COVID-19 vaccine effectiveness and community prevalence of Alpha, Delta and Omicron variants in patients with cirrhosis

We read with interest about the prognostic significance of liver function abnormalities in SARS-CoV-2 infection.[1 2] Although patients with underlying cirrhosis have an increased risk of death following COVID-19, mRNA vaccine administration is associated with an excellent reduction in mortality.[3 4] We aimed to determine the association of the prevalence of the Alpha, Delta and Omicron variants and effectiveness of the BNT162b2 or 1273-mRNA vaccines among participants with cirrhosis.

We performed a test-negative case–control study of participants with cirrhosis in the Veterans Outcomes and Costs Associated with Liver disease cohort, who had a SARS-CoV-2 PCR between 1 February 2021 and 21 January 2022.[5–7]

Participants with a positive PCR were considered as cases, and others, as controls. Propensity score (PS) matching was used to match cases and controls, with PS of being a case derived from a logistic regression that included the participant's age group, sex, race/ethnicity, alcohol, body mass index, diabetes, current tobacco use, Alcohol Use Disorders Identification Test-Concise (AUDIT-C) score, cirrhosis comorbidity index, hypertension, chronic obstructive pulmonary disease, Child-Pugh Score, location, baseline lab results (alanine aminotransferase, platelet count, creatinine, total bilirubin, international normalised ratio and Model For End-Stage Liver Disease-Sodium (MELD-Na)) and COVID-19 test month. The proportion of variants in the community was obtained from the weekly Center for Disease Control genomic surveillance data.[8] Three periods were defined: alpha predominant period from 1 February 2021 to 25 July 2021, Delta predominant from 26 July 2021 to 24 December 2021, and Omicron predominant from 25 December 2021 until 21 January 2022. The effectiveness of mRNA vaccination in preventing COVID-19 infection was examined through a logistic regression model. The model included a categorical variable indicating the most prevalent variant at the time of infection, interaction between vaccination and the prevalent variant, a binary variable to adjust for the receipt of a third dose, and interaction between vaccination and the number of days from full vaccination. Outcomes included symptomatic, and severe/critical COVID-19, defined using the National Institute of Health severity index.[9]

Of the 120 952 patients in the cohort, we excluded participants who did not have a SARS-CoV-2 PCR (n=100 766), liver transplant recipients (n=526), those partially vaccinated (n=1549), viral vector vaccine recipients (n=832) and those with prior COVID-19 (n=749). The study sample had 16 530 participants, including 2140 with a positive SARS-CoV-2 PCR (cases), and 14 165 who were SARS-CoV-2 PCR negative (controls). After matching, 2836 participants were retained, with equal numbers of cases and controls.

Vaccine effectiveness against symptomatic COVID-19 during the Alpha period was 82% at 2 months (adjusted OR (aOR) 0.18, 95% CI 0.10 to 0.32), 77% at 4 months (aOR 0.23, 95% CI 0.13 to 0.42) and 71% at 6 months from full vaccination (aOR 0.29, 95% CI 0.16 to 0.56) (table 1 and figure 1). Vaccine effectiveness against symptomatic COVID-19 in the Delta period dropped from 68% at 2 months from vaccination (aOR 0.32, 95% CI 0.23 to 0.44), to 59% at 4 (aOR 0.41, 95% CI 0.32 to 0.52) and 48% at 6 months (aOR 0.52, 95% CI 0.42 to 0.64). Full vaccination was not effective against symptomatic COVID-19 in the Omicron period at 2 (aOR 0.70, 95% CI 0.37 to 1.35), 4 (aOR 0.90, 95% CI 0.50 to 1.62) or 6 months (aOR 1.16, 95% CI 0.67 to 1.99). However, the receipt of a third dose of an mRNA vaccine was associated with a reduced odds of symptomatic COVID-19 (aOR 0.52, 95% CI 0.37 to 0.71).

Vaccine effectiveness against severe/critical COVID-19 during the Alpha period was 72% at 2 months (aOR 0.28, 95% CI 0.11 to 0.72), but not significant at 4 (aOR 0.44, 95% CI 0.17 to 1.16) or 6 months from vaccination (aOR 0.68, 95% CI 0.24 to 1.95). In contrast, vaccination was effective against severe/critical COVID-19 during the Delta surge-75% at 2 months (aOR 0.25, 95% CI 0.14 to 0.43), 62% at 4 (aOR 0.38, 95% CI 0.26 to 0.57) and 40% at 6 months (aOR 0.60, 95% CI 0.44 to 0.82).

