Immunogenicity and Short-term Clinical Outcomes Following Two Doses of the Sinopharm Vaccine (BBIBP-CorV) in Kidney Transplant Recipients

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ABSTRACT

Background: The seroconversion rate is lower in response to COVID-19 vaccination in immunocompromised patients.

Objective: This study aimed to investigate the humoral immune response and short-term clinical outcomes in kidney transplant recipients vaccinated with the SARS-CoV-2 vaccine (BBIBP-CorV; Sinopharm).

Methods: This prospective cohort was conducted from May to December 2021 in Abu Ali Sina Hospital, Iran. All kidney transplant recipients older than 18 received two doses of the Sinopharm vaccine four weeks apart. Immunogenicity was assessed by evaluating antibodies against the receptor-binding domain (RBD) of SARS-CoV-2 after the first and second vaccine doses. Patients were followed up for six months after vaccination.

Results: Out of 665 kidney transplant patients, 76 patients (11.43%) and 182 patients (27.37%) had acceptable anti-S-RBD immunoglobulin G (IgG) levels after the first and second doses. Forty-six patients (6.91%) were infected with COVID-19, which led to the hospitalization of 34 (5.11%) of them. No deaths were recorded during the follow-up period. An increase in serum creatinine was detected in 86 (12.93%) studied patients. The predominant adverse reactions reported in patients were fatigue, headache, and injection site pain.

Conclusion: Our findings showed that the humoral response rate of kidney transplant recipients to the Sinopharm vaccine is relatively low, and receiving the third dose of the vaccine seems reasonable to a large extent. Also, the care of the COVID-19 disease in people who are in the first year after receiving a kidney transplant should be more accurate and intensive.

KEYWORDS: COVID-19; Kidney transplant; Sinopharm; Vaccination; Humoral response

INTRODUCTION

On May 5, 2023, the World Health Organization (WHO) officially announced the end of the coronavirus disease 2019 (COVID-19) emergency in the world. In January 2020, this organization declared the coronavirus outbreak a public health emergency and international concern. Over 770 million confirmed cases and more than seven million deaths have been reported globally [1]. According to global studies and research, rapid and widespread vaccination is the most effective approach to prevent COVID-19 and reduce its burden on health systems. Nowadays, several different vaccine platforms against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are

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available worldwide, some of which are approved for emergency use [2].

Because solid organ transplant (SOT) recipients have been excluded from many vaccine trials, there is insufficient information on the safety and efficacy of vaccination in such populations [3]. In addition, SOT recipients are at risk for lower immunogenicity than the non-transplant population due to immunosuppressive therapy [4]. Most studies in this field have also focused on messenger ribonucleic acid (mRNA)-based vaccines, which mainly show the low immune responses of SOT recipients against these types of vaccines [4, 5]. In this regard, some studies have reported a mortality rate of COVID-19 in SOT recipients of around 20% [6, 7]. However, only five studies have so far evaluated the immunogenicity of inactivated anti-SARS-CoV-2 vaccines in kidney transplant patients, with mixed results [6-10].

Sinopharm COVID-19 vaccine is an inactivated vaccine produced by Beijing Bio-Institute of Biological Products (BBIBP) and approved for emergency use by the WHO. Its effectiveness against symptoms of COVID-19 and a hospitalization rate of 79% have been reported. According to the strategic advisory group of experts on immunization, the Sinopharm vaccine should be administered in two doses, 3-4 weeks apart [11]. The trials have proven the effectiveness of this vaccine. The most reported side effects were injection site pain and mild fever without serious adverse reactions [12, 13]. Until now, only two relatively large-scale studies have been published on the use of this vaccine in transplant recipients [7, 14].

According to the results of our previous studies [14, 15] and the proven adverse effects of SARS-CoV-2 on the kidneys [16, 17], in this study, we intend to precisely evaluate the humoral response, clinical outcomes and adverse effects of Sinopharm COVID-19 vaccine in a population of renal transplant recipients.

MATERIALS AND METHODS

Study Setting and Patient Selection

This prospective observational cohort study was conducted from May to December 2021 on kidney transplant patients whose transplant date was over six months. Patients received two doses of the COVID-19 vaccine manufactured by the China National Biotechnology Group (CNBG), Sinopharm, four weeks apart at the Shiraz Transplant Center, Abu Ali Sina Hospital, Shiraz, Iran.

