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Effect of COVID-19 Vaccines on the Prevention and Severity of Omicron Strain in Liver Transplant Patient

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Abstract

Background: Because it is still not possible to accurately determine whether the injected vaccines affect the disease incidence and mortality or not in the newly diagnosed strains, the present study aimed to investigate the effect of injected Coronavirus disease 2019 (COVID-19) vaccines on the mortality rate among liver transplant patients infected with COVID-19 in Mashhad, Iran.

Methods: This prospective cross-sectional study was conducted on liver transplant patients with moderate to severe COVID-19 referred to Montaseriyeh Hospital, Mashhad, Iran, from December 2021 to March 2022. The relationship between mortality due to Omicron strain was assessed with various variables.

Results: In general, 97 liver transplant recipients were entered into the present study. Vaccine failure was reported in 43.5% of liver recipients. About 30% of the patients had not received any COVID-19 vaccination, and 2.9%, 40%, and 27.1% had received one, two, and three dosages of COVID-19 vaccination, respectively. Infection with COVID-19 was the cause of mortality in 11.3% of patients. No significant relationship was reported between mortality and the consumption of immunosuppressive agents ($P > 0.05$). Multiple linear regression showed that the number of received vaccine dosages was predictive of mortality due to infection with the Omicron variant in liver recipients ($\beta = 0.13$; $P < 0.005$).

Conclusions: It was found that mortality due to COVID-19 vaccination was higher among the patients with fewer COVID-19 vaccination dosages and, consequently, could be related to vaccine-induced immunity in liver transplant recipients. However, due to the high vaccine failure rate, it seems that neutralizing antibody activity against Omicron variants is high.

Keywords: COVID-19 Vaccines, Liver Transplant Recipients, Mortality, Omicron

1. Background

The Omicron variant, B.1.1.529, is a new type of severe acute respiratory syndrome, Coronavirus 2 (SARS-CoV-2), identified for the first time in South Africa in November 2021 (1). Various hypotheses have been proposed regarding Omicron's origin. Based on the UCL Genetics Institute, the Omicron type has probably evolved during chronic infection in an immunocompromised individual (probably with untreated HIV/AIDS). South Africa has 8.2 million people living with HIV (the highest rate in the world). The beta variant of SARS-CoV-2 may also have originated from an HIV-infected person (2).

The mutations identified in the Omicron variant are twice that of the Delta variant. The genome of the vari-

ant has about 50 mutations, including more than 30 mutations in spike protein, which can divert the immune system from recognizing the virus and increase the risk of Omicron infection (3). Spike protein is the same protein that is targeted by vaccines. Similar to previous variants, the vaccine's safety regarding this new strain is unclear. It has been reported that antibody titers, the neutralization of wild-type (WT) virus, and T-cell responses increased after injecting three doses of mRNA vaccine into transplant recipients. However, with the supplantation of the SARS-CoV-2 Omicron variant with the WT virus as the dominant circulating strain, it is unclear whether the vaccine has its previous effect on this new strain (4, 5). Multiple amino acid substitutions within the spike protein in the Omicron variant have increased the possibility of vaccine escape (6). Another Omicron-type mutation leads to the S-gene target failure, one of the several gene regions targeted by the polymerase chain reaction (PCR) test; thus, Omicron-type mutation increases the false negatives test (7).

It has been reported that vaccination against Coronavirus disease 2019 (COVID-19) decreased the risk of SARS-CoV-2 infection in vaccinated individuals during the Alpha and Delta waves. However, there are limited data on the vaccine's efficacy and safety in solid organ transplant recipients during the Omicron wave.

Patients with solid organ transplant recipients seem to be at higher risk of COVID-19 infection due to the consumption of immunosuppressive medications and comorbidities (7). The severity of illness and mortality rate of the Omicron variant is still unclear in transplant recipients compared to other variants. Considering the increased Omicron variant worldwide, vaccination and booster dose injection are still the most important and best solutions to restrain it in transplant recipients and the healthy population. Research findings have shown that high levels of neutralizing antibodies to the Coronavirus are associated with protection against newer variants. It is possible that the injection of a booster dose of the existing vaccines and the subsequent increase in antibody levels will provide adequate protection and a suitable barrier against Omicron, as it has created protection against the previous strains.

