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RESEARCH LETTERS

Coronavirus Disease 2019 Vaccination Is Associated With Reduced Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Death in Liver Transplant Recipients

Immunocompromised patients, including those who received an organ transplant, were excluded from coronavirus disease 2019 (COVID-19) vaccine clinical trials.[1,2] Transplant patients are at high risk of severe disease[3] but may not manifest adequate antispike antibody responses after COVID-19 vaccination, raising concern for persisting risk.[4,5] The objective of this study was to evaluate the effectiveness of COVID-19 vaccination for the prevention of COVID-19 and COVID-19–related death.

Liver transplant recipients (aged $>$ 18 years) in active care from December 15, 2020 to September 12, 2021 were identified from the Veterans Outcomes and Costs Associated with Liver Disease cohort using International Classification of Diseases codes.[6,7] Patients were considered fully vaccinated 14 days after the second dose of either the Pfizer BNT162b2 mRNA or the Moderna 1273 mRNA. Patients who were unvaccinated, partially vaccinated (received only 1 dose of the vaccine or had fewer than 14 days of follow-up after the second dose) with an mRNA vaccine, or received the Janssen Ad26.SARS CoV2 vaccine were considered as control subjects. Outcomes evaluated included COVID-19 (documented by positive COVID-19 polymerase chain reaction), symptomatic COVID-19, and COVID-19–related death, assessed from the date of full vaccination (14 days after the second dose of an mRNA vaccine) for vaccinated patients and from the first availability of COVID-19 vaccines within the VA system (December 18, 2020) for unvaccinated patients.

Propensity scores were derived through the logistic regression adjusted by the covariates of age group, sex, current smoking, kidney transplantation, comorbidities including chronic obstructive pulmonary disease and hypertension, primary immunosuppression, and antimetabolite therapy in patients who received vaccinations vs unvaccinated control subjects. Inverse propensity weights were calculated and used as weighted score into the unadjusted and adjusted hazard regression.

Descriptive variables were compared using Wilcoxon and χ^2 tests as appropriate. The hazard ratios of COVID-19 infection, symptomatic COVID-19, or COVID-19–related death associated with vaccination were estimated using Cox proportional hazard regression models, controlling for a priori determined variables known to be correlated with surviva,l and probability of being infected including age, body mass index, race, tobacco use, prior receipt of a kidney transplant, and time after transplantation.[3] Event-free cases and control subjects were censored at the end of the study period. Patients who received only 1 dose of an mRNA vaccine or the Ad26.SARS CoV2 vaccine were included as control subjects and censored on the date of receipt of the first dose. Vaccine efficacy was calculated as 1 minus risk ratio, where risk ratio is the ratio of risk after full vaccination among vaccinated to risk after the matched vaccine date among unvaccinated.

Statistical significance was defined using 2-sided tests with $\alpha = 0.05$. Statistical analysis was performed using SAS 4.9 (SAS Inc, Cary, NC). The study was approved by the institutional review boards at all participating VA medical centers.

Of 1924 eligible liver transplant recipients, 1133 (58.9%) were fully vaccinated with 2 doses of an mRNA vaccine. Patients who were vaccinated were more likely to be men, white, have chronic obstructive pulmonary disease, be hypertensive, have received a kidney transplant, have received a calcineurin inhibitor plus antimetabolite, less likely to be active smokers, and were fewer years after transplantation (Supplementary Table 1).

The outcomes of COVID-19 were observed in 24 of 1133 vaccinated and 43 of 791 control subjects, symptomatic COVID-19 in 14 vaccinated and 26 control subjects, and COVID-19–related death in 2 vaccinated and 11 control subjects. On multivariable analysis, full vaccination with a COVID-19 vaccine was associated with a significant reduction in COVID-19 (adjusted hazard ratio, 0.36; 95% confidence interval, 0.26–0.51; $P < .0001$), symptomatic COVID-19 (adjusted hazard ratio, 0.42; 95% confidence interval, 0.27–0.65; $P < .0001$), and COVID-19–related death (adjusted hazard ratio, 0.13; 95% confidence interval, 0.04–0.37; $P = .0002$) (Supplementary Table 2 and Figure 1).

