Chapter 19
Immunogenicity of Inactivated SARS-CoV-2 Vaccine (BBIBP-CorV; Sinopharm) and Short-Term Clinical Outcomes in Vaccinated Solid Organ Transplant Recipients: A Prospective Cohort Study

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Abstract

Background

Immunocompromised patients have lower seroconversion rate in response to COVID-19 vaccination. The aim of this study is to evaluate the humoral immune response with short-term clinical outcomes in solid organ transplant recipients vaccinated with SARS-CoV-2 vaccine (BBIBP-CorV; Sinopharm).

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Methods
This prospective cohort was conducted from March to December 2021 in Abu Ali Sina hospital, Iran. All transplant recipients, older than 18 years were recruited. The patients received two doses of Sinopharm vaccine 4 weeks apart. Immunogenicity was evaluated through assessment of antibodies against the receptor-binding domain (RBD) of SARS-CoV-2 after the first and second dose of vaccine. The patients were followed up for 6 months after vaccination.

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Results
Out of 921 transplant patients, 115 (12.5%) and 239 (26%) had acceptable anti S-RBD immunoglobulin G (IgG) levels after the first and second dose, respectively. Eighty patients (8.68%) got infected with COVID-19 which led to 45 (4.9%) of patients being hospitalized. None of the patients died during follow-up period. Twenty-four (10.9%) liver transplant recipients developed liver enzyme elevation, and increased serum creatinine was observed in 86 (13.5%) kidney transplant patients. Two patients experienced biopsy-proven rejection without any graft loss.

Conclusion
Our study revealed that humoral response rate of solid organ transplant recipients to Sinopharm vaccine was low.

Keywords Liver transplant · Kidney transplant · COVID-19 · Vaccination · Humoral response · Sinopharm

1 Introduction

To date, coronavirus disease 2019 (COVID-19) is still considered as a serious global health problem. By September 5, 2022, more than 604 million infected patients with COVID-19 and 6,493,867 deaths have been identified based on World Health Organization (WHO) statistics [1]. Some studies have reported the mortality rate of COVID-19 in solid organ transplant (SOT) recipients to be approximately 20% [2, 3]. The most effective approach for COVID-19 prevention and reduction of its burden on health systems is rapid and widespread vaccination. Currently, several different vaccine platforms against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; the cause of COVID-19 disease) are available worldwide, some of which are authorized for emergency use. Since SOT recipients have been excluded from vaccine trials, there is insufficient information regarding safety and efficacy of vaccination in this population [4]. SOT recipients receive immunosuppressive therapy and are at risk for lower immunogenicity than the non-transplant population [5]. Most of studies in this context have focused on messenger ribonucleic acid (mRNA)-based vaccines, which mainly indicate low immune responses of SOT recipients against these types of vaccines [5, 6]. However, only eight studies thus far have evaluated the immunogenicity of inactivated anti-SARS-CoV-2 vaccines in SOT patients, and these have had mixed results [7–14].

Sinopharm COVID-19 vaccine or BBIBP-CorV is an inactivated vaccine produced by Beijing Bio-Institute of Biological Products (BBIBP) and authorized for emergency use by the WHO. Its efficacy against symptomatic COVID-19 and hospitalization rate has been reported to be 79%. According to the Strategic Advisory Group of Experts on Immunization, the Sinopharm vaccine should be administered over a two-dose schedule, given 3–4 weeks apart [15]. The trials have proved the

efficacy of this vaccine. The most reported adverse reactions were injection site pain and fever which were mild and safe limiting, with no serious adverse reactions [16, 17]. So far, only one large-scale study has been published on the use of this vaccine in transplant recipients [8].

Here, we present an evaluation of the humoral response, clinical outcomes, and adverse effects of this vaccine in a large population of SOT recipients.

2 Material and Methods

2.1 Study Design and Participants

This prospective observational cohort study was conducted from March to December 2021 on SOT patients whose date of surgery exceeded 6 months. The patients received two doses of COVID-19 vaccine BIBP developed by China National Biotec Group (CNBG), Sinopharm, 4 weeks apart in Shiraz Transplant Center, Abu Ali Sina Hospital, Shiraz, Iran, as the largest SOT center in Asia. The study was approved by the regional board of Shiraz University of Medical Sciences, Iran (#IR.SUMS.REC.1400.447).

The inclusion criteria were as follows: age over 18 years; having been transplanted more than 6 months prior to recruitment; and eligibility to receive COVID-19 vaccination according to relevant guidelines [18]. Exclusion criteria were patients with a laboratory-confirmed diagnosis of SARS-CoV-2 infection either by polymerase chain reaction (PCR) or serology; acute transplant rejection at the time of vaccination; inability to complete study-related procedures; and pregnancy or lactation.

2.2 Immunogenicity Assay

Blood samples were obtained from all participants before the first dose, 4 weeks after the first dose and 4 weeks after the second dose. Samples were tested by antibody-capture enzyme-linked immunosorbent assay (ELISA) [19] which detects immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies against the receptor-binding domain (RBD) of SARS-CoV-2 using commercial kits (Chemobind®, Iran) and an ELISA reader (Awareness Technologies Stat Fax 2100 Microplate Reader; Westport, CT, USA). The commercial anti-RBD IgM kit used in this study had 100% specificity (95% CI: 99.0–100) and 91.8% sensitivity (95% CI 94.9–99.9), while both specificity and sensitivity of the anti-RBD IgG kit were 100% (95% CI: 97.4–99.9). The levels of IgG and IgM antibodies were measured according to the manufacturer's instructions and ELISA index values above 1.1 were considered as a positive response.

2.3 Patients Follow-Up

The demographic and clinical information of all patients was collected in a predesigned form. All patients were monitored daily during the first week after each vaccination dose and then monthly up to 6 months after second dose by trained healthcare providers in Shiraz Transplant Center by telephone or in person. They were evaluated for any sign of vaccine adverse reactions or contracting COVID-19 and its complications. The patients were visited face to face by the transplant team and infectious disease specialist if needed.