It is still impossible to accurately determine whether the injected vaccines affect the incidence, severity, and manifestations of the disease in newly diagnosed strains.

2. Objectives

The present study investigated the effect of injected COVID-19 vaccines on the mortality rate in transplant patients in Mashhad, Iran.

3. Methods

This prospective cross-sectional study was conducted on liver transplant patients with moderate to severe COVID-19 referred to Montaseriyeh Hospital, affiliated with Mashhad University of Medical Sciences, Mashhad, Iran, from December 2021 to March 2022.

3.1. Inclusion and Exclusion Criteria

All liver transplant patients with Severe Acute Respiratory Infection strains without gender and age restrictions were entered into the present study. Patients who were not hospitalized due to infection with COVID-19 were excluded from the study. Patients who were not eligible for the COVID-19 vaccine at the time of hospitalization (i.e., did not belong to the vaccine target group) or lacked the conditions for sampling due to severe septal deviation, obstruction, or other conditions were removed from the study.

3.2. Study Design

The statistical population of the study included liver transplant recipients who were diagnosed with the Omicron strain of COVID-19 based on clinical symptoms with the approval of a specialist doctor, who was admitted to the various departments of Montaseriyeh Hospital from December 2021 to March 2022. The sampling method was through headcount.

Test-negative designs were used to assess the effectiveness of COVID-19 vaccines on mortality prognosis in liver patients infected with the Omicron strain. In the present study, the laboratory results of the SARS-CoV-2 virus among liver recipients with severe acute respiratory infection who were hospitalized for at least one night were investigated. Therefore, liver recipients with a positive PCR test (people whose test was positive within 48 hours of hospitalization or in the last 14 days) or those with all clinical symptoms of the Omicron strain of COVID-19 were considered samples.

3.3. Study Exposures

The vaccination status of liver recipients was the exposure in this study, which included the following:

3.3.1. Fully Vaccinated

Patients were considered fully vaccinated if they received the second or third dose at least 14 days before the onset of symptoms.

3.3.2. Partially Vaccinated

Patients who received only the first dose at least 14 days before the onset of SARS-CoV-2 symptoms were considered partially vaccinated.

3.3.3. Not Vaccinated

Patients with SARS-CoV-2 were considered unvaccinated if they had not received any COVID-19 vaccine or were vaccinated after the onset of symptoms.

Demographic information, such as age and gender, was recorded in a researcher-made checklist. Moreover, the clinical information, including underlying disease (e.g., diabetes, blood pressure, and cardiac disease), length of hospitalization, received immunosuppressive agents, the type of vaccination (Sinopharm, Kovaxin, Barkat, AstraZeneca, Pastococ, and Sputinc V), the number of received doses, the time of receiving the vaccine, history of infected with COVID-19 disease, were recorded.

3.4. Data Analysis

The collected data were entered into SPSS software version 24. Descriptive data, including quantitative and quantitative data, were explained in the form of percentage and mean ± SD, respectively. To compare quantitative variables, the chi-square test was used. Interval variables were compared using a *t*-test or its nonparametric equal. Correlation between variables was performed using the Spearman correlation test. Multiple linear regression was used to assess the predictive value of variables. P-values of less than 0.05% were considered significant.

3.5. Ethical Considerations

This study was extracted from a thesis to obtain an MD degree (4001544). The present study was approved by the Ethics Committee of Mashhad University of Medical Sciences (Code: IR.MUMS.REC.1400.316). All patients were coded, and data were recorded on a checklist without patients' names to maintain confidentiality.

4. Results

In general, 97 liver transplant recipients were entered into the present study, among whom 59.8% (n = 58) and 40.2% (n = 39) cases were male and female, respectively. The patients' mean age was 51.03 ± 16.73 years ranging between 8 and 73 years old. The frequency of underlying diseases in liver transplant recipients is presented in Table 1. The results of the PRC test for SARS-CoV-2 were positive in 26.7% (n = 23) of subjects, while it was negative in 73.3% (n = 63) of patients.