Of the 2 postvaccination COVID-19 deaths, the first was an 80-year-old man who was 9 years post-transplant on tacrolimus, with compensated graft cirrhosis, nonischemic cardiomyopathy, atrial fibrillation, and chronic kidney disease who developed COVID-19 18 days after the second dose of mRNA-1273 vaccine. This patient required mechanical ventilation, pressors, and dialysis and died from respiratory failure. The second patient was an 82-year-old man with coronary artery disease, diabetes mellitus, and chronic kidney disease who was 8 years post-transplant on single-agent tacrolimus and developed COVID-19 pneumonia 10 days after the second dose of the mRNA-1273 vaccine. He required noninvasive ventilation, refused intubation, and died of respiratory failure.

Abbreviations used in this paper: COVID-19, coronavirus disease 2019.

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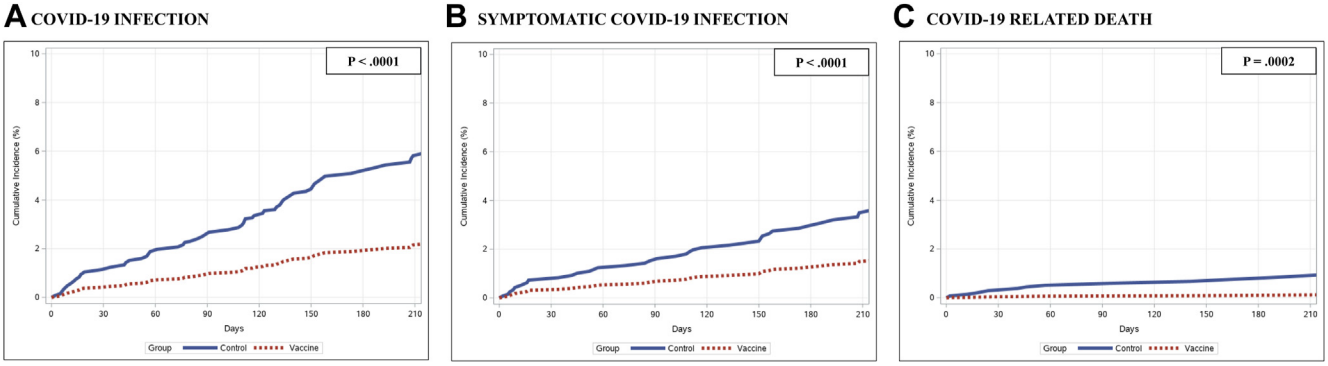

Figure 1. Cumulative incidence of *(A)* COVID-19 infection, *(B)* symptomatic COVID-19, or *(C)* COVID-19–related death in mRNA vaccinated and control liver transplant participants.

Recent studies report concerning data that only 54% of solid organ transplant recipients, 43% on antimetabolite therapy and 46% of kidney transplant recipients, mount antispike antibodies after COVID-19 mRNA vaccine.[4,5] However, our data show that receipt of full vaccination with 2 doses of an mRNA vaccine was associated with a 64%% decrease in COVID-19 infection, 58% decrease in symptomatic COVID-19, and 87% decrease in COVID-19–related death in liver transplant recipients.

Protection from the vaccination may be of lower magnitude than that observed in healthy individuals, yet it exceeds the level of protection predicted by antibody titers.[4,5] In addition to humoral immunity, adaptive T-cell–mediated responses may also confer vaccine protection and require further study. Similar observations have been reported with influenza in liver transplant recipients in whom, despite low antibody titers, vaccination has been associated with significant reduction in hospitalizations and death.[8]

Limitations of the present study include a retrospective design with potential for residual confounding, a male-predominant cohort, small numbers of outcomes, lack of measurement of antispike antibodies or T-cell response to COVID-19, and lack of systematic testing for severe acute respiratory syndrome coronavirus 2. Control subjects could have received the vaccine outside the VA, resulting in misclassification bias toward the null. Individuals in either group may have tested positive for COVID-19 outside the VA system, possibly more likely to have occurred in unvaccinated individuals and again biasing toward the null. The study was completed before the recommendation for a third dose of the mRNA BNT162b2 vaccine. Strengths of the present study include a large sample size for a geographically diverse, national transplant population. We were able to complete this study at a point where we had adequate numbers of unvaccinated control subjects. In summary, our findings show that full vaccination with 2 doses of a COVID-19 mRNA vaccine is associated with a decrease in COVID-19 infection and death in liver transplant recipients.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org and at https://doi.org/10.1053/j.gastro.2021.11.001.

