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Significance of PPD Test for the Relationship Between BCG Vaccine and COVID-19 in Patients on Kidney Transplant Waiting List

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ABSTRACT

Background. The aim of this study was to determine the relationship between purified protein derivative of tuberculin (PPD) values, an indicator of BCG protection, and COVID-19 disease in patients with end-stage renal disease (ESRD) on the kidney transplant waiting list.

Methods. Age, sex, dialysis type, ERSD etiologies, and PPD values of patients on the renal transplant waiting list were recorded. SARS-CoV-2 PCR data, whether the patients were previously infected with the virus, and, if infected, the severity of the disease were noted. Data were statistically compared.

Results. PCR of 87 (47.02%) of 185 patients were studied; 107 of the patients were male and 78 were female, with a mean age of 52.8 years. The test result was positive for 28 patients. Of the patients for whom PCR was studied, 41 had a negative PPD result, while 46 had a positive PPD result. There was no correlation with SARS-CoV-2 PCR positivity in patients with a PPD $\leq$ 5 mm and $>$ 5 mm. However, patients with pneumonic infiltration who required hospitalization had a significantly higher PPD value.

Conclusions. The PPD measurement, which is an indicator of BCG protection, might be a significant parameter for predicting the course of the disease in SARS-CoV-2 pneumonia.

MINOR symptoms such as cough, sore throat, and fever have been reported in the majority of patients with a novel type of coronavirus (ie, COVID-19), which has affected the world since December 2019, and these patients usually have been noted to heal spontaneously [1]. However, some patients have been observed to develop fatal complications such as organ failure, septic shock, pulmonary edema, severe pneumonia, and acute respiratory distress syndrome [2]. Those who require intensive care support are older patients with concomitant cardiovascular, cerebrovascular, endocrine, digestive, or respiratory diseases [3].

Patients with end-stage renal disease (ESRD) also have a high comorbidity rate [4]. Infection (pneumonia with 20%) is the second most common cause of hospital admission and mortality in this patient group. According to the United States data, hemodialysis patients over the age of 65 years are in the high-risk group for COVID-19 [5].

Bacillus Calmette-Guérin (BCG), a weakened strain of *Mycobacterium bovis*, was developed as a vaccine to combat tuberculosis at the beginning of the 20th century and has been widely used for the prevention of tuberculosis [6]. The purified protein derivative of tuberculin (PPD) method is a test that indicates whether an adequate immune response to BCG has been induced. A PPD value $\leq$ 5 mm in renal failure patients is considered to indicate that BCG protection has not been developed or tuberculosis bacillus has not been encountered.

BCG protection against nonspecific respiratory infections has been the subject of research. The molecular similarity between BCG antigens and viral antigens has led to the hypothesis that memory B and T cells can recognize both BCG and respiratory pathogens after BCG vaccination [7]. It has also been hypothesized that the BCG vaccine may be a potent protector against

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SARS-CoV-2 infection or for attenuating the severity of the COVID-19 disease [6].

The aim of this study was to determine the relationship between PPD responses developed by patients on the kidney transplant waiting list who received BCG vaccine and COVID-19.

MATERIALS AND METHODS

Approval was obtained from the local ethics committee of our hospital (2020-61) prior to this study. The requirement for written consent from patients was waived in accordance with the Council for International Organizations of Medical Sciences guidelines. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Selection

The study included patients with end-stage renal disease who were registered in our organ transplant center. Polymerase chain reaction (PCR) results and hospital admission information of patients were obtained from the provincial pandemic center data. Patients with unavailable PCR results were excluded from the study. The files of patients with positive PCR results were retrospectively reviewed. Age, sex, dialysis types, and ESRD etiologies of patients were recorded.

All patients had received BCG vaccine in accordance with the national vaccination program. Antigen PPD, used as a tuberculin skin test, was performed by intracutaneous injection of 0.1 mL of the solution equivalent to 5 tuberculin units with a 27-gauge needle into the 2/3 upper inner part of the left forearm, and then measuring the induration formed within 48-72 hours with the help of a ruler and recording the result in millimeters (mm). The PPD results of patients registered in the system were noted. According to the guideline published by the Ministry of Health, chronic renal failure patients with PPD's above 5 mm were considered to have no BCG protection [8].

Statistical Method

Percentage, mean, and standard deviation were used to evaluate the descriptive results of patients. One-sample Kolmogorov Smirnov test was performed for testing if groups follow a normal distribution. Chi-square test and Mann-Whitney *U* test were used to compare categorical independent variables. A P value $< .05$ was considered statistically significant.

RESULTS

There were 185 patients (107 males and 78 females, with a mean age of 52.8 years) who were on the kidney transplant waiting list of our hospital. Of these patients, 143 were hemodialysis patients and 16 were peritoneal dialysis patients. Twenty-eight patients on the waiting list were preemptive end-stage renal disease patients. The mean duration of dialysis of hemodialysis patients was 43.7 months (minimum: 1 month; maximum: 288 months). The etiology of renal failure was diabetes mellitus for 61 patients, hypertension for 50 patients, idiopathic for 33 patients, polycystic kidney disease for 17 patients, nephrolithiasis for 10 patients, vesicoureteral reflux for 7 patients, bladder obstruction for 2 patients, familial Mediterranean fever for 2 patients, glomerulonephritis for 2 patients, and a neurogenic bladder for 1 patient.

