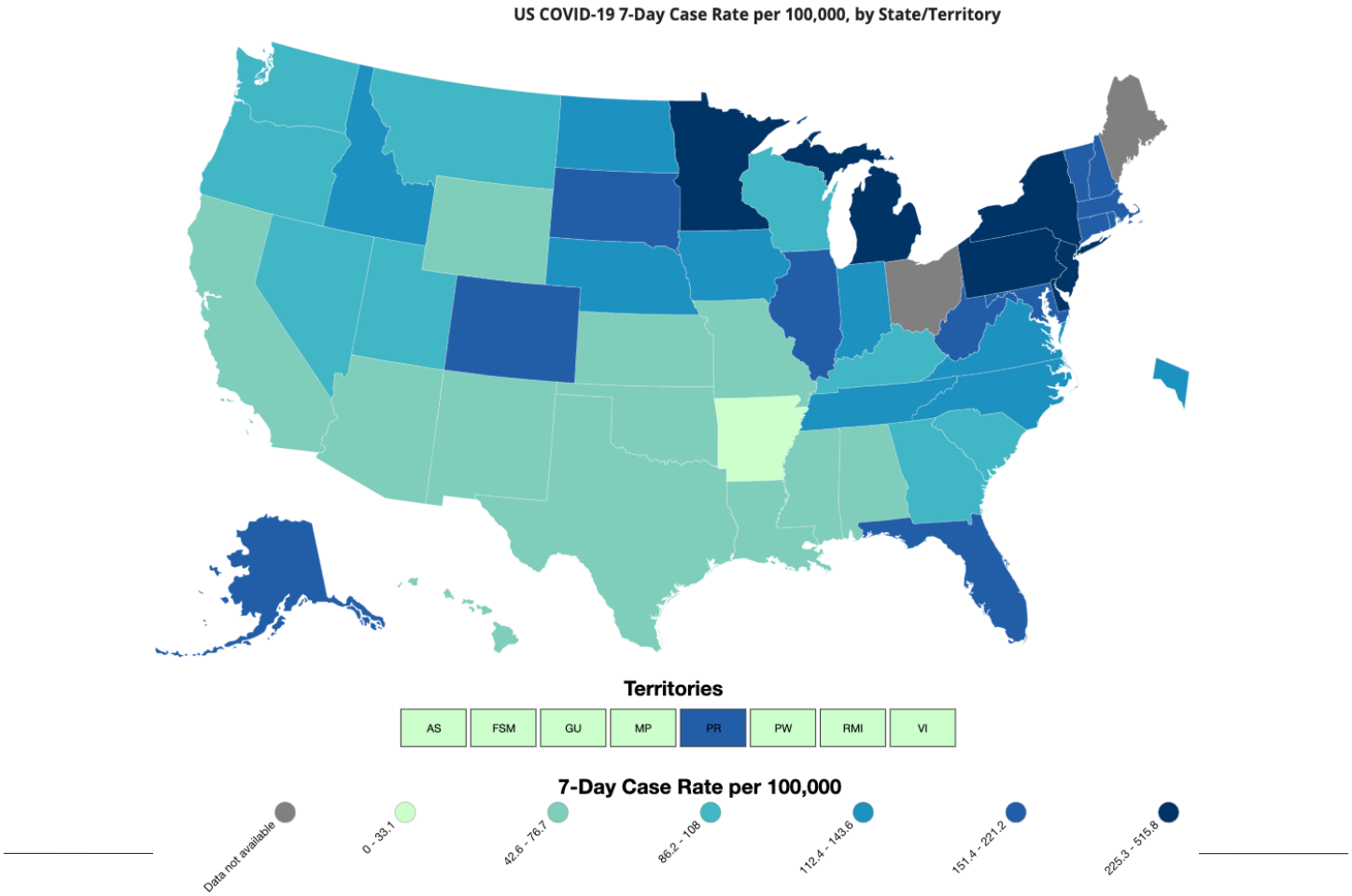
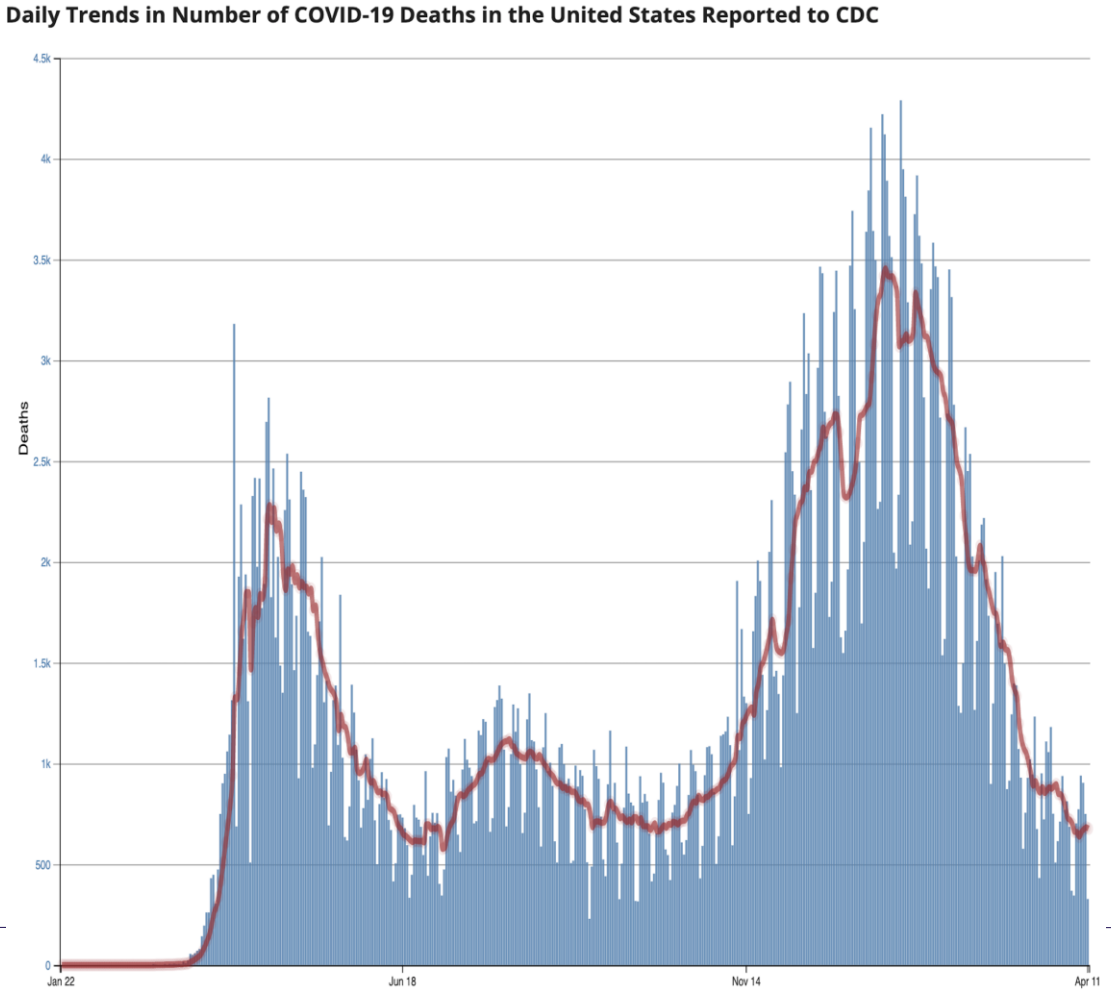