2.4 Statistical Methods

In this study, continuous data were expressed as the mean ± standard deviation (SD) or median (IQR) and categorical data were given as frequency and percentage. In order to compare the responder and non-responder groups, student's t-test was used for continuous data and categorical data were analyzed using Chi-squared or Fisher's exact test. Univariate and multiple logistic regression analyses were performed to assess the potential predictors of non-responsiveness to the vaccination, using variables which were significant at the level of 0.2 ($P \leq 0.2$) in univariate analyses. Data were analyzed using the SPSS 16 package (SPSS Inc., Chicago, IL, USA).

3 Results

3.1 Participant Characteristics

Out of 921 transplant recipients who had received two doses of vaccine, 35.9% were females and 64.1% males (Table 19.1). The mean age of participants was 47.81 ± 13.42 (18–80) years. Overall, 665 and 221 patients had received kidney or liver transplants, respectively. The number of simultaneous pancreas kidney (SPK) and heart transplant recipients were 28 and 7, respectively. The most common comorbidities found were hypertension (44.4%), diabetes mellitus (28.2%), and dyslipidemia (14.8%).

The major underlying causes leading to end-stage renal disease (ESRD) in kidney transplant recipients were hypertension (54.5%), diabetes (24.8%), autosomal-dominant polycystic kidney disease (ADPKD; 15.2%), and systemic lupus erythematosus (SLE; 5.5%). The most important indications for liver transplantation were cryptogenic (23.2%), primary sclerosing cholangitis (PSC; 20.8%), hepatitis B (17.4%), Wilson disease (6.8%), and autoimmune hepatitis [20] (16.4%).

Table 19.1 The solid organ transplant recipient demographic data of those who received first and second dose of Sinopharm COVID-19 vaccine ($N = 921$)

Variables	Responder $N = 239$	Non responder $N = 682$	Total	p-value
Age, *n* (%)				
<30 years old	74 (10.9%)	20 (8.4%)	94 (10.3%)	0.44
30–50 years old	298 (44%)	102 (42.9%)	400 (43.7%)	
>50 years old	306 (45.1%)	116 (48.7%)	422 (46.1%)	
Sex, *n* (%)				0.86
Male	152 (63.6%)	438 (64.2%)	590 (64.1%)	
Female	87 (36.4%)	244 (35.8%)	331 (35.9%)	
Comorbid disease, *n* (%)				
Diabetes mellitus	69(28.9%)	191(28%)	260 (28.2%)	0.79
Hypertension	117 (49%)	292 (42.8%)	409 (44.4%)	0.13
Dyslipidemia	43 (18%)	93 (13.6%)	136 (14.8%)	0.19
Type of transplantation, *n* (%)				0.42
Liver	48 (20.1%)	173 (25.4%)	221 (24.0%)	
Kidney	182 (76.2%)	483 (70.8%)	665 (72.2%)	
Simultaneous pancreas-kidney	7 (2.9%)	21 (3.1%)	28 (3%)	
Heart	2 (0.8%)	5 (0.7%)	7 (0.8%)	
Type of donor, *n* (%)				0.09
Living	50 (21.4%)	93 (14.5%)	143 (16.3%)	
Deceased donor	184 (78.6%)	549 (85.5%)	733 (83.7%)	
Time passed from transplantation, *n* (%)				0.07
6 months–1 year	8 (3.4%)	50 (7.4%)	58 (6.4%)	
1–3 years	48 (20.3%)	144 (21.4%)	192 (21.1%)	
More than 3 years	180 (76.3%)	479 (71.2%)	659 (72.5%)	
Immunosuppressive medications, *n* (%)				
Anti-metabolites	225 (94.5%)	640 (93.8%)	865 (94%)	0.69
Calcineurin inhibitors	201 (84.8%)	593 (87%)	794 (86.4%)	0.40
Corticosteroids	182 (76.5%)	493 (72.3%)	675 (73.4%)	0.27
Mammalian target of rapamycin inhibitors	30 (12.6%)	79 (11.6%)	109 (11.8%)	0.67
Tacrolimus level, ng/ml, mean ± SD	5.96 ± 2.21	6.16 ± 3.86	6.14 ± 3.55	0.58
Everolimus level, ng/ml, mean ± SD	5.88 ± 1.83	5.48 ± 3.2	5.57 ± 2.89	0.79
Alanine transaminase, U/L, mean ± SD	37.10 ± 15.00	39.92 ± 17.23	39.18 ± 16.71	0.42
Aspartate aminotransferase, U/L, mean ± SD	41.00 ± 14.02	45.61 ± 12.00	44.41 ± 12.70	0.38
Serum creatinine, mg/dL, mean ± SD	2.76 ± 1.90	2.97 ± 1.00	2.81 ± 1.71	0.61
Glomerular filtration rate, mL/min/1.73 m2, mean ± SD	81.20 ± 22.18	73.98 ± 25.00	79.32 ± 23.14	0.93

(continued)

Table 19.1 (continued)

