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BRIEF COMMUNICATION

A single-center review of outcomes between COVID-19 vaccinated and unvaccinated liver transplant recipients

Annelise Nolan[1] | Melissa McGowan[1] | Lauren Von Stein[1] | Adrienne Ross[2] | Manjit Kaur[3] | Todd Pesavento[4] | Priyamvada Singh[4]

[1]Wexner Medical Center, Department of Pharmacy, The Ohio State University, Columbus, Ohio, USA

[2]The Ohio State University College of Pharmacy, Columbus, Ohio, USA

[3]Division of Nephrology, The Ohio State University, Columbus, Ohio, USA

[4]Division of Nephrology and Comprehensive Transplant Center, The Ohio State University, Columbus, Ohio, USA

Correspondence
Annelise Nolan, Wexner Medical Center, Department of Pharmacy, The Ohio State University, 410 W. 10th Ave., Columbus, OH 43210, USA.
Email: Annelise.nolan@osumc.edu

Abstract

Background: With the availability of vaccines against SARS-COV-2, recommendations for vaccination of transplant candidates are widespread. At our institution, patients may receive liver transplant (LTx) regardless of vaccine status. The purpose of this study is to compare post-LTx outcomes between vaccinated (VAX) and unvaccinated (UNVAX) LTx recipients.

Methods: This is a retrospective, single-center study of LTx from January 1, 2021–March 30, 2022. The primary outcome is incidence of post-LTx COVID-19. Secondary outcomes include graft function, mortality, graft loss, and COVID-19 treatment.

Results: One hundred and seventy-seven LTx recipients were included, 57% [101/177] VAX and 43% [76/177] UNVAX. Baseline characteristics were similar between groups. Overall, 28 (36.8%) UNVAX and 34 (33.7%) VAX tested COVID-19 positive during the study period ($p = .193$) at a mean of 312.6 [255.4–369.8] days for UNVAX versus 254.6 [215.2–293.9] days for VAX ($p = .084$). COVID-19 treatment was administered in 15 (53.6%) of the UNVAX compared to 22 (64.7%) in the VAX ($p = .374$), although eight (28.6%) of UNVAX required hospital admission for treatment compared with two (5.9%) of VAX ($p = .016$). There were no statistically significant differences in death, and no COVID-19 related death or graft loss. There were no statistically significant differences in liver function tests at 3- and 12-months post LTx.

Conclusion: In a series with a large percentage of UNVAX patients, LTx appears to be safe, with no difference in the rate of COVID-19 or transplant-related outcomes compared to VAX. While we encourage vaccination to prevent severe COVID, based on our results, vaccine status should not be reason to deny lifesaving transplant.

KEYWORDS
coronavirus, COVID, liver transplant, SARS CoV-2vaccine

1 | INTRODUCTION

Management of solid organ transplant recipients has evolved since the beginning of the COVID-19 pandemic. Early reports of infection amongst transplant recipients were concerning for increased mortality in this immunosuppressed population. A multicenter cohort study by Kates et al. which included patients infected with COVID-19 in 2020 demonstrated a 28-day mortality rate of 20.5% amongst transplant patients hospitalized for COVID-19, and one meta-analysis of COVID-19 infected liver transplant recipients showed a 17.4% cumulative mortality rate.[1,2]

Now, the widespread availability of COVID-19 vaccinations has led to recommendations from organizations including the American Association for the Study of Liver Diseases, the American Society of Transplant Surgeons, and the American Society of Transplantation that all adult solid organ transplant candidates and recipients receive SARS-CoV-2 vaccination.[3–5] These recommendations are the result of studies from early on in the pandemic that vaccination may reduce disease severity and death, including amongst liver transplant recipients.[6] In addition, it has been demonstrated that vaccine antibody response rates are reduced when the vaccine is given to immunosuppressed patients after liver transplantation, although it is noted that cirrhotic patients also show poor immune response.[7]

As a result of these recommendations, vaccine mandates became prominent throughout healthcare systems, including prior to listing for transplant at many transplant centers. Several media stories reported cases of transplant recipients denied transplant due to COVID vaccine status.[8,9] According to a recent survey, 35.7% of United States transplant centers require vaccination.[10]

The ethics of mandated vaccination for solid organ transplant patients have been discussed elsewhere, with net utility, stewardship and beneficence listed in support of vaccines, and respect for persons and justice as reasons to avoid mandatory vaccination in transplant candidates.[11] However, this is a rapidly changing landscape with subsequent variants of COVID likely causing less severe disease.[12] Transplant centers do not necessarily require vaccination, and at our institution, SARS-CoV-2 vaccination is strongly encouraged but not required prior to listing for liver transplant. Patients may receive a transplant regardless of vaccination status.