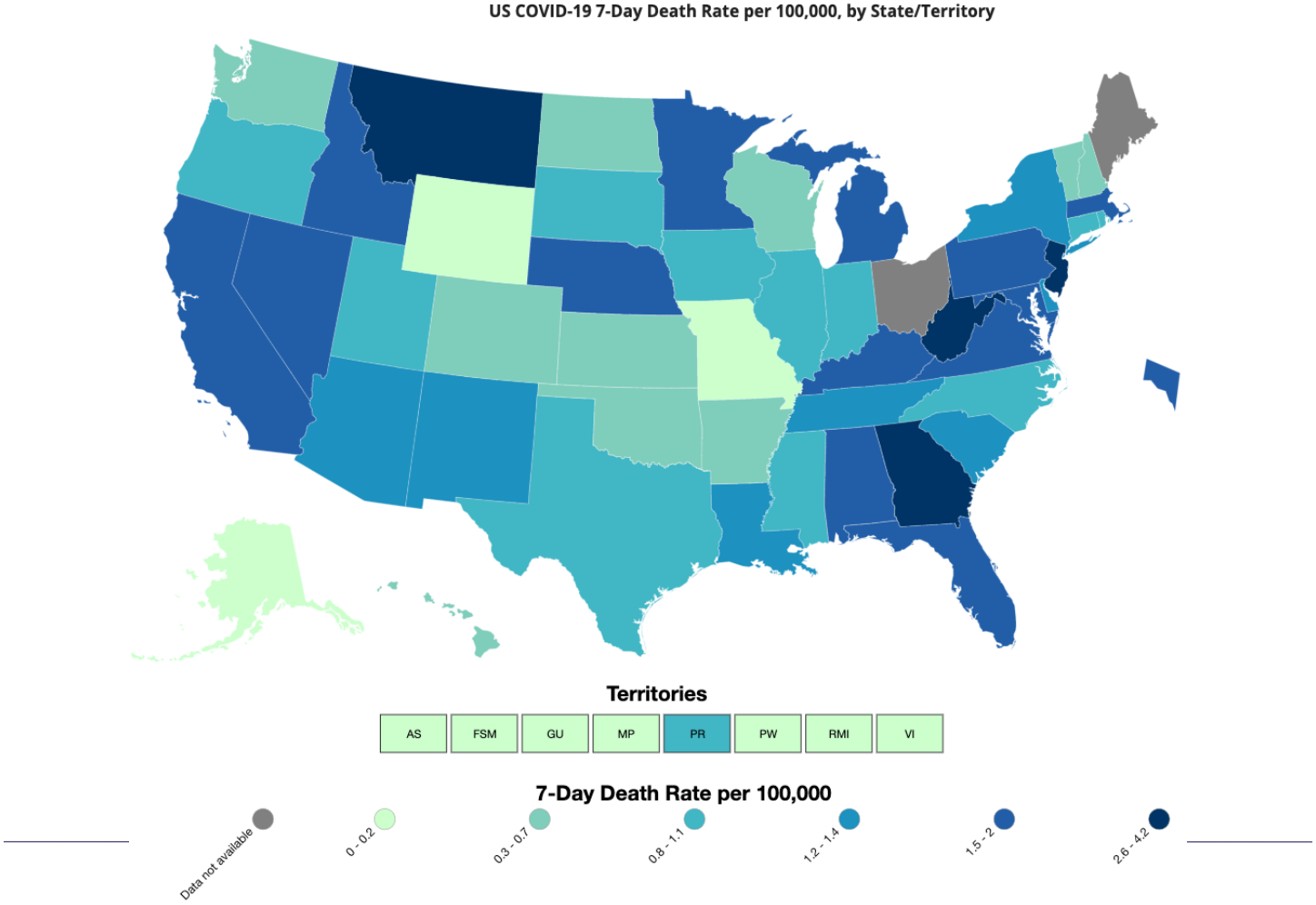
Source: CDC, data pulled 12 Apr 2021



Source: CDC, data pulled 12 Apr 2021



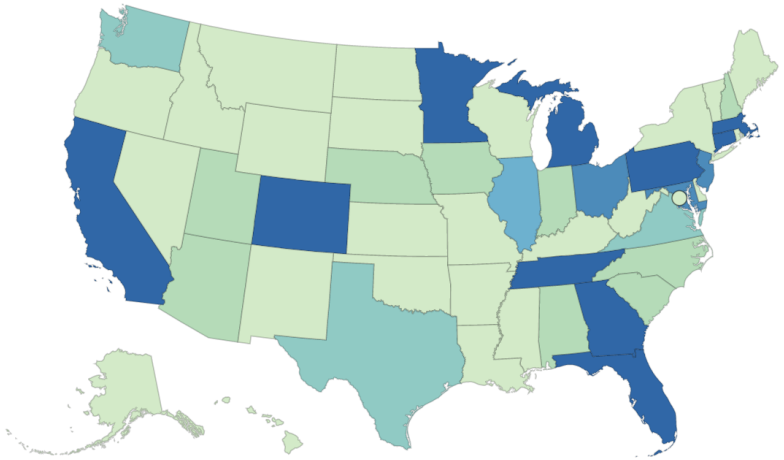
Source: CDC, data pulled 12 Apr 2021



Source: CDC, data pulled 12 Apr 2021

Variant	Reported Cases in US	Number of Jurisdictions Reporting
B.1.1.7	20915	52
B.1.351	453	36
P.1	497	31

Cases of Variants of Concern in the United States*†



Number of Cases

0 to 0
1 to 150
151 to 300
301 to 450
451 to 600
601 to 750
751+

Filters

Variant B.1.1.7

Territories AS GU MH FM MP PW PR VI

	Variant of Interest	Variant of Concern	Variant of High Consequence*
Predicted to be more contagious	Yes	Yes	Yes
Predicted to be more difficult to detect	Yes	Yes	Yes
Evidence of more cases or unique clusters of outbreaks	Yes	Yes	Yes
Evidence shows this variant might require alternative treatments and vaccines might be less effective	No	Yes	Yes
Evidence shows this variant spreads more easily from person to person	No	Yes	Yes
Evidence shows this variant causes more severe disease	No	Yes	Yes
Requires notification to the World Health Organization and CDC	No	Yes	Yes
Evidence shows significant diagnostic testing failures	No	No	Yes
Evidence shows that vaccines are significantly less effective at preventing severe illness	No	No	Yes
Treatment is significantly less effective	No	No	Yes