Variables	Responder $N = 239$	Non responder $N = 682$	Total	p-value
Underlying liver disease, *n* (%)				0.87
Primary sclerosing cholangitis	12 (25.5%)	31 (19.4%)	43 (20.8%)	
Wilson disease	1 (2.1%)	13 (8.1%)	14 (6.8%)	
Hepatitis B	9 (19.1%)	27 (16.9%)	36 (17.4%)	
Cryptogenic	12 (25.5%)	36 (22.5%)	48 (23.2%)	
Non-alcoholic steatohepatitis	4 (8.5%)	15 (9.4%)	19 (9.2%)	
Autoimmune hepatitis	7 (14.9%)	27 (16.9%)	34 (16.4%)	
Budd–Chiari syndrome	1 (2.1%)	7 (4.4%)	8 (3.9%)	
Alcoholic	1 (2.1%)	4 (2.5%)	5 (2.4%)	
Underlying kidney disease, *n* (%)				0.11
Diabetes mellitus	21 (21.2%)	64 (26.2%)	85 (24.8%)	
Hypertension	53 (53.5%)	134 (54.9%)	187 (54.45%)	
Autosomal-dominant polycystic kidney disease	15 (15.2%)	37 (15.2%)	52 (15.2%)	
Systemic lupus erythematosus	10 (10.1%)	9 (3.7%)	19 (5.5%)	
History of rejection 1 year before transplantation, *n* (%)				0.34
Yes	16 (6.7%)	60 (8.8%)	76 (8.3%)	
No	223 (93.3%)	621 (91.2%)	844 (91.7%)	
History of re-transplantation, *n* (%)				0.51
Yes	10 (4.2%)	36 (5.3%)	46 (5%)	
No	228 (95.8%)	644 (94.7%)	872 (95%)	
History of positive COVID-19 PCR before vaccination, *n* (%)				0.33
Yes	28 (11.7%)	65 (9.5%)	93 (10.1%)	
No	211 (88.3%)	617 (90.5%)	828 (89.9%)	
Time of COVID-19 with positive PCR before vaccination, *n* (%)				0.09
1–3 months ago	2 (7.1%)	15 (23.1%)	17 (18.3%)	
3–6 months ago	10 (35.7%)	26 (40%)	36 (38.7%)	
6–12 months ago	16 (57.1%)	24 (36.9%)	40 (43%)	
History of negative PCR but symptomatic COVID-19, *n* (%)				0.15
Yes	24 (10%)	49 (7.2%)	73 (7.9%)	
No	215 (90%)	633 (92.8%)	848 (92.1%)	
Time of symptomatic COVID-19 with negative PCR, *n* (%)				0.07
1–3 months ago	2 (9.5%)	9 (20.9%)	11 (17.2%)	
3–6 months ago	6 (28.6%)	20 (46.5%)	26 (40.6%)	
6–12 months ago	13 (61.9%)	14 (32.6%)	27 (42.2%)	

(continued)

Table 19.1 (continued)

Variables	Responder $N = 239$	Non responder $N = 682$	Total	p-value
History of admission due to COVID-19 before vaccination, *n* (%)				0.10
Yes	16 (6.7%)	28 (4.1%)	44 (4.8%)	
No	233 (93.3%)	654 (95.9%)	877 (95.2%)	
Time of admission due to COVID-19 before vaccination, *n* (%)				0.94
1–3 months ago	2 (15.4%)	5 (19.2%)	7 (17.9%)	
3–6 months ago	4 (30.8%)	10 (38.5%)	14 (35.9%)	
More than 6 months ago	7 (53.8%)	11 (42.3%)	18 (46.2%)	

Among participants, 72.5% had undergone transplantation more than 3 years previously and 6.4% had received transplants 6–12 months prior to study enrollment.

In total, 60.8% of patients were taking calcineurin inhibitors (CNIs), corticosteroids, and antimetabolites at the time of the first and second doses of the vaccine. Also, 3.8% and 17.9% of patients were receiving a combination of mTOR inhibitors, corticosteroids and antimetabolites, and CNIs combined with antimetabolites, respectively.

3.2 SARS-CoV-2 Vaccination Immunogenicity

The median (IQR) plasma level of anti S-RBD IgM and IgG before vaccination was 0.08 [0.06, 0.15] and 0.31 [0.13, 0.57], respectively. Out of the 921 SOT recipients, 115 (12.5%) and 239 (26%) patients had acceptable anti S-RBD IgG levels (>1.1) 4 weeks after the first and second dose, respectively. After omitting cases who had shown a positive PCR test for COVID-19 within 6 months prior to vaccination, 104 (12.6%) and 211 (25.5%) patients had acceptable anti RBD levels 4 weeks after the first and second dose.

3.3 Clinical Outcomes 6 Months Post-Vaccination

A total of 80 patients (8.68%) got infected with COVID-19 after vaccination, eight (0.9%) of those who were infected between the first and second (8.08 ± 2.21 days) dose and 72 (7.8%) were infected 133.90 ± 54.94 days after the second dose. Also, among the COVID-19 infected patients ($n = 80$), 13 and 24 had acceptable anti-RBD IgG levels between the first and second dose and after the second dose, respectively. Forty-five (4.9%) patients were admitted to hospital due to COVID-19 after

Table 19.2 Univariate and multivariate analysis regarding qualitative and quantitative variables between seroconversion and non-seroconversion to Sinopharm COVID vaccine

	Univariate analysis		Multivariate analysis	
Variables	OR (CI)	*P*-value	OR (CI)	*P*-Value
Age				
<30 years old	1.4 (0.81,2.4)	0.20	0.82(0.23, 2.94)	0.77
30–50 years old	1.1(0.81,1.5)	0.51	0.76 (0.44,1.3)	0.32
>50 years old	Ref	–		
Sex				
Male	1.02(0.75,1.39)	0.86		
Female	Ref.	–		
Type of transplantation				
Liver	1.24(0.54,2.84)	0.59		
Kidney	0.91(0.42,1.99)	0.83		
Others	Ref.	–		
Comorbid disease				
Diabetes mellitus	0.95(0.69,1.32)	0.79		
Hypertension	0.78(0.58,1.04)	0.14	0.63 (0.35,1.16)	0.14
Dyslipidemia	0.72(0.48,1.06)	0.17	0.83 (0.46,1.16)	0.52
Time passed from transplantation				
6 months–1 year	2.34(1.09,5.05)	0.02	5.75(1.29, 25.48)	0.02
1–3 years	1.12(0.78,1.63)	0.52	1.22(0.67,2.21)	0.51
More than 3 years	Ref.		Ref.	
Immunosuppressive medications				
Anti-metabolites	0.88(0.46,1.67)	0.69		
Calcineurin inhibitors	1.19(0.78,1.81)	0.49		
Corticosteroids	0.8(0.56,1.13)	0.20	0.69(0.33,1.42)	0.32
Mammalian target of rapamycin inhibitors	0.9(0.58,1.42)	0.67		
Tacrolimus level	1.01(0.95,1.08)	0.58		
Certicane level	0.95(0.67,1.34)	0.78		
Underlying liver disease				
Primary sclerosing cholangitis / Autoimmune hepatitis	0.71(0.31,1.62)	0.42		
Cryptogenic/Non-alcoholic steatohepatitis	0.75(0.32,1.74)	0.51		
Others (Wilson/Budd–Chiari/Alcoholic)	Ref.	–		
Underlying kidney disease				
Diabetes mellitus	1.65(0.82,3.31)	0.15	1.65 (0.78,3.5)	0.18
Hypertension	1.37(0.76,2.45)	0.28	1.62 (0.83,3.12)	0.15
Others (Autosomal-dominant polycystic kidney disease, Systemic lupus erythematosus)	Ref.	–	Ref.	