The inclusion criteria include age over 18 years, more than six months that have passed since transplantation before entering the study, and having the conditions to receive the COVID-19 vaccine according to the relevant guidelines [18]. Patients with laboratory diagnosis of SARS-CoV-2 infection through polymerase chain reaction (PCR) or serology, patients with acute graft rejection at the time of vaccination, pregnant or lactating women, and people who could not complete the study for any reason were excluded from the investigation.

Immunogenicity Assessment

Blood samples were collected from all participants before the initial dosage injection, four weeks following the first dose, and four weeks following the second dose. The samples were analyzed using an antibody-capture enzyme-linked immunosorbent assay (ELISA) to identify immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies targeting the receptor-binding domain (RBD) of SARS-CoV-2. Commercial kits (Chemobind®, Iran) and an ELISA reader (Awareness Technologies Stat Fax 2100 Microplate Reader; Westport, CT, USA) were used. The commercial anti-RBD IgM kit utilized in this work provided a specificity of 100% (95% CI: 99.0–100) and a sensitivity of 91.8% (95% CI 94.9–99.9). Likewise, the anti-RBD IgG kit had 100% specificity and sensitivity (95% CI: 97.4–99.9). The concentrations of IgG and IgM antibodies were quantified according to the manufacturer's guidelines. The ELISA index values over 1.1 were regarded as a positive response.

Table 1: Demographic information of kidney transplant recipients who received the first and second doses of the Sinopharm COVID-19 vaccine (n= 665).

Variables	Responder n= 182	Non-responder n= 483	Total	P-value
Age, n (%)				
<30 years old	18 (9.89%)	54 (11.18%)	72 (10.83%)	
30–50 years old	75 (41.21%)	205 (42.44%)	280 (42.10%)	0.463
>50 years old	89 (48.90%)	224 (46.38%)	313 (47.07%)	
Sex, n (%)				
Male	112 (61.54%)	315 (65.22%)	427 (64.21%)	0.832
Female	70 (38.46%)	168 (34.78%)	238 (35.79%)	
Time passed from transplantation, n (%)				
6 months–1 year	9 (4.95%)	42 (8.70%)	51 (7.67%)	
1–3 years	33 (18.13%)	108 (22.36%)	141 (21.20%)	0.068
More than 3 years	140 (76.92%)	333 (68.94%)	473 (71.13%)	
Immunosuppressive medications, n (%)				
Anti-metabolites	173 (95.05%)	467 (96.69%)	640 (96.24%)	0.568
Calcineurin inhibitors	156 (85.71%)	421 (87.16%)	577 (86.77%)	0.423
Corticosteroids	149 (81.87%)	400 (82.81%)	549 (82.56%)	0.278
Mammalian target of rapamycin inhibitors	17 (9.34%)	44 (9.11%)	61 (9.17%)	0.653
Serum creatinine, mg/dL, mean SD	2.66 ± 1.76	2.78 ± 1.04	2.88 ± 1.74	0.652
Glomerular filtration rate, mL/min/1.73 m², mean SD	86.22 ± 21.17	79.88 ± 26.13	83.31 ± 21.11	0.881
Underlying kidney disease, n (%)				
Diabetes mellitus	21 (11.54%)	64 (13.25%)	85 (12.78%)	
Hypertension	53 (29.12%)	134 (27.74%)	187 (28.12%)	
Autosomal-dominant polycystic kidney disease	15 (8.24%)	37 (7.66%)	52 (7.82%)	0.093
Systemic lupus erythematosus	10 (5.49%)	9 (1.86%)	19 (2.85%)	
History of positive COVID-19 PCR before vaccination, n (%)				
Yes	24 (13.19%)	50 (10.35%)	74 (11.13%)	0.346
No	158 (86.81%)	433 (89.65%)	591 (88.87%)	
History of negative PCR but symptomatic COVID-19, n (%)				
Yes	19 (10.44%)	35 (7.25%)	54 (8.12%)	0.149
No	163 (89.56%)	448 (92.75%)	611 (91.88%)	
History of admission due to COVID-19 before vaccination, n (%)				
Yes	13 (7.14%)	23 (4.76%)	36 (5.41%)	0.161
No	169 (92.86%)	460 (95.24%)	629 (94.59%)	

Table 2: Univariate and multivariate analysis to determine the relationship of different variables with the seroconversion rate to Sinopharm COVID vaccine.