Variants may have one or more of the listed attributes

*none at this time

Total Vaccine Doses

Delivered	237,796,305
Administered	189,692,045

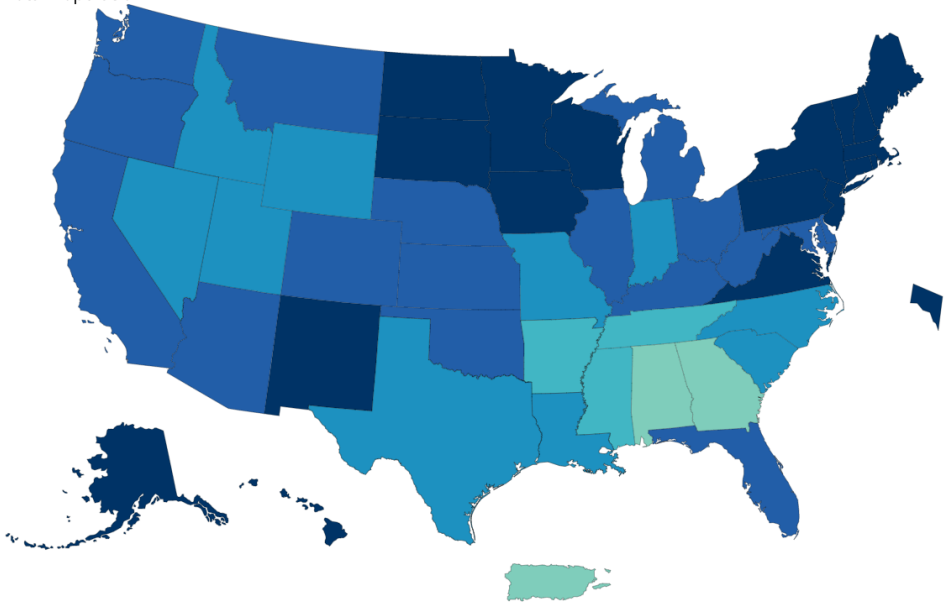
Learn more about the distribution of vaccines.

People Vaccinated	At Least One Dose	Fully Vaccinated
Total	120,848,490	74,066,085
% of Total Population	36.4%	22.3%
Population ≥ 18 Years of Age	119,979,114	73,871,042
% of Population ≥ 18 Years of Age	46.5%	28.6%
Population ≥ 65 Years of Age	43,140,269	33,899,103
% of Population ≥ 65 Years of Age	78.9%	62%

About these data

CDC |Data as of: Apr 12 2021 6:00am ET | Posted: Apr 12 2021 12:28PM ET

Total Doses Administered Reported to the CDC by State/Territory and for Select Federal Entities per 100,000 of the Total Population



Territories

GU AS RP FM MP MH VI

Federal Entities

BoP DoD IHS VHA

* Data for Federal Entities are presented here and are also incorporated into the respective jurisdictional totals

Total Doses Administered per 100,000

No Data 0 1 - 45,000 45,001 - 50,000 50,001 - 55,000 55,001 - 60,000 60,001+

Are lymphoma patients at higher risk of getting sick/dying from COVID19?

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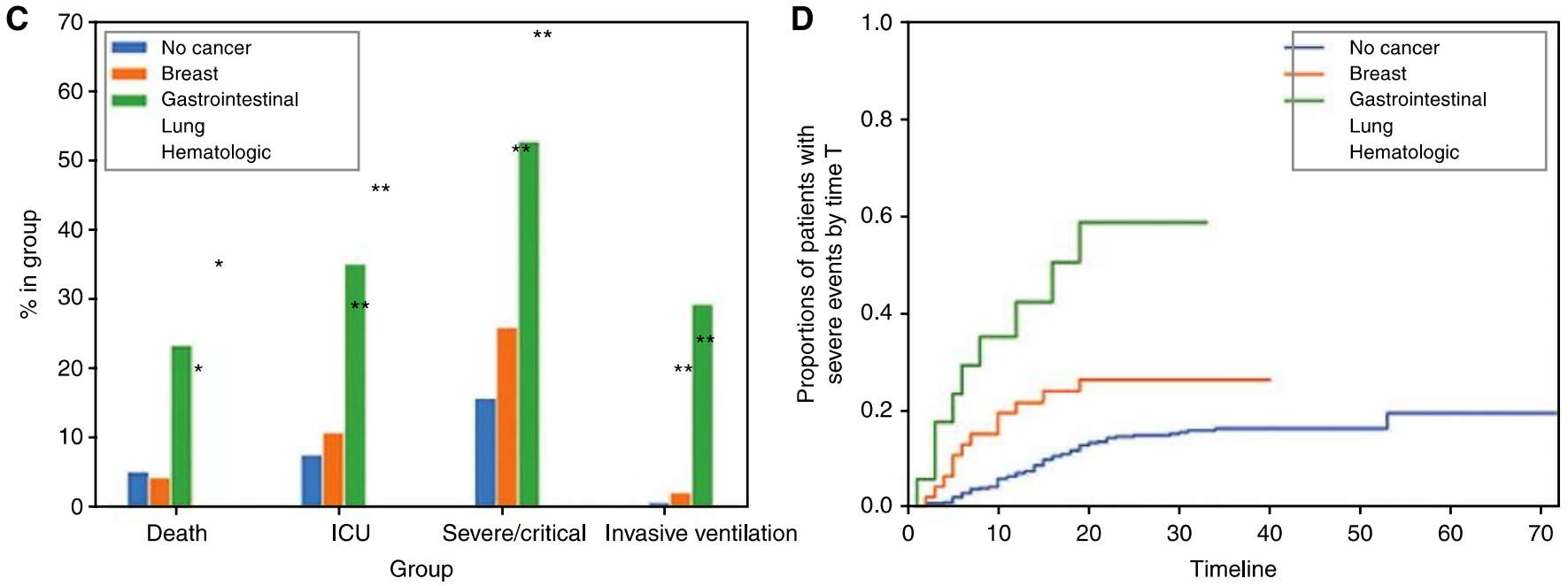
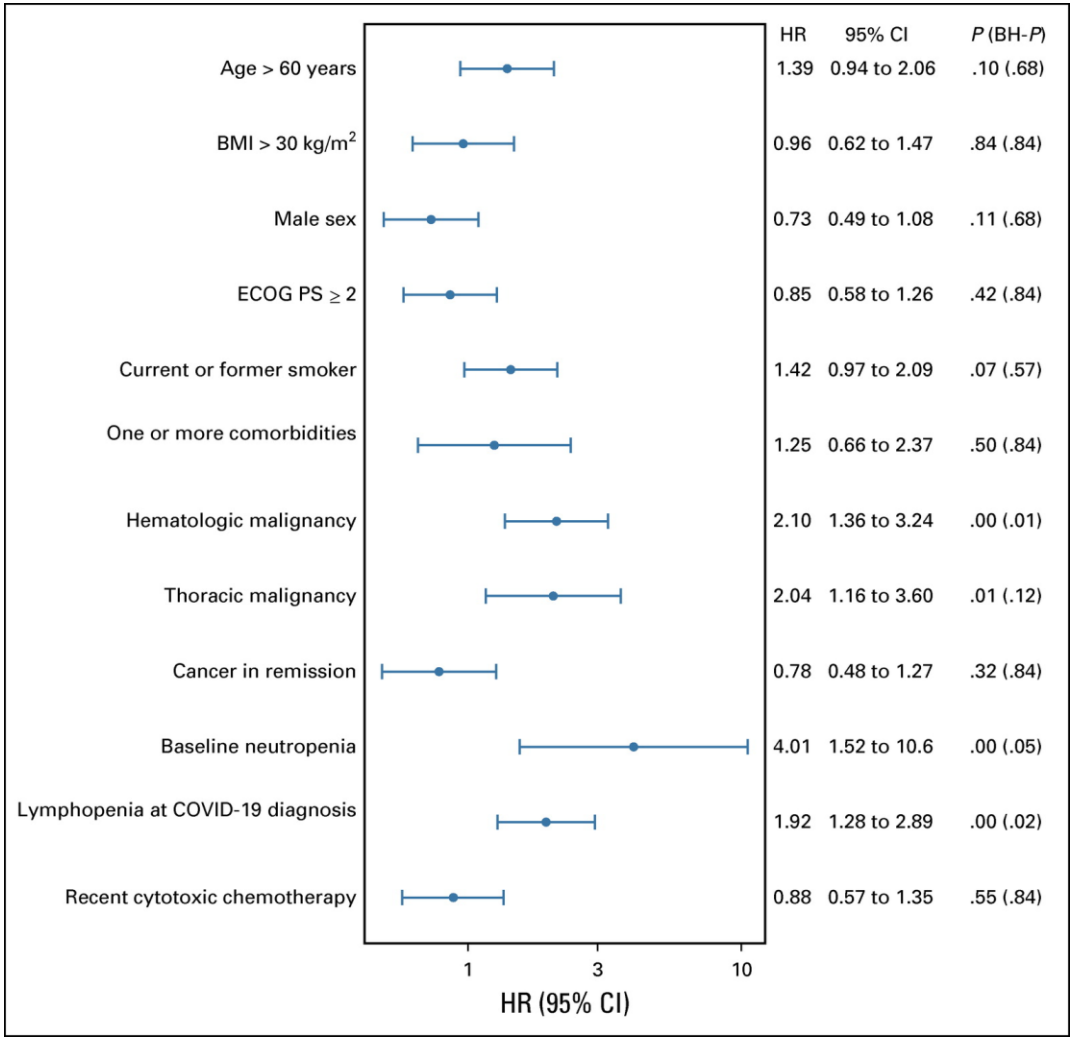
Probably.



