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## Evaluation of SARS-CoV-2 Serum Level in Patients Vaccinated With Sinopharm/BBIBP-CorV With Kidney Transplantation

Maryam Rahbar<sup>a</sup>, Reza Kazemi<sup>b</sup>, Hanieh Salehi<sup>c</sup>, Pouria Ghasemi<sup>d</sup>, Mohammad Naghizageh<sup>d</sup>, Sanaz Dehghani<sup>e</sup>, Maryam Gholamnejad<sup>a</sup>, Mahin Ahmadi Pishkuhi<sup>f</sup>, and Seyed Mohammad Kazem Aghamir<sup>a\*</sup>

<sup>a</sup>Urology Research Center, Tehran University of Medical Sciences, Tehran, Iran; <sup>b</sup>Department of Urology, Al-Zahra Hospital, Isfahan University of Medical Sciences, Isfahan, Iran; <sup>c</sup>School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran; <sup>d</sup>Isfahan University of Medical Sciences, Isfahan, Iran; <sup>e</sup>Organ Procurement Unit, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran; and <sup>f</sup>Pars Advanced and Minimally Invasive Medical Manners Research Center, Pars Hospital, Iran University of Medical Science, Tehran, Iran

### ABSTRACT

**Background.** Every year, a large number of people undergo kidney transplants because of various reasons leading to renal failure. These patients usually have low immunoglobulin levels due to the use of immunosuppressive drugs. In recent years, the COVID-19 pandemic has been a major global health risk. Patients who are immunocompromised or who have diabetes are especially at risk.

**Methods.** In this study, we enrolled 156 patients who had undergone kidney transplant and had received 2 doses of Sinopharm/BBIBP-CorV. The serum antibody levels against COVID-19 spike glycoprotein (immunoglobulin [Ig] G and IgM) were measured using a sandwich enzyme-linked immunosorbent assay kit to evaluate whether different immunosuppressive drugs could affect the body's response to the said vaccine.

**Results.** We found that only patients receiving Rapamune had increased IgM secondary to COVID-19 vaccine. None of the immunosuppressive drugs in this study have shown a positive correlation with increased IgG levels. The only factor that showed a significant effect on both IgM and IgG was a positive history of COVID-19, which was correlated with increased levels of serum IgG/M.

**Conclusions.** Only patients treated with Rapamune showed an acute immune reaction to the vaccine in the form of positive serum IgM levels, and no rise of serum IgM antibody was observed in COVID-19-naïve patients. Patients who had a previous history of COVID-19 infection showed an elevated serum IgM and IgG level, suggesting that vaccines in general and Sinopharm/BBIBP-CorV in particular are not enough to ensure immunity against COVID-19 in transplant recipients. We recommend further studies using different types of vaccines and immunosuppressive drugs.

**C**ORONAVIRUS disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In 2020 COVID-19 was declared a pandemic by the World Health Organization. Vaccination against COVID-19 is one of the known ways to prevent severe forms of the disease [1,2].

The only permanent treatment for end-stage renal disease is kidney transplantation. Because the transplanted kidney is

The study was run under the Tehran University of Medical Sciences ethical committee (IR.TUMS.SINAHOSPITAL.REC.1400.100). All patients signed a written informed consent. All methods were in accordance with the Declaration of Helsinki. The data sets used and/or analyzed during the current study available from the corresponding author on reasonable request.

\*Address correspondence to: Seyed Mohammad Kazem Aghamir, Urology Research Center, Sina Hospital, Hassan Abad Sq., Imam Khomeini Ave, Tehran, Iran 1136746911. Tel: (+9821) 6634 8560; Fax: (+9821) 6634 8561. E-mail: [mkaghamir@tums.ac.ir](mailto:mkaghamir@tums.ac.ir)

technically considered a foreign object by the body, inflammatory and immune response could be triggered by this alien tissue. Therefore, the use of various immunosuppressive drugs must be used to prevent acute rejection of such bonds [3–6].