Vaccination was highly effective against severe/critical COVID-19 during the Omicron period −84% at 2 (aOR 0.16, 95% CI 0.06 to 0.46), 75% at 4 (aOR 0.25, 95% CI 0.10 to 0.63) and 61% at 6 months (aOR 0.39, 95% CI 0.17 to 0.89). Receipt of the third dose was associated with a reduced odds of severe/critical COVID-19 (aOR 0.54, 95% CI 0.32 to 0.92).

In conclusion, COVID-19 vaccination was highly effective against symptomatic COVID-19 during Alpha, and lowest during the Omicron period. However, vaccine effectiveness against severe/critical COVID-19 was highest during Omicron and lowest during the Delta period. The fading effectiveness of vaccination in patients with cirrhosis argues for additional booster dose of an mRNA vaccine in this population.

Binu V John ,[1,2] **Dustin R Bastaich,**[3] **Raphaella D Ferreira,**[2] **Akash Doshi,**[4] **Tamar H Taddei,**[5] **David E Kaplan,**[6] **Seth Spector,**[7,8] **Yangyang Deng,**[3] **Bassam Dahman**[3]

[1]Gastroenterology and Hepatology, University of Miami, Miami, Florida, USA
[2]Gastroenterology and Hepatology, Miami VA Healthcare System, Miami, Florida, USA
[3]Department of Health Behavior and Policy, Virginia Commonwealth University, Richmond, Virginia, USA
[4]Miller School of Medicine, University of Miami, Miami, Florida, USA
[5]Medicine, VA Connecticut Health System West Haven Campus, West Haven, Connecticut, USA
[6]Gastroenterology and Hepatology, Hospital of the Inversity of Pennsylvania, Philadelphia, Pennsylvania, USA
[7]Department of Surgery, University of Miami, Coral Gables, Florida, USA
[8]Department of Surgery, Bruce W Carter Department of Veterans Affairs Medical Center, Miami, Florida, USA

Correspondence to Dr Binu V John, Gastroenterology and Hepatology, University of Miami, Miami, Florida, USA; binu.john@gmail.com

Contributors BVJ and BD had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: JA. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: BVJ, DRB and BD. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: BVJ, DRB, YD and BD. Obtained funding: BVJ and BD. Administrative, technical or material support: All authors Supervision: BVJ and BD.

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Table 1 Adjusted OR of mRNA vaccination on COVID-19 severity between vaccinated and unvaccinated patients at different prevalent variant levels and different times from vaccination

Variable	Symptomatic COVID-19 Adjusted odds ratio (95% CI) P value	Severe/critical COVID-19
Number of total patients	2656	2656
Number of events	1121	286
Vaccinated versus unvaccinated at 2 months from vaccination across prevalent variant levels		
Alpha	0.18 (0.10 to 0.32)	0.28 (0.11 to 0.72)
	<0.001	**0.008**
Delta	0.32 (0.23 to 0.44)	0.25 (0.14 to 0.43)
	<0.001	**<0.001**
Omicron	0.70 (0.37 to 1.35)	0.16 (0.06 to 0.46)
	0.29	**<0.001**
Vaccinated versus unvaccinated at 4 months from vaccination across prevalent variant levels		
Alpha	0.23 (0.13 to 0.42)	0.44 (0.17 to 1.16)
	<0.001	0.10
Delta	0.41 (0.32 to 0.52)	0.38 (0.26 to 0.57)
	<0.001	**<0.001**
Omicron	0.90 (0.50 to 1.62)	0.25 (0.10 to 0.63)
	0.73	**0.003**
Vaccinated versus unvaccinated at 6 months from vaccination across prevalent variant levels		
Alpha	0.29 (0.16 to 0.56)	0.68 (0.24 to 1.95)
	<0.001	0.48
Delta	0.52 (0.42 to 0.64)	0.60 (0.44 to 0.82)
	<0.001	**0.001**
Omicron	1.16 (0.67 to 1.99)	0.39 (0.17 to 0.89)
	0.60	**0.026**
Significance of interaction between vaccine and variant*	**0.006**	0.61
Significance of interaction of vaccine and time from vaccination†	**<0.001**	**<0.001**
Third vaccination dose‡	0.52 (0.37 to 0.71)	0.54 (0.32 to 0.92)
	<0.001	**0.022**

Bold indicates significance at type 1 error=0.05.
Adjusted ORs estimated from coefficients of logistic regression models that included a categorical variable indicating the most prevalent variant at the time of infection, a binary variable to adjust for the receipt of a third dose, interaction between vaccination and the prevalent variant, and interaction between vaccination and the number of days from full vaccination.
*H1: Hypothesis that vaccine efficacy differs against the different variants was demonstrated by the significance of the coefficient of interaction between vaccination and the prevalent variant.
†H2: Hypothesis of fading efficacy of vaccine over time was demonstrated by the significance of the coefficient of interaction of the vaccine and time from vaccination.
‡The effect of the third dose is the overall effect regardless of the variant period.