Among liver transplant recipients, 76.3% (n = 76) cases were hospitalized in the ward, and 14.4% (n = 14) individuals were hospitalized in the intensive care unit. Moreover, 5.2% of liver transplant recipients were isolated, and 4.1% had temporary hospitalizations. The mean hospitalization length was 7.04 ± 8.57 days ranging between 1 and 41 days. Only 23.7% of patients reported that they had contact with a person infected with COVID-19. Among the subjects, 42% were not infected with COVID-19 at all, while 56% had a history of infection with COVID-19 (44% one time, 8% two times, and 6% three times). Infection with COVID-19 after the injection of vaccination was reported in 43.5% of patients.

Due to vaccine selection limitations in Iran, most patients were vaccinated with the Sinopharm vaccine (90%). About 30% of the patients had not received any dosage of COVID-19 vaccination. Others had received at least one dosage of COVID-19 vaccination, among whom 2.9%, 40%, and 27.1% received one, two, and three dosages of COVID-19 vaccination, respectively. The mean interval between the first and second dosages of COVID-19 vaccination was 29.97 ± 3.75 days ranging between 27 and 40 days, and the mean interval between the second and third dosages of COVID-19 vaccination was 164.87 ± 56.02 days ranging between 60 and 267 days.

In general, 41.2% (n = 40) of the patients died, whereas 58.8% (n = 57) survived. Infection with COVID-19 was the cause of mortality in 11.3% (n = 11) of the patients. Regarding the other cases, 35.9% (n = 14) of the individuals passed away due to transplant rejection. Pulmonary problems (n = 3), infection (n = 3), enzyme level enhancement and dialysis (n = 2), and hepatocellular carcinoma recurrence (n = 2) were the other reasons for mortality in our cases.

The mean age scores were estimated at 58 ± 10.84 years (range: 35 - 69) in liver transplant recipients who passed away and 50.13 ± 17.18 years (range: 8 - 73) among those who survived, which showed no significant difference between them (Z = - 1.42, P = 0.15). Moreover, the lengths of hospitalization were 11.2 ± 10.2 (range: 1 - 26) and 6.5 ± 8.2 (range: 1 - 41) days in patients who passed away and those who survived, respectively. The comparison between liver transplant recipients who passed away and those who survived showed no significant difference in terms of hospitalization duration (Z = - 1.08; P = 0.27). Furthermore, no significant difference was reported between patients who passed away and those who survived regarding underlying diseases (χ^2 = 22.44; P = 0.21).

Table 2 compares various variables in liver transplant recipients between those who survived and those who passed away due to infection with the Omicron variant. Based on the obtained results, there was a significant difference between the liver transplant recipients who passed away and those who survived in terms of gender (P = 0.02) and hospitalization department (P = 0.007). Finally, a significant difference was reported between liver transplant recipients who passed away and those who survived in terms of the number of vaccine dosages (χ^2 = 24.09; P < 0.005).

Table 1. Frequency of Underlying Diseases in the Liver Transplant Recipients

Underlying Diseases	No. (%)
Hepatitis B	28 (28.9)
Cryptogenic Cirrhosis	26 (26.8)
Autoimmune hepatitis	12 (12.4)
Primary sclerosing cholangitis	5 (5.2)
Wilson's disease	4 (4.1)
Budd Chiari Syndrome	3 (3.1)
Hepatocellular carcinoma	3 (3.1)
Non-alcoholic steatohepatitis (NASH)	3 (3.1)
Hydatid Cyst	2 (2.1)
Hepatitis C virus	2 (2.1)
Gaucher's disease	1 (1.0)
hemochromatosis	1 (1.0)
Hypercholesterolemia	1 (1.0)
Hepatitis B and C	1 (1.0)
Autoimmune hepatitis and Budd-Chiari Syndrome	1 (1.0)
Crigler-Najjar syndrome	1 (1.0)
Primary biliary cholangitis	1 (1.0)
Drug-induced hepatitis	1 (1.0)
Hemochromatosis	1 (1.0)