(continued)

Table 19.2 (continued)

Variables	Univariate analysis		Multivariate analysis	
	OR (CI)	*P*-value	OR (CI)	*P*-Value
History of rejection 1 year before transplantation				
Yes	1.34(0.76,2.38)	0.35		
No	Ref.	–		
History of positive PCR before vaccination				
Yes	0.79(0.49,1.27)	0.33		
No	Ref.	–		
History of negative PCR but symptomatic COVID-19				
Yes	0.69(0.41,1.15)	0.16	1.04 (0.37, 2.87)	0.93
No	Ref.	–	Ref.	
History of admission due to COVID-19 before vaccination				
Yes	0.59 (0.31,1.12)	0.11	0.71 (0.23,2.13)	0.54
No	Ref.	–	Ref.	

receiving the second dose of vaccine. None of the patients died during the 6-month follow-up period.

The univariate analyses showed that hypertension, dyslipidemia, the time from transplantation, receiving corticosteroid, underlying kidney diseases, history of symptomatic COVID-19 with negative PCR, and history of hospital admission before vaccination due to COVID-19 were considered as risk factors for non-responsiveness to the vaccination (Table 19.2). However, the multivariate analysis demonstrated that time from transplantation was the only significant risk factor for non-responsiveness (OR = 5.75, 95% CI = 1.29–25.48; $p = 0.02$). This showed that the odds of non-responsiveness to the vaccination in patients who had undergone transplantation 6–12 months before vaccination compared to people who were transplanted >3 years before vaccination was 5.75.

3.4 Adverse Events

Figure 19.1 shows the rate of adverse events (AEs) after the first and second dose of the vaccine. Fatigue, injection site pain, and fever were the most frequent AEs found in patients. Five and three patients visited the hospital emergency room due to AEs (allergic reactions, hypotension, and severe headache) after the first and second dose of vaccine, respectively.

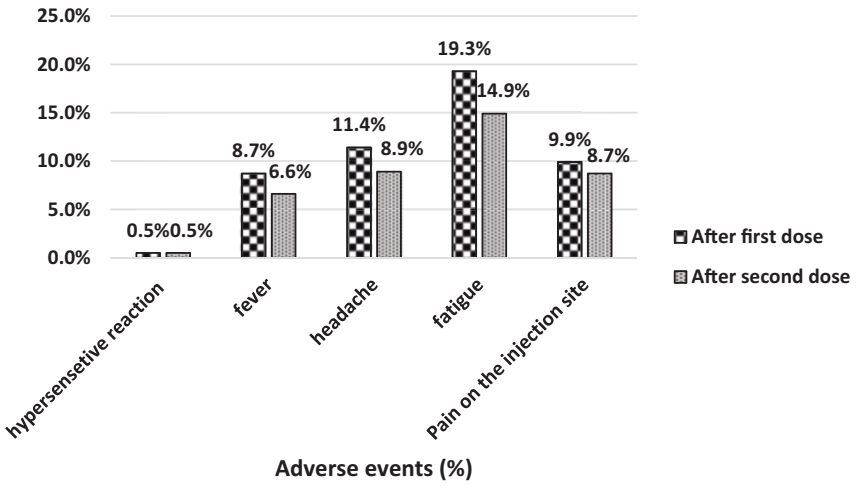

Fig. 19.1 Adverse events following first and second dose of Sinopharm COVID-19 vaccine among solid organ transplant recipients ($N = 921$)

Among the liver transplant recipients (n = 221), 24 (10.9%) developed liver enzyme elevation (17 cases after first dose and 7 patients after second dose). Also, elevated serum creatinine was observed in 86 (13.5%) (44 cases after the first and 42 after the second dose) of the kidney transplant recipients. In all of these patients, other reasons for serum creatinine or liver enzymes elevation were evaluated and ruled out. Two liver transplant recipients who experienced liver enzyme elevation (more than fivefold over the upper limit of normal) needed hospital admission and received corticosteroids. However, none of the above kidney transplant recipients needed hospitalization, hemodialysis, or continuous renal replacement therapy (CRRT).

Among the vaccine recipients, two patients developed antibody-mediated rejection confirmed by biopsy, one of whom was a kidney transplant recipient (8 days post-second dose) and the other patient had received a liver transplant (11 days after the second dose). Both of these patients were admitted, evaluated regarding the cause of rejection and received methylprednisolone. Biopsies after treatment in both patients showed normal histopathology, neither of them experienced graft loss and both were discharged 12 and 9 days after admission.