The objective of this study was to explore the outcomes post-liver transplant in a large unvaccinated cohort. We reviewed our experience in management of liver transplant recipients that were vaccinated compared to those that were unvaccinated against SARS-CoV-2, and hypothesized that overall transplant and survival outcomes would not be different.

2 | METHODS

This institutional review board approved study was a retrospective, single-center review of liver or simultaneous liver–kidney transplant recipients aged 18 or older transplanted from January 1, 2021 through March 30, 2022 at the Ohio State University Wexner Medical Center. The primary outcome was the incidence of COVID-19 infection post-transplant. Secondary outcomes included graft function, graft loss, mortality, severity of COVID-19 including rates of hospitalization, and treatment modalities used for COVID-19.

Statistical analysis was completed using STATA, version 13.1 (StataCorp, College Station, Texas). Descriptive statistics were used for baseline characteristics, represented as mean or n (%). A two-tailed Student's *t*-test was used for normally distributed continuous variables and a chi-squared test was used for categorical variables. A *p*-value of less than or equal to .05 was deemed statistically significant.

3 | RESULTS

Overall, 177 liver or simultaneous liver–kidney transplant recipients were included with a median follow up of 439 days. Fifty-seven percent (101/177) were vaccinated, defined as receiving at least 1 SARS-CoV-2 vaccine currently available at the time (mRNA or viral vector vaccine) prior to transplant, and 43% (76/177) were unvaccinated. Baseline characteristics were similar between groups (Table 1), with no differences in mean age, gender, or MELD score. The majority of patients in each group had an indication for transplant of alcohol-related liver disease or non-alcoholic steatohepatitis. Most patients received steroid induction with tacrolimus, mycophenolate, and steroid maintenance immunosuppression. Only two subjects received antibody-depleting induction.

Results are listed in Table 2. Overall, 28 (36.8%) subjects in the non-vaccinated group and 34 (33.7%) subjects in the vaccinated group tested positive for COVID during the study period ($p = .193$) at a mean of 312.6 [255.4–369.8] days in the non-vaccinated group versus 254.6 [215.2–293.9] days in the vaccinated group ($p = .084$). Treatment for COVID was administered in 15 (53.6%) of the nonvaccinated group compared to 22 (64.7%) in the vaccinated group ($p = .374$), although eight (28.6%) of nonvaccinated subjects required hospital admission for treatment compared with two (5.9%) of vaccinated subjects ($p = .016$). One unvaccinated subject required ICU admission (respiratory failure) compared with zero in the vaccinated group. Overall, 28 (15.8%) subjects had a documented positive COVID test prior to transplant, and there was no difference in incidence of COVID infection between those who had a positive test pre-transplant (15.6%) and those who did not (16.1%), $p = .934$.

Of those subjects that had infection with COVID, there was no difference in induction immunosuppression given, with the majority receiving steroid-only induction. There was no difference in biopsy-proven acute rejection, treatment for cytomegalovirus, or administration of tixagevimab/cilgavimab between vaccinated and unvaccinated subjects who tested positive for COVID.

There were no statistically significant differences in death (nonvaccinated 5.3% vs. 9.9% in vaccinated group, $p = .258$), and no death or graft loss between vaccinated and non-vaccinated subjects related to COVID-19 in either group. There were no statistically significant differences in liver function tests at 3- and 12-months post liver transplant.

TABLE 1 Baseline characteristics.

	Non-vaccinated $n = 76$	Vaccinated $n = 101$	p-value
Age (years), mean	52.9	56.1	.731
Men, *n* (%)	47 (61.8%)	68 (67.3%)	.449
MELD score	22.4	20.3	.082
Body mass Index (kg/m2)	31.1	30.2	.198
Donation after cardiac death (DCD) donor	30 (39.5%)	49 (48.5%)	.231
Steroid-only induction	61 (80.3%)	88 (87.1%)	.215
Received tixagevimab/cilgavimab	17 (22.4%)	14 (13.9%)	.158
Positive COVID test pre-transplant	8 (10.5%)	20 (19.8%)	.094
Indication for transplant			
Alcohol related liver disease	27 (35.5%)	38 (37.6%)	
Non-alcoholic steatohepatitis (NASH)	26 (34.2%)	22 (21.8%)	
Hepatitis C virus	5 (6.6%)	5 (4.9%)	
Primary sclerosing cholangitis	5 (6.6%)	8 (7.9%)	
Primary biliary cholangitis	1 (1.3%)	5 (4.9%)	
Autoimmune hepatitis	1 (1.3%)	2 (2.0%)	
Cryptogenic cirrhosis	4 (5.3%)	7 (6.9%)	
Other	7 (9.2%)	14 (13.9%)	

TABLE 2 Results.