Variables	Univariate analysis		Multivariate analysis	
	OR (CI)	P-value	OR (CI)	P-value
Age, n (%)	1.12 (0.97, 1.29)	**0.121**[a]	1.16 (0.99, 1.37)	0.064
Sex, n (%)	1.17 (0.39, 3.41)	0.782		
Time passed from transplantation, n (%)				
6 months–1 year	2.61 (1.19, 6.15)	**0.020**[a]	6.23 (2.19, 25.25)	**0.016**[*]
1–3 years	1.11 (0.72, 1.59)	0.522	1.09 (0.87, 2.03)	0.564
More than 3 years	Ref.		Ref.	
Immunosuppressive medications, n (%)				
Anti-metabolites	0.16 (0.13, 1.84)	0.440		
Calcineurin inhibitors	1.11 (0.62, 1.77)	0.422		
Corticosteroids	1.89 (0.25, 4.38)	**0.199**[a]	1.30 (0.22, 7.77)	0.768
Mammalian target of rapamycin inhibitors	0.45 (0.05,4.02)	0.473		
Underlying kidney disease, n (%)				
Diabetes mellitus	1.85 (0.72, 4.14)	**0.122**[a]	1.66 (0.73, 3.8)	0.186
Hypertension	1.77 (0.96, 4.19)	**0.180**[a]	1.79 (0.81, 3.32)	0.148
Others (Autosomal-dominant polycystic kidney disease, Systemic lupus erythematosus)	Ref.		Ref.	
History of rejection 1 year before transplantation				
Yes	1.04 (0.72, 1.58)	0.391		
No	Ref.	–		
History of positive PCR before vaccination				
Yes	0.22 (0.15, 9.79)	0.472		
No	Ref.	–		
History of negative PCR but symptomatic COVID-19				
Yes	0.37 (0.09, 1.57)	**0.180**[a]	0.66 (0.40, 0.82)	0.35
No	Ref.	–	Ref.	
History of admission due to COVID-19 before vaccination				
Yes	0.49 (0.07, 3.19)	**0.190**[a]	0.76 (0.24, 2.36)	0.32
No	Ref.	–	Ref.	

[a]Statistically significant variables (P-value≤ 0.2) in univariate analysis were enrolled in multiple logistic regression models.
[*]Statistically significant variables (P-value≤ 0.05) in multivariate analysis were considered.

Participants Follow-Up

Demographic, clinical, and laboratory information of participants was collected by asking the patients or reviewing their medical records in a researcher-made questionnaire. All patients were monitored daily in the first week after each round of vaccination and then

monthly until six months after the second round by trained healthcare providers at the Shiraz Transplant Center by telephone or in person. They were evaluated for any signs of adverse effects from the vaccine or infection with COVID-19 and its complications. Patients were visited face-to-face by the transplant team and infectious disease specialist if needed.

Ethical Considerations

This study was approved by the ethics committee of Shiraz University of Medical Sciences (IR.SUMS.MED.REC.1401.430). The methods and objective of the study were explained to all the patients meeting the inclusion criteria, and written informed consent was taken from those willing to participate in the study.

Statistical Analysis

All factors, including demographic and clinical data, were compared between the two studied (responder and non-responder) groups. The independent t-test was used to evaluate continuous data having a normal distribution, whereas the Mann–Whitney U test was used to compare non-normal variables. Using the chi-square or Fisher's exact test, we investigated categorical variables. To identify the potential predictors of non-responsiveness to the vaccination, statistically significant variables (P-value≤ 0.2) in univariate analysis were enrolled in multiple logistic regression models. The continuous data were expressed as the mean ± standard deviation (SD) or median (IQR), and categorical data were given as frequency and percentage. The level of statistical significance was set at P-value≤ 0.05. Data analyses were performed using the SPSS 27 package (SPSS Inc., Chicago, IL, USA).

RESULTS

Baseline Characteristics of Participants

Of 665 kidney transplant recipients who received two vaccine doses, 35.79% were females, and 64.21% were males (Table 1). The participants had a mean age of 48.23±13.24 years (18–80). Among kidney transplant patients, the most frequent underlying conditions contributing to end-stage renal disease (ESRD) were hypertension (28.12%), diabetes (12.78%), autosomal dominant polycystic kidney disease (ADPKD) (7.82%), and systemic lupus erythematosus (SLE) (2.85%). Of the participants, 71.13% had transplantation over three years ago, whereas 7.67% had received transplants 6-12 months before entering the research. At the time of the first and second vaccination doses, 72.03% of patients were on corticosteroids, antimetabolites, and calcineurin inhibitors (CNIs). Furthermore, 4.81% of patients received a combination of mTOR inhibitors, corticosteroids, and antimetabolites, while 85.71% were administered with CNIs with antimetabolites.