4 Discussion

Immunosuppressed patients, including SOT recipients, have a weaker humoral and cellular immune response compared to normal population regarding vaccination. In this study, the humoral response rate to Sinopharm COVID-19 vaccine and short-time clinical outcomes were evaluated. Nearly 13% and 25.5% of patients had

acceptable anti-spike protein RBD IgG levels after the first and second dose of vaccine, respectively. The trials on Sinopharm vaccine immunogenicity in the general population demonstrated a seroconversion rate after receiving two doses of vaccine to be more than 90% [21, 22]. In the case of SOT recipients, a number of vaccine types have been tested. Boyarsky et al. evaluated the immunogenicity of the SARS-CoV-2 mRNA vaccines in SOT recipients and observed that only 15% and 54% of patients had acceptable antibody level after the first and second dose, respectively [23]. Also, it has been reported that the antibody response to the Janssen viral vector-based COVID-19 vaccine was 16% [5]. Another study showed that 24% and 34.8% of heart transplant patients vaccinated with ChAdOx1 (AZD1222), another viral vector vaccine, developed a detectable antibody response after the first and second dose [24]. In one study on kidney transplant recipients vaccinated with inactivated Sinopharm-CoronaVac vaccine (BBIBP-CorV), it was demonstrated that only 9% of the transplant recipients had an acceptable antibody level, while the antibody level was acceptable in 100% of participants in the control group [25]. These differences in seroconversion rates across the various vaccine types may have been caused by the type of vaccine platform, number of participants, and factors affecting seroconversion in transplant recipients, such as type of immunosuppressive regimens, time passed since transplantation, and underlying diseases. However, the lower rates of seroconversion in transplant recipients compared to the normal population have been a common finding across these studies.

The univariate analysis revealed that age, diabetes, hypertension, a recent transplant operation, history of hospitalization due to COVID-19 before vaccination, and kidney transplantation secondary to diabetes or hypertension were risk factors for low immunogenicity response. However, logistic regression demonstrated that the only significant predictor of low immunogenicity response was vaccination within 6 months to 1 year following transplantation. Advanced age is one of the well-established risk factors for lower antibody titers in transplant and non-transplant patients receiving influenza, hepatitis B, and pneumococcal vaccines [26]. Also, many studies have identified advanced age as one of the strongest risk factors for a weak response to COVID-19 vaccines [27–30]. Diabetes and hypertension were among risk factors for poor response to vaccination in our patients, especially among kidney transplant recipients. Such metabolic disorders are common among SOT patients, mainly due to treatment with immunosuppressants such as CNIs and corticosteroids. For example, Mazzola et al. found that diabetes was a risk factor for lack of response to vaccination among kidney transplant recipients [31], and similar results were reported with seasonal influenza vaccination in diabetic patients in some countries [32, 33]. It seems that low antibody response is secondary to diabetes-induced immune dysfunction. Furthermore, two studies evaluating risk factors for attenuated response to mRNA COVID-19 vaccines found that the presence of hypertension was for a contributor to poor seroconversion due to its negative effect on immune function [34, 35].

Transplant recipients who have recently undergone transplantation are expected to have lower seroconversion rate to COVID-19 vaccination due to their need for treatment with higher doses of immunosuppressive medications, particularly

antimetabolites [30, 36, 37]. Marta et al. found that the unfavorable effect of mycophenolate mofetil (MMF) on seroconversion was dose-dependent and MMF dose modification prior to vaccination can improve the immune system response to COVID-19 vaccination [38]. Also, our study revealed that receiving corticosteroids can have a negative effect on seroconversion. The COViNEPH Project, which evaluated different aspects of COVID-19 infection in nephrology including effective factors on humoral immune response to COVID-19 vaccination, found that seroconversion rate was 66.7% in patients who did not receive corticosteroids in their maintenance immunosuppressive regimen [37]. Also, a similar result was observed in immunocompromised hematologic cancer patients receiving prednisolone [39]. Although some studies have demonstrated that COVID-19 infection prior to vaccination leads to increased immunogenicity of COVID-19 vaccines in transplant and non-transplant patients [31, 40], this association was not observed in our study. Moreover, our results showed that transplant patients with a history of COVID-19 and COVID-19-related hospitalization had a lower response rate to vaccination. It is possible that a high percentage of patients with prior COVID-19 infections in our study became infected or were hospitalized due to COVID-19 more than 6 months prior to vaccination. Previous studies have shown that IgG levels against the SARS-CoV-2 spike protein decrease with time [41, 42]. In addition, Yalcin et al. demonstrated that the patients who had been infected more than 6 months prior to COVID-19 vaccination had the lowest antibody titers and antibody responses were highest in patients who had been infected 3–6 months before vaccination [40]. Another possible explanation involves the potential negative effect of corticosteroids on response to vaccination [43]. Administration of high doses of corticosteroids to our transplant recipients suffering from moderate to severe COVID-19 infection could possibly have caused low response rates to vaccination in spite of prior COVID-19 infection [44].

Our results showed that nearly 1% of patients became infected with COVID-19 after their first vaccination and just under 8% were infected within 3 months after receiving the second dose. Among the infected patients, only 5% were hospitalized due to COVID-19 during the time period of 6 months after vaccination and no COVID-19-related mortality occurred. Previous studies revealed that getting COVID-19 is possible after vaccination in transplant recipients due to their lower rates of seroconversion [31, 45]. A multicenter study showed that COVID-19 related hospitalization, critical COVID-19, and subsequent mortality were more prevalent in transplant recipients compared to normal population groups (7% vs. 2%), which indicates the importance of the third dose of vaccine in transplant recipients [46]. In support of this, a recently published meta-analysis found that transplant recipients who were seronegative after two doses of COVID-19 vaccines turned seropositive after receiving the third dose [47].

Our findings are in line with other studies which showed that fatigue, injection site pain, and fever were the most frequent AEs of Sinopharm vaccination [16, 48]. In our study, liver enzyme elevation occurred in 11% of patients, two of them required medical intervention. Similar findings and new onset or activation of autoimmune hepatitis have also been reported following administration of mRNA

(Pfizer-BioNTech; Moderna Biotech) and viral vector-based (OxfordAstraZeneca) vaccines [49–51]. Hepatic artery thromboembolism has also been reported which resulted in death in some cases [52]. A rise in serum creatinine in kidney transplant patients following vaccination has been observed in our research and in other studies [53, 54]. Also, some investigations have reported cases of acute kidney injury and minimal change disease following COVID-19 vaccination [55]. A possible explanation of this is that interferon-γ (INF-γ), tumor necrosis factor-α (TNF-α), and interleukin-2 (IL-2) produced as a result of T-cell responses to foreign mRNA could lead to podocytopathies and B-cell production of disease-specific antibodies in susceptible patients and to aggravation of subclinical or quiescent glomerular diseases. Also, SARS-CoV-2 infection itself can cause activation of diverse autoimmune and alloimmune renal diseases by a similar pathogenesis [56].