Dai M et al. Cancer Discovery, 2020.



Risk Factors for Severe/Critical COVID19 Infection

Jee J et al, JCO. 2020.

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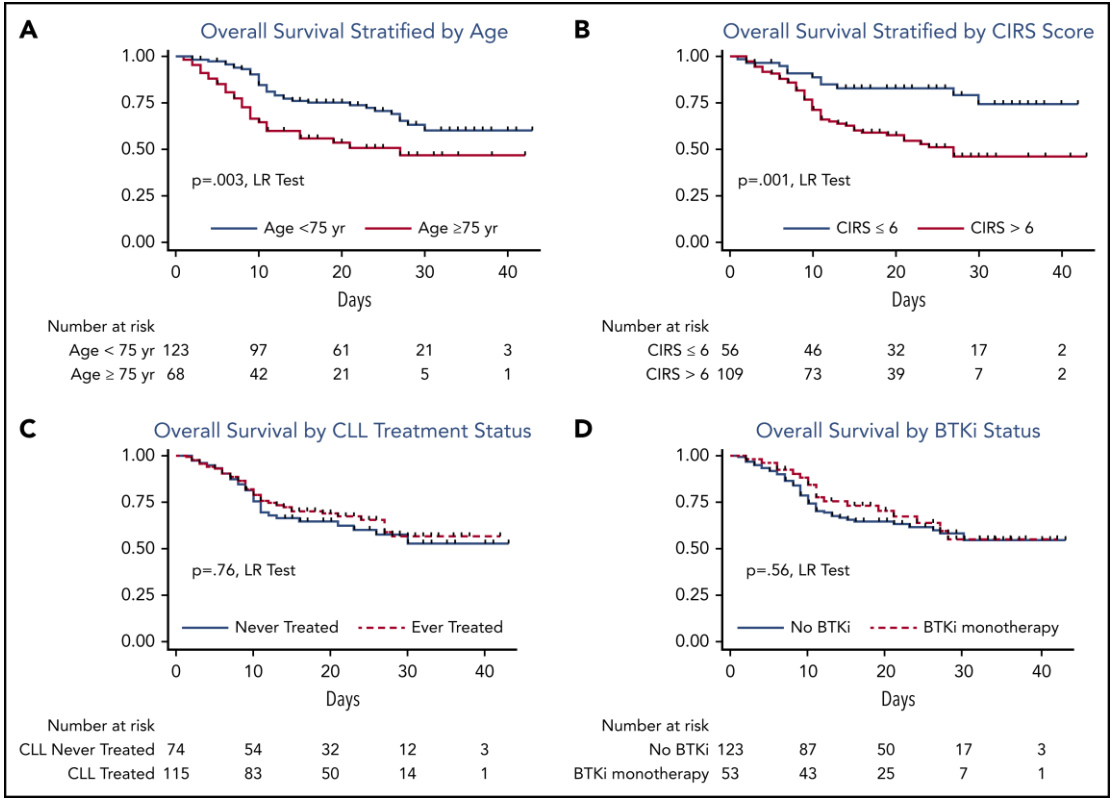
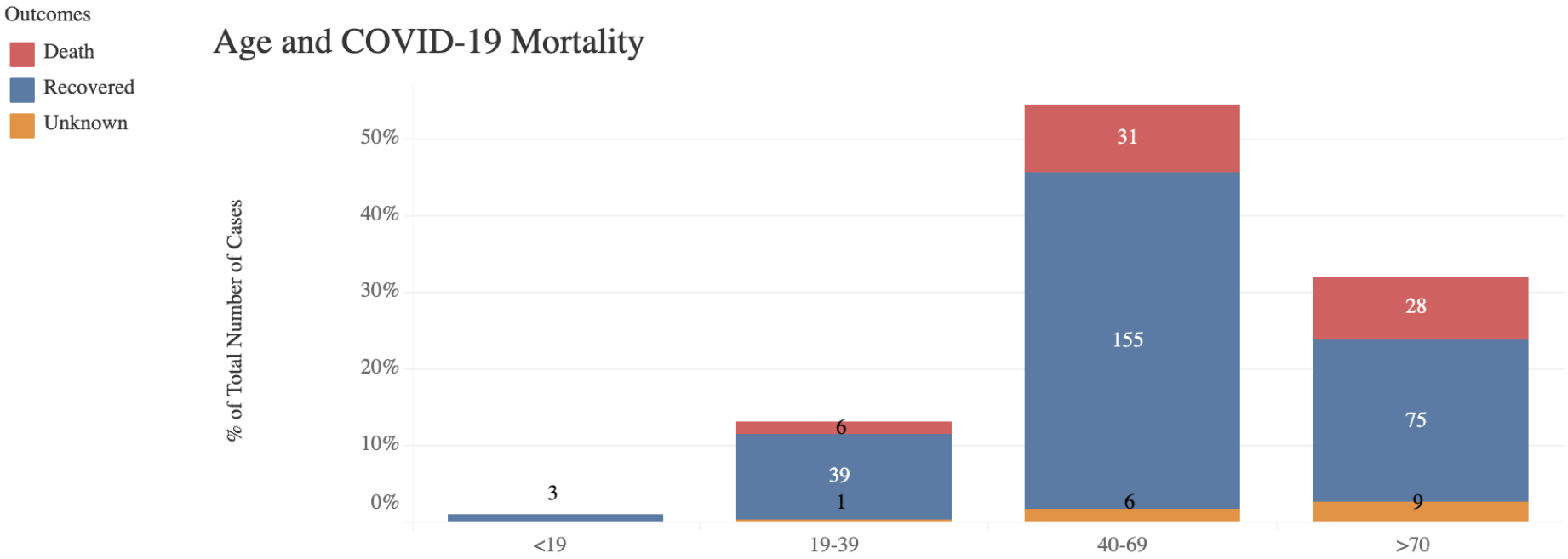
Outcomes of COVID-19 in patients with CLL: a multicenter international experience



Mato AR et al. Outcomes of COVID-19 in patients with CLL: a multicenter international experience, Blood, 2020, Figure 2.