SARS-CoV-2 PCR was studied for 87 patients (47.02%) who presented to the emergency department or COVID-19 outpatient clinic with various symptoms such as fever, respiratory distress, and fatigue. The data of patients for whom SARS-CoV-2 PCR were studied are shown in Table 1. There was no significant difference between PCR characteristics and age, sex, dialysis type, and etiology of these patients ($P = .48$, $P = .68$, $P = .61$, $P = .47$).

Of the PCR-positive patients (n = 87), 41 had a negative PPD result, while 46 had a positive PPD result. In this group, there was no significant difference between PCR positivity and negativity, and PPD negativity and positivity ($P = .31$)

There was no statistically significant difference between PPD value and PCR ($P = .14$). However, there was a statistically significant difference between SARS-CoV-2 PCR-positive patients with pneumonia (n = 11, 12%) and patients with positive PPD (Table 2; $P = .04$).

All 11 patients with PCR-positive pneumonia had PPD values > 5 mm (minimum: 5; maximum: 20; mean: 12.63).

None of the patients died in any groups.

When the relationship between pneumonia and PPD was evaluated, area under the receiver-operator curve (AUC) (95%) was calculated as 0.724 (0.552-0.896), cut off value 11.5, P value 0.017, sensitivity 72.7%, and specificity 57.9%. The correlation between PCR negativity and PPD was calculated as AUC (95%) 0.592 (0.455-0.728), cut off value 8.50, P value 0.169, sensitivity 57.6% and specificity 53.6%.

DISCUSSION

There are numerous studies conducted on comorbid pathologies in the COVID-19 pandemic [9]. Our study demonstrated no significant difference between positive or negative SARS CoV-2 PCR and age, sex, type of dialysis, and primary ESRD etiology.

In our country, BCG vaccination is performed in the pediatric age group and vaccination of all individuals is mandatory in accordance with the public health policy. Although the goal is to be protected from an endemic disease such as tuberculosis, some studies have stated that it also provides protection against other infections. Wardhana et al found that BCG reduced the incidence of RSV infection in Indonesia [10]. Ohrui et al also found that recurrent

Table 1. Characteristics of Patients

	PCR Positive (n: 28)	PCR Negative (n: 59)
Sex (Male/Female)	16/12	31/28
Age mean (min-max)	54.53 (21-72)	52.83 (26-72)
Dialysis type		
Hemodialysis	25 (38.5 mo)	51 (40.3 mo)
Peritoneal dialysis	0	2
Preemptive	3	6
Etiology		
Diabetes Mellitus	13	19
Hypertension	9	13
Idiopathic	3	14
Polycystic kidney disease	1	7
Nephrolithiasis	1	2
Bladder outlet obstruction	1	1
Familial Mediterranean Fever	0	2
Vesicoureteral reflux	0	1

PCR, polymerase chain reaction.

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Table 2. Characteristics of Patients According to the Presence of Pneumonia

	Pneumonia (+)	Pneumonia (-)	*P* values
Sex (Male/Female)	9/2	38/38	.04
Age mean (y; min-max)	55.63 (36-70)	53.05 (21-72)	.73
Dialysis type			.84
Hemodialysis	10	66	
Peritoneal dialysis	0	2	
Preemptive	1	8	
PPD value (mean-mm)	12.6	6.3	.02

PPD, purified protein derivative of tuberculin.

pneumonia rates were lower in patients with a negative tuberculin test in Japan [11]. Various studies have reported a lower number of infections and a lower mortality rate from COVID-19 in countries mandating BCG vaccination, hypothesizing based on these data that BCG vaccination may have a protective effect in COVID-19 [12]. Considering the cross-protection reported for BCG vaccination, it has been suggested that BCG vaccination may have protective effects against viral respiratory infections and COVID-19 infection [13−15]. Randomized controlled studies from the Netherlands and Australia reported that COVID-19 was less frequent in adults who received BCG vaccine following the administration of BCG vaccine or placebo saline injection to health care workers [16,17]. However, these studies have some limitations, such as different demographics and genetics of populations in different places; different non-pharmaceutical interventions such as quarantine and social distancing; differences in diagnosis; and disruptions in reporting COVID-19 cases [18].

End-stage renal disease is defined as one of the potential risk factors for severe COVID-19 [19]. A multicenter study reported a severe COVID-19 disease rate of 41.9% for ESRD patients receiving hemodialysis treatment, 15.8% for the control group, a mortality rate of 16% for ESRD, and 14% for the control group [20]. In our study, the rate of pneumonia requiring admission was lower, which was thought to be related to the number of ESRD patients who were preemptive and receiving peritoneal dialysis.

A study of a group of 10482 patients by Ng et al reported that 72.7% of ESRD patients with COVID-19 had a mild form of the disease without being admitted to the hospital, while 25.6% of patients died [21]. None of the patients died in our study.

Strikingly, our study showed that the frequency of COVID-19 pneumonia was higher in PCR-positive patients with a PPD > 5 mm, with more frequent hospital admission in these patients with low BCG protection.

In conclusion, although no relationship was found between the PPD value and SARS-CoV-2 PCR positivity, the PPD values of ESRD patients with pneumonic infiltration who required admission were found to be higher, suggesting that BCG protection is be important in SARS-CoV-2 pneumonia.

DATA AVAILABILITY

No data was used for the research described in the article.

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