Table 3 presents the comparison between deceased and survived liver transplant patients in terms of the consumption of immunosuppressive agents, which showed no significant difference in this regard ($P > 0.05$). The correlation between different variables in liver transplant recipients is summarized in Table 4. The results of univariate linear regression showed that gender ($\beta = 0.14$; $P = 0.02$), hospitalization department ($\beta = -0.09$; $P = 0.01$), and the number of received vaccine dosages ($\beta = 0.15$; $P < 0.005$) were predictive of mortality due to infection with Omicron variant in liver transplant recipients. Multiple linear regression showed that only the department of hospitalization ($\beta = -0.13$; $P = 0.005$) and the number of received vaccine dosages ($\beta = 0.13$; $P < 0.005$) were predictive of mortality due to infection with the Omicron variant in liver transplant recipients.

5. Discussion

In summary, vaccine failure against the Omicron variant was reported in 43.5% of patients. Infection with the Omicron variant caused mortality in 11.3% of the patients. It was also found that mortality was unrelated to age, underlying disease, hospitalization length, and immunosuppressive agent consumption. A difference was reported between patients who passed away and those who survived regarding the number of vaccine dosages received. The results of multiple linear regression showed that the number of received vaccine dosages was predictive of mortality due to the Omicron variant in liver transplant recipients.

Based on the World Health Organization guidelines, the injection of three dosages of the mRNA vaccine is recommended for transplant recipients. It seems that antibody titers and T-cell responses increased after the injection of three dosages of the mRNA vaccine. Due to vaccine selection limitations in Iran, most patients in our study were vaccinated with the Sinopharm vaccine.

Based on the findings of a study by Solera et al., the risk of severe disease decreased in recipients receiving at least 3 dosages of mRNA vaccine in the course of infection. The mortality rate of recipients who received less than 3 vaccine dosages had been reported at 13.9%. No mortality rate was reported in recipients who received 3 dosages of vaccine or higher (8). In our study, the mortality rate of liver recipients was 11.3%, which was higher among recipients who received fewer vaccine dosages. Based on the study, as mentioned earlier, older age and multiple comorbidities were the main factors determining the risk of severe disease (8). However, in the current study, the severity of the disease in liver recipients was not assessed. Based on

Table 2. Comparison of Frequency of Mortality in Transplant Patients Regarding Measured Variables

Variables	No. (%)		χ^2	P-Value
	Expire	Survive		
Gender			4.99	0.02
Male	10 (90.9)	48 (55.8)		
Female	1 (9.1)	38 (44.2)		
PCR test			3.12	0.07
Positive	5 (45.5)	18 (20.9)		
Negative	5 (45.5)	58 (67.4)		
Hospitalization department			11.98	0.007
Ward	4 (36.4)	70 (81.4)		
ICU	5 (45.5)	9 (10.5)		
Temporary hospitalization	1 (9.1)	3 (3.5)		
Isolation	1 (9.1)	4 (4.7)		
Infection after Vaccination			-	-
Yes	-	10 (43.5)		
No	-	13 (56.5)		
Contact with a person infected with COVID-19			1.09	0.29
Yes	4 (36.4)	19 (22.1)		
No	7 (63.6)	67 (77.9)		
Number of received vaccine dosages			24.09	< 0.005
None	11 (100)	12 (19.7)		
One	0 (0)	2 (3.3)		
Two	0 (0)	28 (45.9)		
Three	0 (0)	19 (31.1)		

Table 3. Comparison of Frequency of Mortality in Transplant Patients Regarding the Consumption of Immunosuppressive Agents

Immunosuppressive Agents	No. (%)			χ^2	P-Value
	Expire	Survive	Total		
Prograph				1.48	0.22
Yes	7 (63.6)	38 (44.2)	45 (46.4)		
No	4 (36.4)	48 (55.8)	52 (53.6)		
Prednisolone				0.72	0.39
Yes	7 (63.6)	43 (50)	50 (51.5)		
No	4 (36.4)	43 (50)	47 (48.5)		
Mycophenolic				0.07	0.78
Yes	7 (63.6)	51 (59.3)	58 (59.8)		
acid					
No	4 (36.4)	35 (40.7)	39 (40.2)		
Sirolimus				0.09	0.76
Yes	5 (45.5)	35 (40.7)	40 (41.2)		
No	6 (54.5)	51 (59.3)	57 (58.8)		