Immunogenicity of the SARS-CoV-2 Vaccination

The median (IQR) plasma concentration of anti-S-RBD IgM and IgG before vaccination was 0.09 [0.07, 0.15] and 0.45 [0.18, 0.59], respectively. Among the 665 kidney transplant recipients, 76 patients (11.43%) and 182 patients (27.37%) showed sufficient levels of anti-S-RBD IgG (>1.1) 4 weeks post the first and second doses, respectively. Following excluding individuals who were detected positive for COVID-19 using PCR within six months before vaccination, 70 (10.52%) and 162 (24.36%) patients showed satisfactory levels of anti-RBD four weeks after the first and second dose, respectively.

Post-vaccination Clinical Outcomes

Six months after vaccination, 46 participants (6.91%) were infected with COVID-19; of these, 2 (0.30%) were infected between the first and second dose and 44 (6.62%) were infected following the second dose. Furthermore, among the COVID-19-infected individuals (n= 46), 6 and 13 showed adequate anti-RBD IgG levels between the first and second doses and after the second dose, respectively. Following the second vaccination dose, 34 (5.11%) individuals were hospitalized due to COVID-19. There was no death in the six-month follow-up of the patients.

The univariate analyses revealed that age,

the duration since transplantation, treatment with corticosteroids, pre-existing kidney diseases (diabetes and hypertension), previous symptomatic COVID-19 with negative PCR results, and prior hospitalization due to COVID-19 were identified as risk factors for non-responsiveness to the vaccination (Table 2).

Nevertheless, the multivariate analysis revealed that the duration since transplantation was the only identifiable risk factor for non-responsiveness (OR= 6.23, 95% CI= 2.19–25.25; p= 0.016). These findings indicate that the likelihood of patients who underwent transplantation 6-12 months before immunization not responding to the vaccine was 6.23 times higher than those who had transplantation more than three years before vaccination.

Adverse Reactions

Fig. 1 illustrates the incidence of adverse reactions following the administration of the first and second doses of the vaccine. The predominant adverse reactions reported in patients were fatigue, headache, and injection site pain. Following the first and second doses of the vaccine, three and two patients need medical attention at the hospital emergency department due to adverse events (allergic responses and severe headache), respectively.

Elevated serum creatinine was observed in 86 (12.93%) (44 cases after the first and 42 after the second dose) of participants. However, none of them needed hospitalization, hemodialysis, or continuous renal replacement therapy (CRRT). One patient developed antibody-mediated rejection among the vaccine recipients, confirmed by biopsy. This patient was admitted, evaluated regarding the cause of rejection and received methylprednisolone. Biopsy after treatment showed normal histopathology; he did not experience graft loss and was discharged 12 days after admission.

DISCUSSION

In general, due to immunosuppressive therapy, SOT recipients often experience diminished immune responses post-vaccination compared to the general population. The current study investigated the humoral immune response to the Sinopharm COVID-19 vaccine and short-term clinical outcomes in kidney transplant patients. Approximately 12% and 28% of patients had acceptable anti-RBD IgG spike protein levels after the first and second vaccine doses. In comparison, clinical trials on the immunogenicity of the Sinopharm vaccine in the general population have shown that the seroconversion rate after receiving two doses of the vaccine is more than 90% [19, 20]. Several vaccines have been investigated for SOT recipients so far. Evaluating SARSCoV-2 mRNA vaccine immunogenicity in SOT recipients showed that only 15% and 54% of patients had suitable antibody levels after the first and second doses [21].

In another study, kidney transplant recipients were vaccinated with the inactivated Sinopharm-CoronaVac (BBIBP-CorV) vaccine; results showed that only 9% of transplant recipients had adequate antibody levels, while antibody levels in 100% of participants in the control group were acceptable [22]. Differences in the type of vaccine platform, the number of participants, and factors affecting seroconversion in transplant recipients, such as the type of immunosuppressive regimens, time elapsed after transplantation, and underlying diseases, can influence seroconversion rates in different vaccine types. However, lower seroconversion rates in transplant recipients compared to the general population have been confirmed in most studies.