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Conflicts of interest
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Disclaimer
The authors prepared this work in their personal capacity. The opinions expressed in this article are the author's own and do not reflect the view of the Department of Veterans Affairs or the United States government.

Supplementary Table 1. Baseline Characteristics of Study Participants

Variables	Vaccine (n = 1133)	Control (n = 791)	*P*
Patient who received the first dose			…
Pfizer BNT162b2 mRNA vaccine	539 (47.6)	…	
Moderna 1273 mRNA vaccine	596 (52.4)	…	
Sex			<.0001
Male	1106 (97.6)	736 (93.1)	
Female	27 (2.4)	55 (6.9)	
Median age, y (IQR)	68.9 (7.9)	68.6 (8.7)	.4629
Age group			.0184
<50 y	30 (2.6)	37 (4.7)	
50–59.9 y	110 (9.7)	76 (9.6)	
60–69.9 y	516 (45.5)	341 (43.1)	
70–84.9 y	477 (42.1)	333 (42.1)	
>85 y	0 (0.0)	4 (0.5)	
White	755 (66.6)	479 (60.6)	.0062
Median body mass index (IQR)	30.2 (5.5)	30.2 (4.8)	.3851
Current smoker	227 (20.0)	180 (22.8)	.1505
Chronic obstructive pulmonary disease	319 (28.2)	137 (17.3)	<.0001
Hypertension	917 (80.9)	562 (71.1)	<.0001
Kidney transplantation	223 (19.7)	117 (14.8)	.0057
Tacrolimus	917 (80.9)	454 (57.4)	<.0001
Cyclosporine	78 (6.9)	47 (5.9)	.4092
Calcineurin inhibitor–based primary immunosuppression	1055 (93.1)	568 (71.8)	<.0001
Mycophenolate	610 (53.8)	331 (41.8)	<.0001
Azathioprine	86 (7.6)	36 (4.5)	.0071
Antimetabolites	696 (61.4)	367 (46.4)	<.0001
Median year from transplantation (IQR)	5.6 (5.0)	8.4 (7.5)	<.0001

Values are n (%) unless otherwise defined. IQR, interquartile range.

Supplementary Table 2. Inverse Probability of Treatment Weighting Multivariable Hazard Ratios for the Risk of COVID-19, Symptomatic COVID-19, and COVID-19–related Death, Comparing Liver Transplant Recipients Who Are Fully Vaccinated for COVID-19 With an mRNA Vaccine vs Control Subjects

	COVID-19		Symptomatic COVID-19		COVID-19 related death	
Variable	aHR (95% CI)	*P*	aHR (95% CI)	*P*	aHR (95% CI)	*P*
Number of patients	1924		1924		1924	
Control	791		791		791	
Vaccine	1133		1133		1133	
Number of events	67		40		13	
Control	43		26		11	
Vaccine	24		14		2	
Group						
Control	REF		REF		REF	
Vaccine	0.36 (0.26–0.51)	<.0001	0.42 (0.27–0.65)	<.0001	0.13 (0.04–0.37)	.0002
Age	1.03 (0.97–1.04)	.7228	1.03 (0.98–1.03)	.8007	1.16 (1.05–1.28)	.0026
Body mass index	1.03 (1.01–1.06)	.0016	1.06 (1.03–1.09)	<.0001	1.09 (1.04–1.14)	.0001
Race						
Nonwhite	REF		REF		REF	
White	1.29 (0.93–1.78)	.1309	1.11 (0.74–1.67)	.6146	1.56 (0.63–3.90)	.3404
Tobacco use						
Current nonsmoker	REF		REF		REF	
Current Smoker	1.20 (0.84–1.71)	.3154	1.48 (0.96–2.28)	.0780	2.54 (1.21–5.31)	.01353
Kidney transplantation						
No	REF		REF		REF	
Yes	1.11 (0.75–1.64)	.6085	1.03 (0.61–1.74)	.9079	1.32 (0.59–2.92)	.5010
Year from transplantation	0.94 (0.90–0.97)	.0007	0.96 (0.91–1.01)	.0847	0.94 (0.83–1.05)	.2778