ASH RESEARCH COLLABORATIVE
Accelerating Progress in Hematology

COVID-19 Registry



https://www.ashresearchcollaborative.org/s/covid-19-registry/data-summaries; accessed 12 Apr 2021

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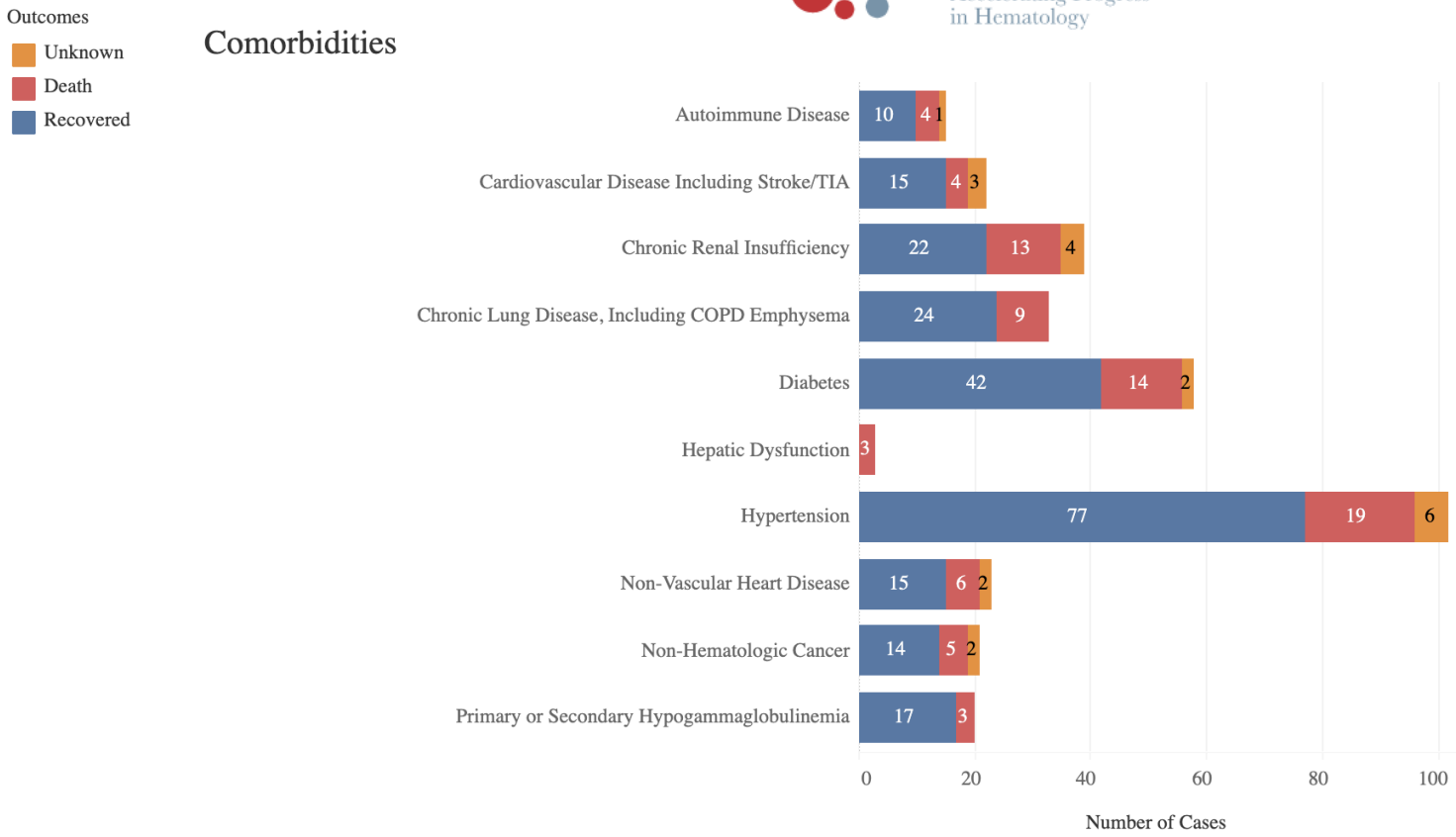
COVID-19 Registry

Comorbidities



https://www.ashresearchcollaborative.org/s/covid-19-registry/data-summaries; accessed 12 Apr 2021

Are lymphoma/CLL patients less likely to respond to a vaccine?

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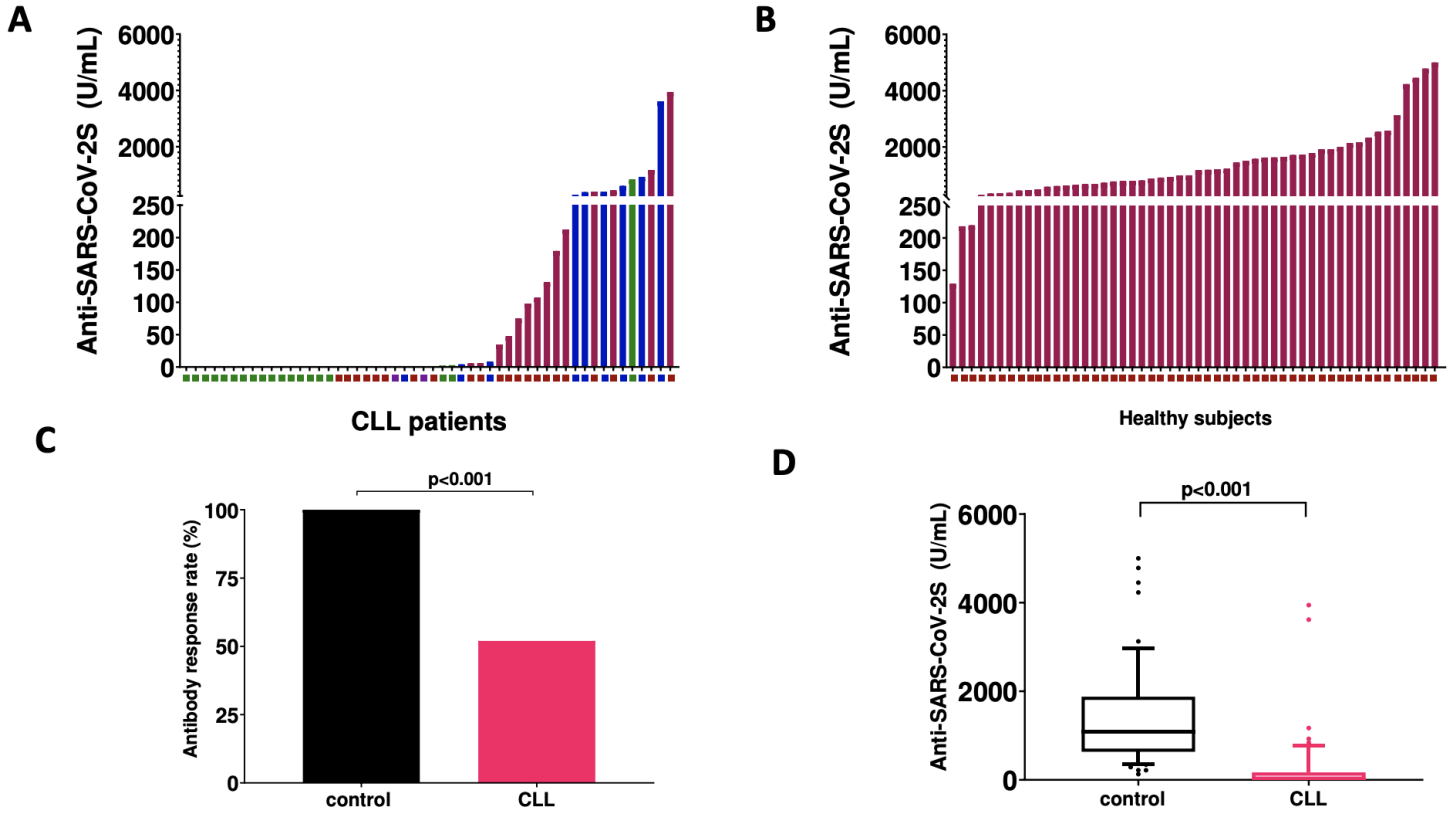
Probably.