Because kidney transplant recipients have a high risk of developing a severe form of the disease, SARS-CoV-2 vaccination is a must to prevent COVID-19 infection. As noted before, these patients are immunosuppressed and thus should be given priority for vaccination. However, the innate immune response by the body to the vaccine is somewhat subdued because of the said immunosuppressive drugs [7,8], making immunocompromised patients uniquely susceptible to COVID-19 infection, even if they have received prior vaccination. These patients are also at a higher risk of death and have poorer prognosis [9–11].

Studies have demonstrated that patients treated with costimulation blockade have lower immune responses after vaccination compared to other patients. Other risk factors for decreased immune response include the time since transplantation and lymphocyte-depleting induction therapy [12,13].

One way to strengthen the immune response in these patients is to use an additional dose of vaccination [14]. BIBP-CorV is an inactivated vaccine developed at Sinopharm's Beijing Institute in China [15]. According to a study by Rahman et al in February 2022, 2 doses of this vaccine can be up to 78.1% effective against Delta variant [16].

There have been many studies on mRNA vaccines and their effects on lowering immunoglobulin levels in transplanted kidneys [17–19], but few studies have been performed on inactivated COVID-19 vaccines. In addition, due to the serious need for immunosuppressive drugs by patients receiving kidney transplants and the consequent susceptibility of these individuals to various infections, our aim was to evaluate the immune response and coronavirus antibody production in kidney transplant recipients and to evaluate the factors associated with reduced immunogenicity. Because immunocompromised patients are at high risk for many different diseases, it is vital to study and evaluate the response to vaccines and whether different treatment options could affect such a response. Because of the difference in genetics among our patients and the type of vaccination received from other countries, the difference in the amount of antibodies produced using different immunosuppressive drugs was examined and analyzed for the first time.

## MATERIALS AND METHODS

The present study is a cross-sectional study performed from April 2021 to January 2022, approved by the Tehran University of Medical Sciences Committee of Ethics (IR.TUMS.SINAHOSPITAL.REC.1400.100). Of the 1152 patients who underwent kidney transplantation at Sina Hospital in Tehran, Iran, 156 patients agreed to participate in the study, signed a written informed consent, and returned for a visit a minimum of 2 weeks and a maximum of 6 weeks after the second dose of the vaccine [20]. All of the patients had received 2 doses of Sinopharm/BIBP-CorV. Information on comorbid conditions and the drugs used was collected in their medical records. Patient history was taken to determine the cause of their end-stage renal disease. Blood samples were measured for evaluation of anti-SARS-CoV-2 spike glycoprotein antibodies and immunoglobulin G or M (IgG, IgM) 2 weeks after vaccination. Patients

were excluded from the study if there was no informed consent and if complete patient information was not available for analysis.

Five milliliters of blood were taken in the laboratory to test for SARS-CoV-2 spike glycoprotein antibody. To detect serum antibodies to the SARS-CoV-2 spike glycoprotein (IgM and IgG) levels, a sandwich enzyme-linked immunosorbent assay (ELISA) kit (Pishtaz Teb, Tehran, Iran; lot numbers 99006 [IgM] and 99012 [IgG]) was used. To detect IgM, a volume of 100  $\mu$ L of diluted serum (1:100) was applied to a 96-well microplate (coated with N protein). To detect IgG, the dilution factor was adjusted (1:20), and the cutoff value was changed (Optical density of the blank well + 0.15).

Statistical analysis was performed using IBM SPSS v24.0. Continuous variables are described as mean with standard deviation or median with respect to data distribution. The distribution of parameters was evaluated using the Kolmogorov-Smirnov test. The groups were analyzed using independent *t* test or Mann-Whitney U test. Classified variables were described as frequencies and percentages and analyzed by Fisher's exact test. The 2 variables of antibody titer with other variables were tested by calculating Spearman coefficient.  $P < .05$  was considered statistically significant for all analyses.