Two of the participants in our study experienced organ rejection after the second dose of vaccine. However, those grafts were recovered after administration of methyl prednisolone to both patients. Some studies have reported organ rejection after receiving COVID-19 vaccines although rejection prognoses were generally good [57–59]. However, one case of steroid-resistant acute cellular rejection was reported in a liver transplant recipient vaccinated with a COVID-19 mRNA vaccine [60]. Although the possibility of rejection following vaccination exists in SOT recipients, the association with vaccination has not been proved in large studies or trials. Some studies have mentioned that nonspecific immune activation (adjuvant effect) or induction of cross-reactive immunity coincident with vaccinations is responsible for cellular or humoral antidonor alloresponses and consequently rejection [61, 62]. Although the majority of organ rejections after vaccination have occurred following administration of mRNA vaccines, it cannot be concluded that a definite correlation exists between vaccine platform and organ rejection. This finding may be a result of higher percentage of SOT recipients vaccinated with mRNA vaccines.

4.1 Limitations

Although our study is one of the largest studies conducted on inactivated COVID-19 vaccination in SOT recipients, it should be interpreted cautiously due to some limitations. First, only the inactivated Sinopharm BBIBP-CorV vaccine was investigated. This obviated comparisons of the results with other vaccines. Second, no control group was included in this study and, therefore, a comparison between transplant and non-transplant patients was not possible. Furthermore, due to the 6-month follow-up period, data regarding a third vaccine dose was not available. Finally, this study focused on humoral immune response, while evaluation of cellular immune responses can provide more comprehensive information regarding vaccination efficacy.

4.2 Conclusion

The results of our study are consistent with those of previous investigations which showed that the humoral response rate to the Sinopharm vaccine was low in SOT recipients. The short time interval between transplantation and vaccination may cause low seroconversion rates in SOT recipients, due to the high dosages of immunosuppressive medications used during this period. It is recommended that a third dose of a different vaccine type or use of adjuvants may be employed in SOT recipients who have been previously vaccinated with two doses of inactivated vaccine. For example, a third vaccine dose using one of the new bivalent versions of the spike protein mRNA vaccines from Pfizer/BioNTech and Moderna Biotech [63] to giver better protection against the SARS-CoV-2 Omicron sub-variants.

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Disclosure The authors of this manuscript have no conflicts of interest to disclose.

Declarations

Ethics Approval and Consent to Participate

The study was approved by the regional board of Shiraz University of Medical Sciences, Iran (#IR.SUMS.REC.1400.447). Informed consent from each study participant was also obtained before data collection.

Consent for Publication

Not applicable.

Availability of Data and Materials

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Competing Interests

The authors declare that we do not have any conflict of interest.

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References

1. World Health Organization; Coronavirus disease (COVID-2019) situation reports. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/. Accessed 24 February 2022
2. Kates OS, Fisher CE, Stankiewicz-Karita HC, et al (2020) Earliest cases of coronavirus disease 2019 (COVID-19) identified in solid organ transplant recipients in the United States. Am J Transplant 20(7):1885–1890
3. Ali Malekhosseini S, Nikoupour H, Gholami S, et al (2021) A Report of 85 Cases of COVID-19 and Abdominal Transplantation From a Single Center: What Are the Associated Factors With Death Among Organ Transplantation Patients. Transplantation 105(1):90–99
4. Negahdaripour M, Shafiekhani M, Moezzi SMI et al (2021) Administration of COVID-19 vaccines in immunocompromised patients. Int Immunopharmacol 99:108021 https://doi.org/10.1016/j.intimp.2021.108021