The following immunocompromised patient populations could have attenuated or absent response to SARS-CoV-2 vaccines:

a. Primary a. Primary and secondary immunodeficiencies involving adaptive immunity
b. Splenectomy or functional asplenia [e.g., sickle cell disease]
c. B cell directed therapies (e.g., blocking monoclonal antibodies against CD20 or CD22, bispecific agents like blinatumomab, CD19 or CD22-directed chimeric antigen receptor T cell [CAR-T] therapies, Bruton tyrosine kinase [BTK] inhibitors)
d. T-cell-directed therapies (e.g., calcineurin inhibitors, antithymocyte globulin, alemtuzumab)
e. Many chemotherapy regimens
f. High-dose corticosteroids (≥20 mg per dose or >2 mg/kg/day daily prednisone or equivalent)
g. Hematopoietic cell transplantation (HCT), especially within the first three to six months after autologous HCT and often longer after allogeneic HCT
h. Underlying aberrant immunity (e.g., graft-vs.-host disease, graft rejection, absent or incomplete immune reconstitution, neutropenia ANC <500/µL, lymphopenia ALC <200/µL)

https://www.hematology.org/covid-19/ash-astct-covid-19-and-vaccines; accessed 12 Apr 2021

Figure 1.



Herishanu Y et al. Blood, 2021.

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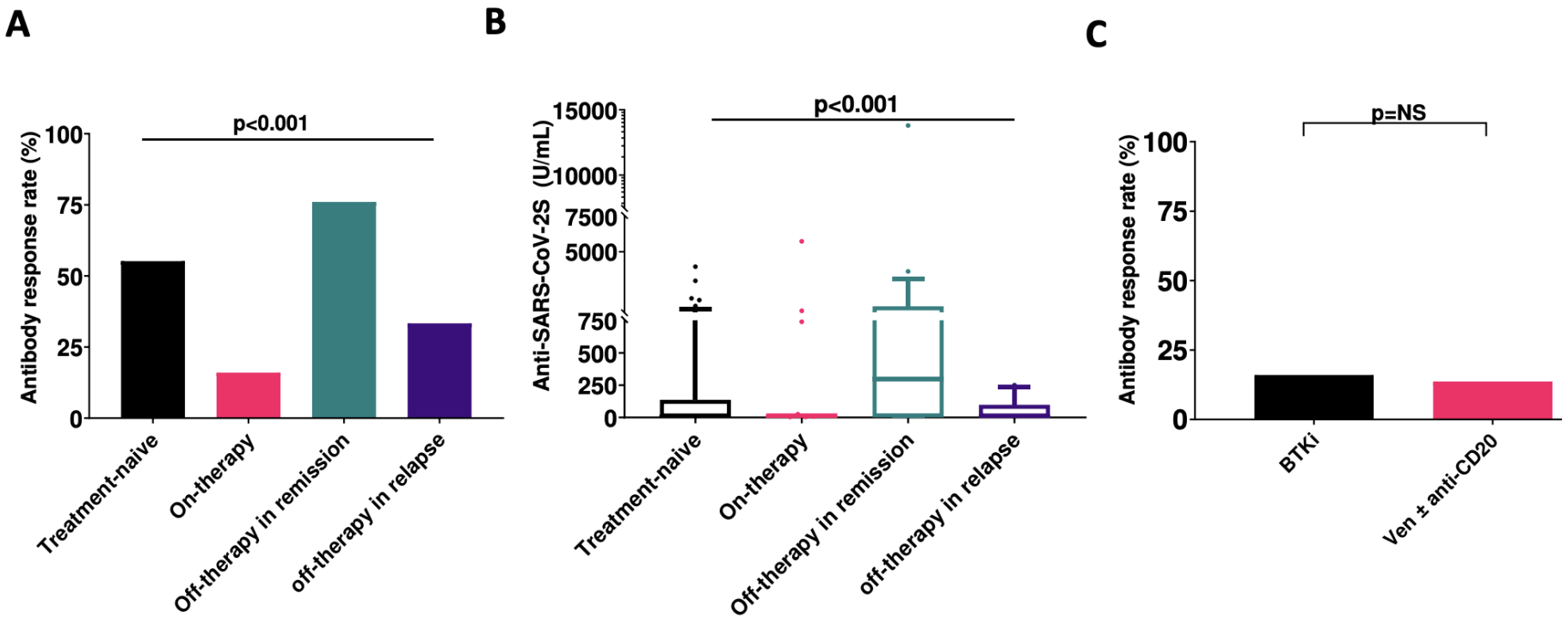
Figure 2.



Herishanu Y et al. Blood, 2021.

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So…when should patients get vaccinated?

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Very patient-dependent.

Vaccine Timing and Considerations

"If plans to proceed with the SARS-CoV-2 vaccine are made, vaccination is recommended **at least two to four weeks prior to the planned immunosuppressive therapy**, transplant, or splenectomy. **If the patient is receiving or has received immunosuppressive therapy, consider vaccination six months after the patient has been taken off therapy to increase the likelihood of developing immunity**."

"Whether or not an immunocompromised patient is known to have been previously infected with SARS-CoV-2 should not affect the decision of whether to vaccinate. Although some immunity is anticipated from experiencing a COVID-19 clinical infection, this immunity may be insufficient or wane, especially in immunocompromised hosts."

"Although measuring titers may eventually be helpful to assess response, more information is needed. Giving more inoculations or higher doses of an approved SARS-CoV-2 vaccine is not recommended at this time."

https://www.hematology.org/covid-19/ash-astct-covid-19-and-vaccines; accessed 12 Apr 2021

Vaccine Timing and Considerations

"Despite varied approaches to local allocation of vaccines among states and U.S. territories, **HCT and CAR T cell recipients should be amongst the first patients to receive vaccination**, when available, although data on vaccine safety and efficacy are not yet available within the HCT or CAR T cell recipient populations and the vaccine immune response is likely to be blunted compared to healthy individuals. However, despite the lack of data, the high level of protection afforded to those vaccinated in the clinical trials and overall safety of the vaccine in clinical trials and post-EUA experience, **the American Society of Transplantation and Cellular Therapy (ASTCT) and the American Society of Hematology (ASH) strongly support early access to vaccines for these vulnerable patients, along with their caregivers, family, and household contacts when and if vaccine supply permits."**

https://www.hematology.org/covid-19/ash-astct-covid-19-vaccination-for-hct-and-car-t-cell-recipients; accessed 12 Apr 2021

Vaccine Timing and Considerations

"Based on prior antigen-based vaccine trials in allogeneic HCT recipients, initiating vaccination series three months versus six months after transplantation did not affect induction of immunogenicity."