Table 4. The Correlation Between Different Variables in Liver Transplant Recipients

Variables	Mortality	
	r	P-Value
Age	- 0.14	0.15
Gender	0.22	0.02
Underlying disease	0.03	0.77
Hospitalizati on section	- 0.31	0.001
Number of vaccinates dosages	0.49	< 0.005
Hospitalizati on duration	- 0.11	0.28
Prograph	0.12	0.22
Prednisolone	0.08	0.39
Cellcept	0.02	0.78
Sirolimus	0.03	0.76
Receiving one type of immunosuppressive agent	0.006	0.95
Contact With a person infected with COVID-19	0.106	0.300

our study's results, advanced age was not related to mortality in liver transplant recipients. This discrepancy in the results may be due to differences in the characteristics of the samples or the type of vaccine against COVID-19. Moreover, gender was introduced as a predictive factor of mortality due to the Omicron variant in liver recipients, which found no similar finding in the literature to confirm.

Dimitriadis et al. studied liver transplant recipients and autoimmune hepatitis patients to assess the immune responses to the fourth vaccine dosage against the SARS-CoV-2 Omicron variant. The results revealed a low SARS-CoV-2 specific antibody response after two COVID-19 vaccines in liver recipients, which might increase after receiving the third and fourth dosages of the vaccine. An increase in anti-spike antibody titers after both the third and fourth vaccines were reported in liver recipients without SARS-CoV-2 specific antibody responses after two dosages. In this regard, it should be mentioned that the immunosuppressed liver recipients develop robust T-cell responses to WT and Omicron independent of anti-spike antibody titers (9). However, in a study by Kumar et al., a poor neutralizing antibody response has been reported in transplant recipients for Omicron compared to WT and Delta, even with three dosages of mRNA vaccine. The results were the same even 3 months after the third dosage. The high number of vaccine failures with the Omicron variant could be explained by the decrease in neutralization titers over time, which are several times lower for Omicron than for WT and Delta variants. The findings of the aforementioned study showed that the receptor binding domain titers were higher in patients who could neutralize Omicron. However, despite detectable receptor-binding domain antibodies, most subjects lacked neutralizing capacity against the Omicron variant. Therefore, standard antibody measurements should be interpreted cautiously due to the remarkable overlap at titers of > 1,000 U/mL (10). The results of another study by Kumar et al. indicated a low neutralizing antibody positivity after two dosages of mRNA vaccine, both for Alpha and Beta variants, which was increased with dosages of mRNA vaccine. Similar to other studies, they could not detect sufficient neutralization response in patients against the SARS-CoV-2 WT (11).

In a study by Benning et al., a stronger neutralization of the SARS-CoV-2 WT and the Delta variant was reported in transplant recipients after the third vaccine dosage. However, neutralizing antibodies above the threshold were not reported in 41% of kidney transplant recipients to detect the neutralization of SARS-CoV-2 WT or Delta variant. The same results were obtained even after the injection of the third dosage of the vaccine. Moreover, it should be mentioned that the neutralizing antibody activity against the Omicron variants was reported in 43% of transplant recipients. The number of breakthrough infections increased 6 months after receiving the third vaccine dosage, reported even in seroconverted recipients, emphasizing the insufficient neutralization against Omicron variants (12). Similarly, the results of a study by Chavarot et al. reported low antibody levels or no seroconversion after the third mRNA vaccine dosage in patients undergoing belatacept maintenance therapy (13).

Based on the findings of a study by Davidov et al., liver transplant recipients' humoral and cellular immune response decreased 4 months after receiving the third dosage of the vaccine. Moreover, liver transplant recipients

showed a lower immune response than healthy controls. They reported a weak immune response 3 weeks after the third vaccine dosage against the Omicron variant, which was null among recipients receiving combined immunosuppression (14). Although immune response against the Omicron variant has been reported in various studies, the results of the present study showed no relationship between mortality and immunosuppressive agent consumption in liver transplant patients. Having found no similar study assessing the correction of our findings, we recommend future studies in this area.