5. Boyarsky BJ, Chiang TP, Ou MT, et al (2021) Antibody Response to the Janssen COVID-19 Vaccine in Solid Organ Transplant Recipients. Transplantation 105(8):e82-e83
6. Cucchiari D, Egri N, Bodro M, et al (2021) Cellular and humoral response after MRNA-1273 SARS-CoV-2 vaccine in kidney transplant recipients. Am J Transplant 21(8):2727–2739
7. Eren Sadioğlu R, Demir E, Evren E, et al (2021) Antibody response to two doses of inactivated SARS-CoV-2 vaccine (CoronaVac) in kidney transplant recipients. Transpl Infect Dis 23(6):e13740. https://doi.org/10.1111/tid.13740
8. Medina-Pestana J, Covas DT, Viana LA, et al (2022) Inactivated Whole-virus Vaccine Triggers Low Response Against SARS-CoV-2 Infection Among Renal Transplant Patients: Prospective Phase 4 Study Results. Transplantation 106(4):853–861
9. Erol Ç, Yanık Yalçın T, Sarı N, et al (2021) Differences in Antibody Responses Between an Inactivated SARS-CoV-2 Vaccine and the BNT162b2 mRNA Vaccine in Solid-Organ Transplant Recipients. Exp Clin Transplant 19(12):1334–1340
10. Seija M, Rammauro F, Santiago J, et al (2021) Comparison of antibody response to SARS-CoV-2 after two doses of inactivated virus and BNT162b2 mRNA vaccines in kidney transplant. Clin Kidney J 15(3):527–533
11. Dheir H, Tocoglu A, Toptan H, et al (2022) Short and mid-term SARS-CoV-2 antibody response after inactivated COVID-19 vaccine in hemodialysis and kidney transplant patients. J Med Virol 94(7):3176–3183
12. Tu ZH, Jin PB, Chen DY, et al (2022) Evaluating the Response and Safety of Inactivated COVID-19 Vaccines in Liver Transplant Recipients. Infect Drug Resist 15:2469–2474
13. Mendizabal M, Ducasa N, Benencio P, et al (2022) Heterologous adenovirus-vector/messenger RNA regimen is associated with improved severe acute respiratory syndrome coronavirus 2 humoral response in liver transplant recipients. Hepatol Commun 6(10):2850–2859
14. Duan B, Zhang G, Wang W, et al (2022) Immunogenicity profiling and distinct immune response in liver transplant recipients vaccinated with SARS-CoV-2 inactivated vaccines. Front Immunol 13:954177. https://doi.org/10.3389/fimmu.2022.954177
15. Strategic advisory group of experts on immunization (2021) Evidence Assessment:Sinopharm/BBIBP COVID-19 vaccine. https://cdn.who.int/media/docs/defaultsource/immunization/sage/2021/april/2_sage29apr2021_criticalevidence_sinopharm.pdf
16. Xia S, Duan K, Zhang Y, et al (2020) Effect of an Inactivated Vaccine Against SARS-CoV-2 on Safety and Immunogenicity Outcomes: Interim Analysis of 2 Randomized Clinical Trials. JAMA 324(10):951–960
17. Xia S, Zhang Y, Wang Y, et al (2021) Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: a randomised, double-blind, placebo-controlled, phase 1/2 trial. Lancet Infect Dis 21(1):39–51
18. Kute V, Meshram HS, Sharma A, et al (2021) Update on Coronavirus 2019 Vaccine Guidelines for Transplant Recipients. Transplant Proc 54(6):1399–1404
19. Raschetti R, Morgutti M, Menniti-Ippolito F, et al (1999) Suspected adverse drug events requiring emergency department visits or hospital admissions. Eur J Clin Pharmacol 54(12):959–963
20. Cao B, Wang Y, Wen D, et al (2020) A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19. New Engl J Med 382(19):1787–1799
21. Feng Y, Chen J, Yao T et al (2021) Safety and immunogenicity of inactivated SARS-CoV-2 vaccine in high-risk occupational population: a randomized, parallel, controlled clinical trial. Infect Dis Poverty 10(1):138–138
22. Ferenci T, Sarkadi B (2022) RBD-specific antibody responses after two doses of BBIBP-CorV (Sinopharm, Beijing CNBG) vaccine. BMC Infect Dis 22(1):87–87
23. Boyarsky BJ, Werbel WA, Avery RK, et al (2021) Antibody Response to 2-Dose SARS-CoV-2 mRNA Vaccine Series in Solid Organ Transplant Recipients. JAMA 325(21):2204–2206
24. Tanner R, Starr N, Chan G, et al (2022) Humoral response to SARS-CoV-2 adenovirus vector vaccination (ChAdOx1 nCoV-19 [AZD1222]) in heart transplant recipients aged 18 to 70 years of age. J Heart Lung Transplant 41(4):492–500

25. Bruminhent J, Setthaudom C, Chaumdee P et al (2021) SARS-CoV-2-specific humoral and cell-mediated immune responses after immunization with inactivated COVID-19 vaccine in kidney transplant recipients (CVIM 1 study). Am J Transplant 2(3):813–822
26. Kao TM, Hsieh SM, Kung HC, et al (2010) Immune response of single dose vaccination against 2009 pandemic influenza A (H1N1) in the Taiwanese elderly. Vaccine 28(38):6159–6163
27. Nace DA, Kip KE, Mellors JW, et al (2021) Antibody Responses After mRNA-Based COVID-19 Vaccination in Residential Older Adults: Implications for Reopening. J Am Med Dir Assoc 22(8):1593–1598
28. Collier DA, Ferreira I, Kotagiri P, et al (2021) Age-related immune response heterogeneity to SARS-CoV-2 vaccine BNT162b2. Nature 596(7872):417–422
29. Rabinowich L, Grupper A, Baruch R, et al (2021) Low immunogenicity to SARS-CoV-2 vaccination among liver transplant recipients. J Hepatol 75(2):435–438
30. Stumpf J, Siepmann T, Lindner T, et al (2021) Humoral and cellular immunity to SARS-CoV-2 vaccination in renal transplant versus dialysis patients: A prospective, multicenter observational study using mRNA-1273 or BNT162b2 mRNA vaccine. Lancet Reg Health Eur 9100178. https://doi.org/10.1016/j.lanepe.2021.100178
31. Mazzola A, Todesco E, Drouin S, et al (2021) Poor Antibody Response after Two Doses of SARS-CoV-2 vaccine in Transplant Recipients. Clin Infect Dis 74(6):1093–1096
32. Yang L, Nan H, Liang J et al (2017) Influenza vaccination in older people with diabetes and their household contacts. Vaccine 35(6):889–896
33. Jiménez-Garcia R, Lopez-de-Andres A, Hernandez-Barrera V, et al (2017) Influenza vaccination in people with type 2 diabetes, coverage, predictors of uptake, and perceptions. Result of the MADIABETES cohort a 7 years follow-up study. Vaccine 35(1):101–108
34. Drummond GR, Vinh A, Guzik TJ, et al (2019) Immune mechanisms of hypertension. Nat Rev Immunol 19(8):517–532
35. Watanabe M, Balena A, Tuccinardi D, et al (2022) Central obesity, smoking habit, and hypertension are associated with lower antibody titres in response to COVID-19 mRNA vaccine. Diabetes Metab Res Rev 38(1):e3465 doi: https://doi.org/10.1002/dmrr.3465
36. Caillard S, Thaunat O (2021) COVID-19 vaccination in kidney transplant recipients. Nat Rev Nephrol 17(12):785–787
37. Dębska-Ślizień A, Ślizień Z, Muchlado M, et al (2021) Predictors of Humoral Response to mRNA COVID19 Vaccines in Kidney Transplant Recipients: A Longitudinal Study-The COViNEPH Project. Vaccines (Basel) 9(10). https://doi.org/10.3390/vaccines9101165
38. Kantauskaite M, Müller L, Kolb T, et al (2022) Intensity of mycophenolate mofetil treatment is associated with an impaired immune response to SARS-CoV-2 vaccination in kidney transplant recipients. Am J Transplant 22(2):634–639
39. Ehmsen S, Asmussen A, Jeppesen SS, et al (2021) Antibody and T cell immune responses following mRNA COVID-19 vaccination in patients with cancer. Cancer Cell 39(8):1034–1036
40. Yalçın TY, Topçu DI, Doğan Ö, et al (2022) Immunogenicity after two doses of inactivated virus vaccine in healthcare workers with and without previous COVID-19 infection: Prospective observational study. J Med Virol 94(1):279–286
41. Ibarrondo FJ, Fulcher JA, Goodman-Meza D, et al (2020) Rapid Decay of Anti-SARS-CoV-2 Antibodies in Persons with Mild Covid-19. N Engl J Med 383(11):1085–1087
42. Strömer A, Rose R, Grobe O, et al (2020) Kinetics of Nucleo- and Spike Protein-Specific Immunoglobulin G and of Virus-Neutralizing Antibodies after SARS-CoV-2 Infection. Microorganisms 8(10). https://doi.org/10.3390/microorganisms8101572
43. Deepak P, Kim W, Paley MA, et al (2021) Glucocorticoids and B Cell Depleting Agents Substantially Impair Immunogenicity of mRNA Vaccines to SARS-CoV-2. medRxiv. https://doi.org/10.1101/2021.04.05.21254656
44. Shafiekhani M, Shahabinezhad F, Niknam T, et al (2021) Evaluation of the therapeutic regimen in COVID-19 in transplant patients: where do immunomodulatory and antivirals stand? Virol J 18(1):228 https://doi.org/10.1186/s12985-021-01700-2