"**Based on the current evidence of high efficacy and safety in the general patient population, including individuals with underlying conditions, the current mRNA SARS-CoV-2 vaccines could be offered as early as three months to HCT and CAR T cell recipients to prevent infection and severe disease…At this time, no preference of vaccine formulation is recommended, and patients are encouraged to receive whichever formulation is available."**

https://www.hematology.org/covid-19/ash-astct-covid-19-vaccination-for-hct-and-car-t-cell-recipients; accessed 12 Apr 2021

NCCN Advisory Committee

Table 1. COVID-19 Vaccination Recommendations for Cancer Patients

Patients Treatment/Cancer Type	Timing[†,‡,¶]
Hematopoietic Cell Transplantation (HCT)/Cellular Therapy	
Allogeneic transplantation Autologous transplantation Cellular therapy (eg, CAR T-cell)	At least 3 months post-HCT/cellular therapy[a,b]
Hematologic Malignancies	
Receiving intensive cytotoxic chemotherapy (eg, cytarabine/anthracycline-based induction regimens for acute myeloid leukemia)	Delay until absolute neutrophil count (ANC) recovery[c]
Marrow failure from disease and/or therapy expected to have limited or no recovery	When vaccine available
Long-term maintenance therapy (eg, targeted agents for chronic lymphocytic leukemia or myeloproliferative neoplasms)	When vaccine available[c]

https://www.nccn.org/docs/default-source/covid-19/2021_covid-19_vaccination_guidance_v2-0.pdf

Vaccine Timing and Considerations

"Additionally, studies in allogeneic HCT recipients receiving influenza vaccination prior to transplantation had poor immunogenic responses. **At this time, transplant candidates should not be offered the COVID-19 vaccine prior to transplantation or CAR T cell therapy unless in the context of a research protocol."**

"Vaccinating stem cell donors prior to stem cell harvesting has not been shown to benefit HCT recipients in prior studies. It is also difficult and not feasible in cases of unrelated donors. Stem cell donors should not be offered the COVID-19 vaccine for the sole purpose of benefiting the HCT recipient unless under a research protocol. However, if the donor has been vaccinated, it may be desirable to wait at least two weeks after the second vaccine dose before stem cell donation (if possible) as it may provide some protective effect to the recipient."

https://www.hematology.org/covid-19/ash-astct-covid-19-vaccination-for-hct-and-car-t-cell-recipients; accessed 12 Apr 2021

Vaccine Timing and Considerations

"As the role of serologic testing postvaccination in HCT and CAR T cell recipients is not clear, we do not recommend routine testing with serology unless done under a research protocol."

"On the other hand, if serologic testing is desired by the patient or health care providers, we recommend testing for SARS-COV-2 antibodies against the spike protein anytime between 30 and 90 days after the second dose of the vaccine…we do not recommended testing for SARS-CoV-2 antibodies within four weeks of IVIG infusion due to possible false-positive results."

https://www.hematology.org/covid-19/ash-astct-covid-19-vaccination-for-hct-and-car-t-cell-recipients; accessed 12 Apr 2021

LYMPHOMA RESEARCH · FOUNDATION

Practical recommendations for physicians and patients

- Develop sensible and evidence-based patient and provider guidelines
  - — This should include directions and support for patients to retain records and information related to their inoculation
- Generate tables for general practitioners to guide vaccination around the timing of different treatments
  - — Encourage physicians to consult ASH and the comprehensive Memorial Sloan Kettering Cancer Center recommendation document
- Create guidelines for different community spread levels and different local vaccination levels
- Create discussion points to communicate during vaccination counseling
- Advocate for a sustained negative PCR as a test of cure for patients being treated for hematological malignancies

https://lymphoma.org/wp-content/uploads/2021/04/Proceedings-of-the-COVID-19-Vaccine-Panel_LRF-White-Paper_April-2021.pdf

What about monoclonal antibodies?

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"Efficacy of mRNA vaccines in HCT and CAR T cell recipients is unknown as clinical trials did not include these patient populations. However, if SARS-CoV-2 infection is acquired after receiving the COVID-19 vaccine, **these patients are still eligible for monoclonal antibodies under EUA guidance or convalescent plasma as part of treatment of COVID-19."**

"Immunocompromised patients less likely to be protected by vaccination and at higher risk for progression to severe disease would in theory be a target population for early administration of passive antibody therapies or CCP."

"Recent concern has arisen due to evidence for resistance of several increasingly prevalent SARS-CoV-2 viral variants to the available monoclonal antibodies. The EUAs for these antibodies have been amended to reflect this new information. Polyclonal antibodies contained in CCP or generated by vaccine are less effective against variants carrying the E484K spike mutation but still show some activity. **There is concern that variants are arising and being selected for in immunocompromised patients being treated with CCP or antibody therapies.**"

https://www.hematology.org/covid-19/ash-astct-covid-19-vaccination-for-hct-and-car-t-cell-recipients; accessed 12 Apr 2021

https://www.hematology.org/covid-19/covid-19-and-convalescent-plasma; accessed 12 Apr 2021

Should care be different right now?

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Therapy

- Most patients should get/continue treatment

- Patients with indolent (slow growing) lymphomas might decide with their doctors to delay treatment or stop maintenance therapy

Therapy: HL

Are you changing your approach to initial therapy?

Overall, the treatment approach for Hodgkin lymphoma has not yet been impacted significantly in the front-line setting. There are however instances in which there are multiple treatment alternatives with different toxicity profiles or requirements for hospital visits.

Are you changing therapies for patients who have already started treatment?

The experts have not yet modified treatment plans already underway but are giving greater consideration to the use of growth factor support, prophylactic antibiotics, and telemedicine visits on days when treatment is not scheduled.

Are you changing your approach to supportive care?

Some experts are recommending more routine use of G-CSF. To avoid increasing the risk of bleomycin pneumonitis, three to five days of filgrastim mid-cycle is used by some to eliminate severe neutropenia when treating with ABVD. Growth factor support is required when AAVD (Echelon-1) is prescribed and is recommended when treating older patients. Experts are commonly prescribing prophylactic antibiotics for neutropenic patients or those expected to become neutropenic.

https://hematology.org/covid-19/covid-19-and-hodgkin-lymphoma

Are you changing your treatment recommendations for relapsed/refractory disease?

Outpatient second line regimens such as gemcitabine-based treatment are being used more commonly rather than regimens that require hospitalization. Some centers are using brentuximab vedotin or PD1 antibodies (administered q4 weeks to reduce visits) when possible instead of chemotherapy and will consider consolidating responses to second line therapy with radiotherapy instead of an autologous peripheral blood stem cell transplant (PBSCT) especially in late relapses. Other centers are proceeding with autoPBSCT. Blood shortages are occurring in some regions. Whether patients who become infected with SARS-CoV-2 during treatment with checkpoint inhibitors have worse outcomes than patients with Hodgkin Lymphoma undergoing other treatments is unknown. Allogeneic stem cell transplant is not commonly used in Hodgkin Lymphoma, but would not be considered in the current situation.