Due to impaired neutralization against Omicron variants in healthy individuals because of various mutations in the spike region of the variants facilitating immune escape, a similar situation is observed in transplant recipients (15-17). Therefore, it is possible that seroconverted transplant recipients are not completely protected against Omicron variants. In comparison to the general population, the risks of breakthrough infections, hospitalization, and death due to COVID-19 are higher among transplant recipients. In addition, the proportion of non-responders, even after the third vaccine dosage, is higher among transplant recipients than in the general population.

In this regard, a combination of various vaccines with a heterologous vaccination regimen has been suggested to enhance the immunization response in transplant recipients. In a study by Benning et al., one or two doses of ChAdOx1 were administered to 185 recipients before the third mRNA vaccine dosage. In all three assays, seropositive was reported in 44% of recipients receiving heterologous vaccination, while 55% among recipients who received three dosages of an mRNA vaccine (12). However, no clinical evidence supports the superior effectiveness of heterologous vaccination regimens considering seroconversion rates in transplant recipients (18, 19). Immunosuppression modulation is the other approach to improving the vaccine-induced immune response in transplant recipients. Some evidence has introduced the number and type of immunosuppressive agents as major determinants of seroconversion failure in transplant recipients, which could affect the vaccination outcome. The humoral responses and spike-specific T cells seem to depend on immunosuppressive treatment during vaccine administration in patients with an autoimmune disease (20-22). However, we found no relationship between mortality and the use of an immunosuppressive regimen. Similarly, the findings of a study by Benning et al. showed no differences in the type of immunosuppressive regimen between responders and non-responders after the third mRNA vaccine dosage (12). The reason for this may root in the low sample size of two studies or various immunosuppressive regimens taken by transplant recipients in the various studies.

Moreover, Benning et al. reported that seronegative was reported in transplant recipients who were transplanted recently, even after the third vaccine dosage (12). As a result, patients' immunosuppressive maintenance therapy is reduced, which leads to a better vaccination response. A similar finding with a higher immunologic response after two dosages of vaccination was reported by D'Offizi et al. in a study conducted on liver transplant recipients (23).

The other approach to optimizing vaccination response in solid organ transplant recipients is injecting the fourth vaccine dosage. Some evidence shows an improved humoral response after administering the fourth vaccine dosage in people with a weakened immune system (24, 25). It seems it is necessary to take additional measures to reach vaccine-induced immunity in poor responders (26).

Moreover, some evidence shows that passive immunization of patients with no immune response to therapeutic antibodies can be used against SARS-CoV-2 variants, especially Omicron variants, which are resistant to vaccines, to protect transplant patients against COVID-19.

Two vaccine dosages against COVID-19 disease increased the correlation between quantitative and functional CD4+ T-cell responses and anti-S1 immunoglobulin G antibodies in kidney and liver transplant recipients (23, 27). Therefore, anti-spike titers could be applied as a surrogate parameter to measure the immunologic response after COVID-19 vaccination.

5.1. Advantages and Limitations

This was the first study conducted on liver transplant recipients in Mashhad, Iran, which could provide appropriate data on the vaccination of transplant patients. Despite its strengths, our study had limitations, such as its small sample size and single-center nature. Since our study was limited to one center, it is impossible to generalize its results to other populations regarding the safety or effectiveness of vaccination. Moreover, our data cannot be generalizable to other transplant recipients. The present data were also at the risk of selection bias because treatment options for liver transplant recipients were unavailable for all patients. Additionally, we lacked data on the liver transplant recipients who sought care at other institutions.

5.2. Conclusions

Based on the results, it can be concluded that the mortality due to COVID-19 vaccination was higher among patients with fewer COVID-19 vaccination dosages and, consequently, could be related to vaccine-induced immunity in liver transplant recipients. However, due to the high vaccine failure rate, neutralizing antibody activity against

Omicron variants seems to be high. The variant should be considered an immune-escape variant; therefore, the vaccination strategies should be optimized for vulnerable liver transplant recipients.

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Footnotes

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Ethical Approval: The present study was approved by the Ethics Committee of Mashhad University of Medical Sciences (Code: IR.MUMS.REC.1400.316). All patients were coded, and data were recorded in a checklist without patients' names to maintain confidentiality.

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