## RESULTS

A total of 156 vaccinated patients were included in the study. The median age of patients was 50 years; 41 patients were over 60 years old. Among the patients, 67% were male and 33% were female. There were several reasons for kidney transplantation, of which hypertension was the most common (32%), followed by diabetes mellitus and urological complications, respectively. The median time between the patients' transplant and our study was 8 years. Eighty-nine of the kidneys were taken from cadaver (57%) and 55 patients had a history of transplantation rejection and the need for a retransplant (35%). For 31% of patients, an increase in creatinine was reported after kidney transplantation. Regarding patients' underlying disease, hypertension had the highest prevalence (53%), followed by diabetes (25%), cytomegalovirus infection (10%), and stroke (3%). Surprisingly, all of the drugs we studied were insignificantly correlated with serum IgG levels. However, the drug sirolimus (Rapamune) had a significant correlation with serum IgM levels, showing that this drug could increase the odds of the patient having positive serum IgM levels after COVID-19 vaccination (odds ratio [OR] = 4.00,  $P = .043$ ). A positive history of COVID-19 was significantly correlated with a high antibody titer. It was significantly correlated with an increased probability of positive serum IgM (OR = 4.00,  $P = .020$ ) and IgG (OR = 2.57,  $P = .016$ ) titer (Tables 1, 2). With Sinopharm/BIBP-CorV efficacy being around 80% [21], most of our patients showed a lower antibody titer than expected. We also found the dosage of drugs to be of no consequence regarding whether the patient developed antibodies. As such, we chose not to include the data.

## DISCUSSION

The COVID-19 pandemic is, at the time of the publication, ongoing worldwide. Because of the immunosuppressed situation of patients posttransplant, they are at a unique risk of

**Table 1. Demographic and Clinical Characteristics Between Kidney Transplant IgM Antibody Statuses**

	Total <i>n</i> = 156	IgM Antibody Status		<i>P</i> Value	
		Positive <i>n</i> = 12 (8%)	Negative <i>n</i> = 144 (92%)		
Baseline characteristics					
Median age (IQR), y	50 (39, 60)	45 (38, 58)	51 (39, 60)	.456	
Age ≥60 y, <i>n</i> (%)	41 (26)	2 (17)	39 (27)	.431	
Men, <i>n</i> (%)	105 (67)	9 (75)	96 (67)	.554	
Median BMI (IQR), kg/m <sup>2</sup>	26 (23, 29)	26 (25, 29)	26 (23, 29)	.860	
Causes of KT, <i>n</i> (%)	HBP	50 (32)	2 (17)	48 (33)	.066
	DM/HBP	17 (11)	4 (33)	13 (9)	
	Urology	24 (15)	2 (17)	22 (15)	
	Other	65 (42)	4 (33)	61 (42)	
Median time after KT (IQR), y	8 (4, 13)	7 (4, 15)	8 (4, 13)	.902	
Cadaver graft, <i>n</i> (%)	89 (57)	8 (67)	81 (56)	.484	
Retransplant, <i>n</i> (%)	16 (10)	1 (8)	15 (10)	.819	
Rejection transplantation, <i>n</i> (%)	54 (35)	5 (42)	49 (34)	.593	
Creatinine increasing, <i>n</i> (%)	48 (31)	4 (33)	44 (31)	.841	
Hypertension, <i>n</i> (%)	83 (53)	7 (58)	76 (53)	.711	
Cardiovascular disease, <i>n</i> (%)	16 (10)	0 (0)	16 (11)	.223	
Diabetes, <i>n</i> (%)	39 (25)	4 (33)	35 (24)	.488	
Stroke, <i>n</i> (%)	5 (3)	0 (0)	5 (3)	.999	
Kidney problem, <i>n</i> (%)	82 (53)	8 (67)	74 (51)	.309	
CMV infection, <i>n</i> (%)	15 (10)	2 (17)	13 (9)	.388	
Drug treatment					
CellCept (mycophenolate mofetil), <i>n</i> (%)	101 (65)	6 (50)	95 (66)	.266	
Tacrolimus, <i>n</i> (%)	63 (40)	3 (25)	60 (42)	.258	
Azathioprine, <i>n</i> (%)	21 (13)	1 (8)	20 (14)	.588	
Sirolimus (Rapamune), <i>n</i> (%)	14 (9)	3 (25)	11 (8)	<b>.043</b>	
Prednisolone, <i>n</i> (%)	148 (95)	12 (100)	136 (94)	.402	
Cyclosporine, <i>n</i> (%)	85 (55)	6 (50)	79 (55)	.745	
History of COVID-19, <i>n</i> (%)	68 (44)	9 (75)	59 (41)	<b>.020</b>	