Should patients with Hodgkin lymphoma receive a vaccine for SARS-CoV-2?

In general, it is considered safe and appropriate for patients with Hodgkin lymphoma to be vaccinated against SARS-CoV2. Specific to SARS-CoV-2, data regarding the safety and efficacy of vaccines in immunocompromised patients are not yet available. As a general statement, we recommend that patients with Hodgkin lymphoma receive a SARS-CoV-2 vaccine although they may not mount a robust immune response.

https://hematology.org/covid-19/covid-19-and-hodgkin-lymphoma

Therapy: Agressive NHL

Are you changing your approach to initial therapy?
R-CHOP continues to be the standard of care for diffuse, large B-cell lymphoma, with DA-EPOCH-R indicated only for double-hit and primary mediastinal B-cell lymphomas. Whereas DA-EPOCH-R targets myelosuppression with dose escalation until there is neutropenia and/or thrombocytopenia, it is of necessity a more toxic regimen, and in most institutions requires hospitalization. Centers with the capacity to deliver this therapy on an outpatient basis are encouraging that approach. Others are weighing benefits and risks for the individual patient with double-hit or primary mediastinal B-cell. R-CHOP (or R-CHOP-14) +/- consolidative radiotherapy for some PMBCL patients is an alternative to DA-EPOCH-R but with the additional long-term risks associated with irradiation of the mediastinum.

For those who are at high risk for CNS involvement (CNS-IPI >5, testicular, renal/kidney involvement), high-dose methotrexate is recommended, the timing of which must be individualized. The optimal number of cycles is also unknown, but at least two are recommended. For patients receiving DA-EPOCH-R, high-dose methotrexate is not easily integrated into the program, and IT methotrexate is an alternative.

For limited stage disease, R-CHOP X 4 rather than combined modality therapy is recommended to reduce the number of hospital visits.

For those who tolerate the first dose of rituximab given intravenously, subcutaneous administration is an option going forward that reduces time spent in the clinic.

https://hematology.org/covid-19/covid-19-and-aggressive-lymphoma

Therapy: Indolent NHL

Are you changing your indications for therapy?

Given COVID-19, the threshold for initiating treatment should be high and watchful waiting should be the preferred strategy whenever possible. Treatment is recommended in symptomatic patients, but if the indication for therapy is borderline, (e.g. if the patient meets GELF criteria but is asymptomatic) treatment deferral and close monitoring with repeat imaging may be prudent. Treatment for asymptomatic patients with rituximab monotherapy is not recommended. Vaccination against SARS-CoV-2 is recommended prior to initiating treatment when feasible. Based on results in immunocompetent patients immunized with the mRNA vaccines, rituximab-containing therapy should be delayed two weeks from the second vaccination (for two-dose vaccines) to allow for the development of neutralizing antibodies and T-cell responses. However, no information is yet available on responses to vaccination in immunocompromised individuals.

Are you changing your approach to initial therapy?

When treatment is indicated, rituximab monotherapy rather than R-chemotherapy should be given consideration.

https://hematology.org/covid-19/covid-19-and-indolent-lymphomas

Therapy: Indolent NHL

Are you changing therapies for patients who have already started treatment?

For patients who have already achieved an excellent response to R-chemotherapy, a reduced number of cycles may be considered or a switch in therapy to less immunosuppressive or myelosuppressive approaches. Maintenance rituximab continues to be prescribed by some of the experts, but not others. Many have discontinued maintenance rituximab in anticipation of the SARS-CoV-2 vaccines.

Are you changing therapy to minimize visits? For example, changing to oral or less frequent regimens?

Some experts are switching patients to oral options in CLL/SLL, marginal zone lymphoma, or mantle cell lymphoma, rather than continuing intravenous chemotherapy, in an effort to reduce the risk of infection and limit the number of visits to the outpatient clinic. Some patients may be eligible to receive up to a three month supply of their oral medication; this approach, with labs obtained locally and telehealth visits may allow patients to stay at home for the time being. Patients who are on “watchful waiting” may have visits delayed with telemedicine alternatives, with labwork obtained locally or delayed if risk is low.

https://hematology.org/covid-19/covid-19-and-indolent-lymphomas

Transplant/CAR-T

- Most patients should be able to receive autologous therapies (at least for lymphomas)

- Things may be more complicated for allogenic transplants, especially for MUDs

Radiation

SPECIAL REPORT | MAY 21, 2020

ILROG emergency guidelines for radiation therapy of hematological malignancies during the COVID-19 pandemic

Joachim Yahalom , Bouthaina Shbib Dabaja , Umberto Ricardi , Andrea Ng , N. George Mikhaeel , Ivan R. Vogelius , Tim Illidge , Shunan Qi , Andrew Wirth , Lena Specht on behalf of the International Lymphoma Radiation Oncology Group (ILROG)

Shortening RT Course: *using alternative hypofractionation RT regimens when RT could not be omitted or delayed.*

Blood. 2020; 135(21): 1829-1832

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COVID19 Patient Registries

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The COVID-19 & Cancer Consortium

ASCO® Registry

VTE and COVID19

	Moderate State		Severe State	
	Therapeutic	Usual Care	Therapeutic	Usual Care
Need for organ support*	~16%	~23%	N/A	N/A
Mortality	40/699 (5.7%)	54/699 (7.7%)	160/453 (35.3%)	144/442 (32.6%)
Thrombotic events †	16/853 (1.9%)	24/742 (3.2%)	31/460 (6.7%)	53/448 (11.8%)
ISTH major bleeding	14/853 (1.6%)	7/742 (0.9%)	17/460 (3.7%)	8/448 (1.8%)

https://www.hematology.org/covid-19/covid-19-and-vte-anticoagulation

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VTE and COVID19

For both ICU and non-ICU levels of care: **The ASH guideline panel suggests using prophylactic-intensity** over intermediate-intensity or therapeutic-intensity anticoagulation in patients with COVID-19–related illness who do not have suspected or confirmed VTE (conditional recommendation based on very low certainty in the evidence about effects).

Post discharge?
“Patients hospitalized for acute medical illness are at increased risk for VTE for up to 90 days after discharge. A symptomatic VTE incidence of between 0-0.6% at 30-42 days post–COVID-19 discharge has been reported in observations studies of patients with COVID-19. Whether post-discharge thromboprophylaxis is warranted is being investigated in clinical trials and enrollment is encouraged. “

https://www.hematology.org/covid-19/covid-19-and-vte-anticoagulation

How have clinical trials been affected?

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Are trials still happening?

- In most cases, *yes*
  - Unfortunately, cancer doesn't read the news
  - "Non-Critical" studies may still be on hold

How might studies be different?

For studies under CTEP IND with oral investigational agents, the Pharmaceutical Management Branch is extending the alteration of its standard operating procedures to allow the Dispensing Pharmacy to ship oral investigational agents directly to patients through **May 31, 2021**. Consideration can include possible shipment of multiple treatment cycles to study patients, if feasible, based on supply availability and protocol requirements.

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Likely some of this will be here to stay…

- Increased use of telemedicine
- Increased allowances for local labs or treatments to reduce travel
- Increased allowances for drugs to go directly to patients
- Remote study start ups and monitoring?