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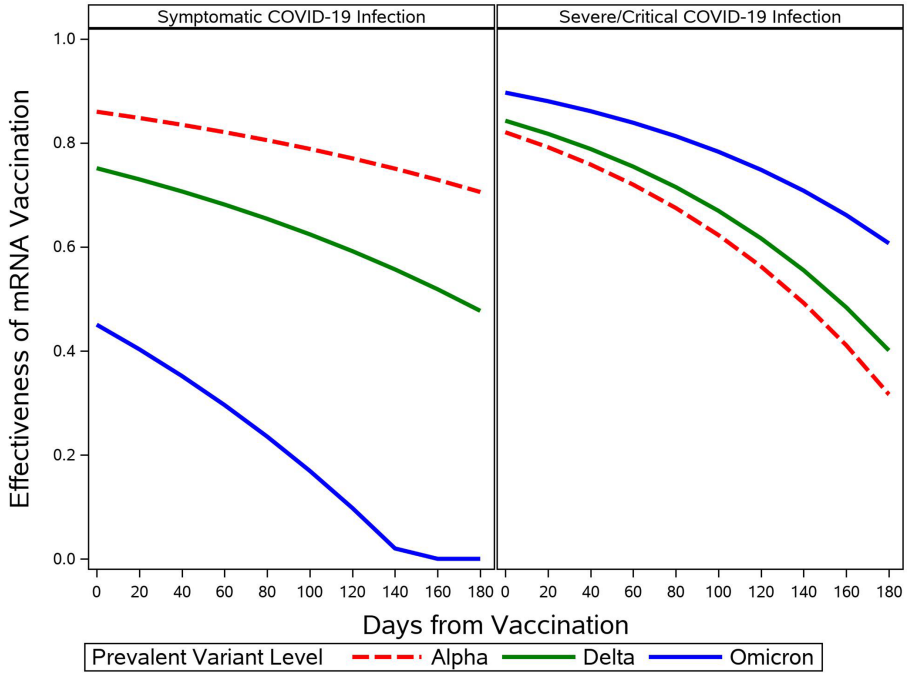

Figure 1 Vaccine effectiveness across levels of the community prevalence of Alpha, Delta and Omicron variant, and days from vaccination, by COVID-19 severity groupings.

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ORCID iD
Binu V John http://orcid.org/0000-0002-2002-9682

REFERENCES

1 Weber S, Hellmuth JC, Scherer C, *et al*. Liver function test abnormalities at hospital admission are associated with severe course of SARS-CoV-2 infection: a prospective cohort study. *Gut* 2021;70:1925–32.
2 Weber S, Mayerle J, Irlbeck M, *et al*. Severe liver failure during SARS-CoV-2 infection. *Gut* 2020;69:1365–7.
3 Ge J, Pletcher MJ, Lai JC, *et al*. Outcomes of SARS-CoV-2 infection in patients with chronic liver disease and cirrhosis: a national COVID cohort collaborative study. *Gastroenterology* 2021;161:1487–501.
4 John BV, Deng Y, Scheinberg A, *et al*. Association of BNT162b2 mRNA and mRNA-1273 vaccines with COVID-19 infection and hospitalization among patients with cirrhosis. *JAMA Intern Med* 2021;181:1306–14.
5 John BV, Deng Y, Schwartz KB, *et al*. Postvaccination COVID-19 infection is associated with reduced mortality in patients with cirrhosis. *Hepatology* 2022;76:126–38.
6 John BV, Deng Y, Khakoo NS, *et al*. Coronavirus disease 2019 vaccination is associated with reduced severe acute respiratory syndrome coronavirus 2 infection and death in liver transplant recipients. *Gastroenterology* 2022;162:645–7.
7 John BV, Aitcheson G, Schwartz KB, *et al*. Male sex is associated with higher rates of liver-related mortality in primary biliary cholangitis and cirrhosis. *Hepatology* 2021;74:879–91.
8 COVID data tracker-Variant proportions. Available: https://covid.cdc.gov/covid-data-tracker/#variant-proportions [Accessed 18 May 2022].
9 COVID-19 Treatment Guidelines Panel. Coronavirus disease 2019 (COVID-19) treatment guidelines. National Institutes of health. Available: https://www.covid19treatmentguidelines.nih.gov/ [Accessed 18 May 2022].