*P* values were calculated based on Mann-Whitney U test, chi-square tests, Fisher's exact test, or the Monte Carlo method.

BMI, body mass index; COVID-19, coronavirus disease 2019; CMV, cytomegalovirus; DM, diabetes mellitus; HBP, high blood pressure; Ig, immunoglobulin; IQR, interquartile range; KT, kidney transplant.

Bold value indicates demographic and clinical characteristics between kidney transplant IgM antibody statuses.

different diseases. In the setting of the COVID-19 pandemic, these problems are multiplied and transplant recipients are at a very high risk of COVID-19. A very important piece of the COVID-19 immune response puzzle is the production of IgM and IgG antibodies. The levels of serum IgG and IgM are good indications of vaccine efficacy and immunization [22–24]. These antibodies could also be used to assess previous or acute infections with COVID-19.

However, as stated before, immunosuppressed patients have subdued or even completely suppressed immunogenicity and have significantly lower levels of serum immunoglobulins after receiving one or even 2 doses of COVID-19 vaccination, irrespective to the type of vaccine used [25,26]. With Sinopharm/BBIBP-CorV being around 80% effective, our patients showing a lower-than-expected titer of antibody was also expected. Our data also reflect this reduced immunogenicity. We also analyzed whether the different immunosuppressive drugs, comorbidities, or a history of previous COVID-19 infection could change this serum immunoglobulin level.

In our study we found that among drugs used to suppress the immune system in kidney transplant recipients such as CellCept, tacrolimus, azathioprine, and so on, the only one that seemed to still allow the patient to develop humoral immunity

against COVID-19 and with which we still see immune response in the form of IgM formation against COVID-19 was sirolimus (Rapamune). Other studies have also been done on Rapamune's effects on COVID-19 vaccination. It was hypothesized by Zurlo et al [27], based on Rapamune's effect on the influenza vaccine, that it could help bolster the effects of COVID-19 vaccination. Patients receiving sirolimus had an odds ratio of positive serum IgM levels of 4, which is comparable to the patient having a positive history of previous COVID-19 infection (OR = 4.00). This was hypothesized before in other studies. Bischof et al showed that rapamycin and other mammalian target of rapamycin inhibitors could help prevent COVID-19 infection and/or improve the mortality and morbidity due to the disease [28]. However, this finding was isolated to IgM and such finding could not be applicable to IgG levels, meaning that sirolimus mostly suppresses the long-term immunogenicity and not the acute response unit of the immune system. This finding is in line with many other studies, showing that drugs such as tacrolimus [29], mycophenolate mofetil (CellCept) [30], azathioprine [31], and so on, are correlated with a negative seroconversion. The only factor that was found to affect both IgG and IgM production in our patients was, unsurprisingly, a positive history of previous COVID-19 infection. Due to the wide