In the present study, univariate analysis showed that age, a recent transplant, history of hospitalization due to COVID-19 before vaccination, and kidney transplantation secondary to diabetes or hypertension are risk factors for low immunogenic response. However, logistic regression confirmed that the only significant predictor of low immunogenicity response was vaccination within six months to 1 year after transplantation. Previous studies have shown that advanced age is a proven risk factor for decreased antibody titers in transplant and non-transplant patients receiving influenza, hepatitis B, and pneumococcal vaccines [23]. Moreover, many studies have identified

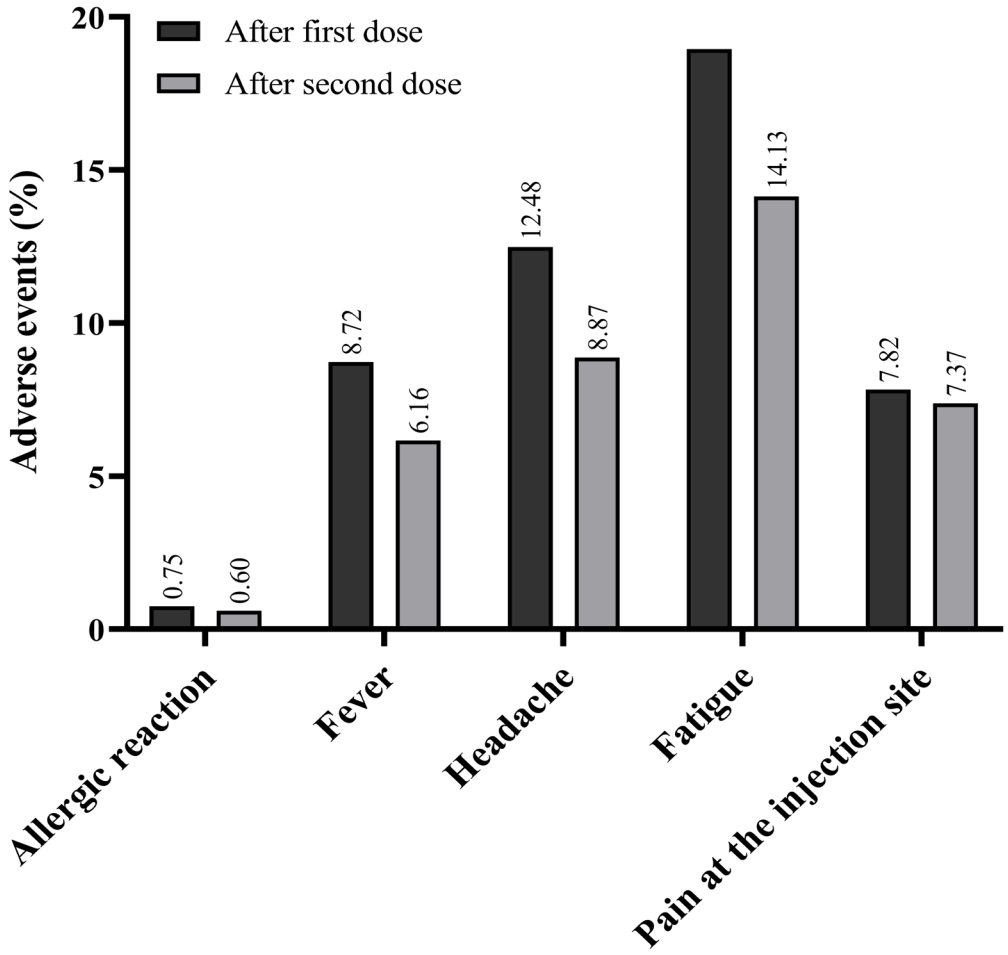

Figure 1: Adverse events following first and second dose of Sinopharm COVID-19 vaccine among kidney transplant recipients (n= 665).

advanced age as one of the well-known risk factors for severe disease and poor response to COVID-19 vaccines [24-27]. High blood pressure was a risk factor for inadequate response to vaccination in our patients. The results of two other studies that evaluated risk factors for poor response to mRNA COVID-19 vaccines showed that hypertension was a factor in poor seroconversion due to its negative impact on immune function [28, 29].