	Non-vaccinated $n = 76$	Vaccinated $n = 101$	p-value
Positive COVID test post-transplant	28 (36.8%)	34 (33.7%)	.193
Death	4 (5.3%)	10 (9.9%)	.258
Treated cytomegalovirus	22 (28.9%)	19 (18.8%)	.119
Biopsy-proven acute rejection	11 (14.4%)	7 (6.9%)	.108
Aspartate aminotransferase (AST) at 3 months	19.96 [17.07–22.86]	18.89 [16.48–21.28]	.568
Alanine transaminase (ALT) at 3 months	22.18 [18.28–26.08]	22.39 [16.45–28.33]	.956
Alkaline phosphatase (ALP) at 3 months	101.028 [87.21–114.84]	123.20 [105.10–143.304]	.067
Total bilirubin at 3 months	.502 [.444–.559]	.579 [.492–.666]	.167
Albumin at 3 months	3.97 [3.86–4.09]	3.83 [3.73–3.95]	.086
AST at 1 year*	25.59 [19.11–32.08]	18.42 [16.26–20.59]	.133
ALT at 1 year*	32.33 [23.67–40.77]	20.51 [17.83–23.20]	.063
ALP at 1 year*	105.87 [92.92–118.82]	104.62 [92.50–116.75]	.903
Total bilirubin at 1 year*	.619 [.536–.702]	.642 [.498–.787]	.759
Albumin at 1 year*	4.1375 [4.04–4.22]	4.017 [3.86–4.17]	.157

*107 subjects had labs available at 1 year.

4 | DISCUSSION

The development of vaccines to prevent morbidity and mortality related to COVID-19 disease has led to criteria amongst some transplant centers to require vaccination prior to listing. In this large series of liver transplants that included both vaccinated and unvaccinated patients, there was no difference in the rate of COVID-19 or transplanted-related adverse outcomes including graft loss or death between groups. However, it was noted that more unvaccinated subjects did require inpatient treatment for COVID compared to vaccinated subjects. In our results, the majority of patients who were positive for COVID-19 were able to be treated as outpatients.

Overall, in-hospital mortality has declined since the beginning of the COVID-19 pandemic, with factors such as higher levels of immu-

nity due to infection or vaccination, improvements in early treatment including new antiviral agents, and lower pathogenicity of newer subvariants of Sars-CoV-2 all likely contributing.[12] The predominant variants of COVID-19 in our region shifted throughout the course of this study period, beginning with B.1.2 through Alpha, Delta, and Omicron.

Limitations of this retrospective study include the changing landscape of COVID-19 during the study period, including changes in predominant variants as well as recommendations for number of vaccines and boosters to be considered fully vaccinated, as well as advances in prophylaxis and treatment for COVID-19 infection. In addition, the availability COVID-19 testing changed during the course of this study. Further studies are needed as the pandemic continues to progress with changes in treatment as well as pathogenicity of the virus.

5 | CONCLUSIONS

While vaccination should be encouraged to prevent severe COVID-19 disease and patients should be informed of the risks associated with not receiving vaccination, including potential increased risk of hospitalization, based on our results, vaccine status may not be a reason to deny lifesaving liver transplant.

AUTHOR CONTRIBUTIONS

All authors contributed to the design and conduct of the study. Annelise Nolan contributed to the data collection, analysis, interpretation of the data and wrote the first draft of the manuscript. Annelise Nolan, Lauren Von Stein, Melissa McGowan, Adrienne Ross, Manjit Kaur collected data. Annelise Nolan, Melissa McGowan, Lauren Von Stein, Adrienne Ross, Manjit Kaur, Todd Pesavento, and Priyamvada Singh reviewed, edited, and approved the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Annelise Nolan https://orcid.org/0000-0002-3831-2056
Priyamvada Singh https://orcid.org/0000-0002-4353-3320

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