45. Rozen-Zvi B, Yahav D, Agur T, et al (2021) Antibody response to SARS-CoV-2 mRNA vaccine among kidney transplant recipients: a prospective cohort study. Clin Microbiol Infect 27(8):1173.e1171–1173.e1174. https://doi.org/10.1016/j.cmi.2021.04.028
46. Saharia KK, Anjan S, Streit J, et al (2021) Clinical characteristics of COVID-19 in solid organ transplant recipients following COVID-19 vaccination: A multicenter case series. Transpl Infect Dis 24(2):e13774. https://doi.org/10.1111/tid.13774
47. Efros O, Anteby R, Halfon M, et al (2022) Efficacy and Safety of Third Dose of the COVID-19 Vaccine among Solid Organ Transplant Recipients: A Systemic Review and Meta-Analysis. Vaccines (Basel) 10(1). https://doi.org/10.3390/vaccines10010095
48. Saeed BQ, Al-Shahrabi R, Alhaj SS, et al (2021) Side effects and perceptions following Sinopharm COVID-19 vaccination. Int J Infect Dis 111:219–226
49. Londoño MC, Gratacós-Ginès J, Sáez-Peñataro J (2021) Another case of autoimmune hepatitis after SARS-CoV-2 vaccination - still casualty? J Hepatol 75(5):1248–1249
50. Bril F, Al Diffalha S, Dean M, et al (2021) Autoimmune hepatitis developing after coronavirus disease 2019 (COVID-19) vaccine: Causality or casualty? J Hepatol 75(1):222–224
51. Rela M, Jothimani D, Vij M, et al (2021) Auto-immune hepatitis following COVID vaccination. J Autoimmun 123:102688. https://doi.org/10.1016/j.jaut.2021.102688
52. Sohrabi M, SobheRakhshankhah E, Ziaei H, et al (2022) Acute liver failure after vaccination against of COVID-19; a case report and review literature. Respir Med Case Rep 35:101568. https://doi.org/10.1016/j.rmcr.2021.101568
53. Haskin O, Ashkenazi-Hoffnung L, Ziv N, et al (2021) Serological Response to the BNT162b2 COVID-19 mRNA Vaccine in Adolescent and Young Adult Kidney Transplant Recipients. Transplantation 105(11):e226-e233
54. Marion O, Del Bello A, Abravanel F et al (2021) Safety and Immunogenicity of Anti-SARS-CoV-2 Messenger RNA Vaccines in Recipients of Solid Organ Transplants. Ann Intern Med 174(9):1336–1338
55. Lebedev L, Sapojnikov M, Wechsler A, et al (2021) Minimal Change Disease Following the Pfizer-BioNTech COVID-19 Vaccine. Am J Kidney Dis 78(1):142–145
56. Bomback AS, Kudose S, D'Agati VD (2021) De Novo and Relapsing Glomerular Diseases After COVID-19 Vaccination: What Do We Know So Far? Am J Kidney Dis 78(4):477–480
57. Bau JT, Churchill L, Pandher M, et al (2022) Acute Kidney Allograft Rejection Following Coronavirus mRNA Vaccination: A Case Report. Transplant Direct 8(2):e1274 https://doi.org/10.1097/txd.0000000000001274
58. Medina-Pestana J, Cristelli MP, Viana LA, et al (2022) Clinical Impact, Reactogenicity, and Immunogenicity After the First CoronaVac Dose in Kidney Transplant Recipients. Transplantation 106(1):e95-e97
59. Del Bello A, Marion O, Delas A, et al (2021) Acute rejection after anti-SARS-CoV-2 mRNA vaccination in a patient who underwent a kidney transplant. Kidney Int 100(1):238–239
60. Vyhmeister R, Enestvedt CK, VanSandt M, et al (2021) Steroid-Resistant Acute Cellular Rejection of the Liver After Severe Acute Respiratory Syndrome Coronavirus 2 mRNA Vaccination. Liver Transpl 27(9):1339–1342
61. Candon S, Thervet E, Lebon P, et al (2009) Humoral and cellular immune responses after influenza vaccination in kidney transplant recipients. Am J Transplant 9(10):2346–2354
62. Haddadin Z, Krueger K, Thomas LD, et al (2021) Alternative strategies of posttransplant influenza vaccination in adult solid organ transplant recipients. Am J Transplant 21(3):938–949
63. European Medicines Agency; Adapted COVID-19 vaccines. https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/vaccines-covid-19/covid-19-vaccines-authorised. Accessed October 30, 2022