**Table 2. Demographic and Clinical Characteristics Between Kidney Transplant IgG Antibody Status**

	Total <i>n</i> = 156	IgG Antibody Status		<i>P</i> Value
		Positive <i>n</i> = 34 (22%)	Negative <i>n</i> = 122 (78%)	
Baseline characteristics				
Median age (IQR), y	50 (39, 60)	51 (40, 61)	49 (38, 60)	.475
Age ≥60 y, <i>n</i> (%)	41 (26)	9 (27)	32 (26)	.977
Men, <i>n</i> (%)	105 (67)	26 (77)	79 (65)	.198
Median BMI (IQR), kg/m <sup>2</sup>	26 (23, 29)	26 (24, 29)	26 (23, 30)	.746
Causes of KT, <i>n</i> (%)	HBP	50 (32)	6 (18)	.076
	DM/HBP	17 (11)	7 (21)	
	Urology	24 (15)	5 (15)	
	Other	65 (42)	16 (47)	49 (40)
Median time after KT (IQR), y	8 (4, 13)	7 (4, 11)	8 (4, 14)	.647
Cadaver graft, <i>n</i> (%)	89 (57)	21 (62)	68 (56)	.530
Retransplant, <i>n</i> (%)	16 (10)	1 (3)	15 (12)	.112
Rejection transplantation, <i>n</i> (%)	54 (35)	11 (32)	43 (35)	.754
Creatinine increasing, <i>n</i> (%)	48 (31)	10 (29)	38 (31)	.846
Hypertension, <i>n</i> (%)	83 (53)	15 (44)	68 (56)	.230
Cardiovascular disease, <i>n</i> (%)	16 (10)	3 (9)	13 (11)	.755
Diabetes, <i>n</i> (%)	39 (25)	11 (32)	28 (23)	.263
Stroke, <i>n</i> (%)	5 (3)	1 (3)	4 (3)	.999
Kidney problem, <i>n</i> (%)	82 (53)	22 (65)	60 (49)	.109
CMV infection, <i>n</i> (%)	15 (10)	6 (18)	9 (7)	.072
Drug treatment				
CellCept (mycophenolate mofetil), <i>n</i> (%)	101 (65)	24 (71)	77 (63)	.420
Tacrolimus, <i>n</i> (%)	63 (40)	11 (32)	52 (43)	.280
Azathioprine, <i>n</i> (%)	21 (13)	3 (9)	18 (15)	.370
Sirolimus (Rapamune), <i>n</i> (%)	14 (9)	4 (12)	10 (8)	.520
Prednisolone, <i>n</i> (%)	148 (95)	31 (91)	117 (96)	.269
Cyclosporin, <i>n</i> (%)	85 (55)	19 (56)	66 (54)	.853
History of COVID-19, <i>n</i> (%)	68 (44)	21 (62)	47 (39)	.016

*P* values were calculated based on Mann-Whitney U test, chi-square tests, Fisher's exact test, or the Monte Carlo method.

BMI, body mass index; COVID-19, coronavirus disease 2019; CMV, cytomegalovirus; DM, diabetes mellitus; HBP, high blood pressure; Ig, immunoglobulin; IQR, interquartile range; KT, kidney transplant.

distribution of vaccines in recent months in Iran and the third dose of vaccination, there is a need to study the level of Ig with 3 doses of vaccine.

### Limitations

The limitations of this study include the heterogeneity in Iranian genetics and the inaccuracy of the sandwich ELISA kits. If the results appear inconclusive, we suggest redoing the tests with more accurate ELISA kits. We did not have a baseline for patients' serum antibody levels, and many could have contracted COVID-19 but not shown any significant symptoms necessary for diagnosis. These patients could show a heightened serum Ig level. This study began when the Delta variant was most prevalent. But by the end of 2021, with the spread of the new Omicron variant and the coincidence of the Omicron outbreak and this study, Ig level may be different with different variants of COVID-19. Another limitation in this study was the rather narrow focus on the vaccine used. We studied only the effect of Sinopharm/BIBP-CorV. In our patients, vaccine use according to the number of injected doses was Sinopharm (BIBP-CorV), Oxford-AstraZeneca (AZD1222), Sputnik V (Gam-COVID-Vac), Covaxin (BBV152). It should be noted

that the BIBP-CorV vaccine has been used more than twice as often as all other vaccines combined. Therefore, our study solely focused on Sinopharm/BIBP-CorV, though other vaccines may have higher or lower efficacy and immunogenicity. Sinopharm/BIBP-CorV is an inactivated virus vaccine, which may affect the results, because mRNA vaccines have different results. We suggest that this study be performed with patients who received different vaccines.

### ACKNOWLEDGMENTS

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