Recently transplanted patients are expected to have lower seroconversion rates to COVID-19 vaccination due to the need for treatment with higher doses of immunosuppressive drugs, especially antimetabolites [26, 30, 31]. Marta et al. found that the adverse effect of mycophenolate mofetil (MMF) on seroconversion was dose-dependent, and changing the dose of MMF before vaccination could improve the immune response to COVID-19 vaccination [32]. In this regard, our study showed that receiving corticosteroids can have an undesirable effect on seroconversion. The COViNEPH project, which evaluated various aspects of COVID-19 infection in nephrology, including factors influencing the humoral immune response to COVID-19 vaccination, found that the seroconversion rate in patients who did not receive corticosteroids in their maintenance immunosuppressive regimen was 66.7% [31].

Although some studies have shown that pre-vaccination COVID-19 infection leads to increased immunogenicity of COVID-19 vaccines in transplant and non-transplant individuals [33, 34], this relationship was not

confirmed in our study. In addition, our results showed that transplant patients with a history of hospitalization for COVID-19 had a lower response rate to vaccination. Likely, a high percentage of patients with previous COVID-19 infections in our study were infected or hospitalized for COVID-19 more than six months before vaccination. Also, previous studies have shown that IgG levels against SARS-CoV-2 spike protein decrease over time [35, 36]. Furthermore, previous studies have demonstrated that patients infected with COVID-19 more than six months before vaccination had the lowest antibody titers, and antibody responses in patients infected 3 to 6 months before vaccination had the highest rate [34]. Another possible explanation includes the potential negative effect of corticosteroids on the response to vaccination [37]. The administration of high doses of corticosteroids to transplant recipients suffering from moderate to severe COVID-19 infection may result in low response rates to vaccination despite prior COVID-19 infection [38].

Our results showed that less than 1% of patients became infected with COVID-19 after their first vaccination, and only less than 7% became infected within three months of receiving the second dose. Of the infected patients, only 5% were hospitalized for COVID-19 in the six months after vaccination, and there were no COVID-19-related deaths. Previous studies also showed that post-vaccination COVID-19 infection is possible in transplant recipients due to their lower seroconversion rate [33, 39]. The results of a multicenter study showed that hospitalizations associated with COVID-19, critical COVID-19, and subsequent mortality were more common in transplant recipients compared with general population groups (7% vs. 2%), suggesting the importance of the third dose vaccine in transplant recipients [40]. In agreement, the results of a recent meta-analysis have shown that seronegative transplant recipients after two doses of the COVID-19 vaccine became positive after receiving the third dose [41].

Our results are consistent with other studies that show fatigue, headache, and injection site pain are the most common adverse reactions of Sinopharm vaccination [12, 42]. Our research and other studies have observed an increase in serum creatinine following immunization [43, 44]. Also, cases of acute kidney injury and minimal-change disease were reported following COVID-19 vaccination [45]. A probable explanation of this is that interferon-γ (INF-γ), tumor necrosis factor-α (TNF-α), and interleukin-2 (IL-2) produced due to T-cell responses to foreign mRNA could lead to podocytopathies and B-cell production in susceptible patients and to worsening of subclinical or inactive glomerular diseases. Likewise, SARS-CoV-2 infection itself can stimulate diverse autoimmune and alloimmune renal diseases [46].

Although our study is one of the relatively large studies conducted on inactivated vaccination of COVID-19 in kidney transplant recipients, there were some limitations. First, only the inactivated Sinopharm BBIBP-CorV vaccine was investigated. This does not allow for the comparison of results with other vaccines. Secondly, no control group was included in this study because comparing transplanted and non-transplanted patients was impossible. In addition, due to the 6-month follow-up period, data on the third vaccine dose were unavailable. Finally, this study focused on the humoral immune response, whereas assessment of cellular immune responses could provide more comprehensive information on vaccination efficacy.

In conclusion, our results are consistent with previous research, which showed that the humoral response rate to the Sinopharm vaccine in kidney transplant recipients is low. The short interval between transplantation and vaccination may decrease the seroconversion rate in kidney transplant recipients due to the high doses of immunosuppressive drugs used during this period. It is recommended that a third dose of a different type of vaccine or adjuvants be used in kidney transplant recipients who have previously been vaccinated with two doses of an inactivated vaccine. One of the new bivalent versions of spike protein mRNA vaccines from Pfizer/BioNTech and Moderna

Biotech [47] could be used as a third dose of the vaccine and possibly lead to better protection against SARS-CoV-2 Omicron subtypes, which Kidney transplant recipients are potentially vulnerable to them [48].

CONFLICT OF INTEREST: None declared.

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