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Original Article

Latent Tuberculosis Infection in Potential Renal Transplant Recipients and Live Donors in a Tertiary Level Transplant Center in Nepal

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Abstract

Background

Active tuberculosis in transplant recipients can result from latent infection with *Mycobacterium Tuberculosis* in the transplant recipients, donor tissue or de novo post-transplant infection. This study aimed to determine the prevalence of latent tuberculosis infection in potential renal transplant recipients and live donors at a tertiary-level transplant center.

Materials and Methods

This observational study was conducted from July to October 2020 among 72 potential kidney transplant recipients and their potential donors from the Department of Nephrology, Tribhuvan University Teaching Hospital. The biochemical parameters and health behaviors were measured to find the association with latent tuberculosis infection.

Results

The prevalence of latent tuberculosis infection according to *Mycobacterium tuberculosis*-specific interferon-gamma release assays was 20.8% in potential recipients and 16.6% in potential donors, whereas the prevalence with tuberculin skin test was 9.7% in potential recipients and 33.3% in potential donors. Low levels of hemoglobin, calcium, albumin, vitamin D and history of smoking were associated with the development of latent tuberculosis infection among potential recipients. Alcohol drinking was significantly associated with the development of latent tuberculosis infection among donors.

Conclusion

Potential renal transplant recipients and donors have a significant burden of latent tuberculosis in the pre-transplantation phase. Diagnosis and treatment of latent tuberculosis before transplantation can prevent ominous complications.

Keywords: *Kidney Transplantation, Latent infection, Mycobacterium Tuberculosis*

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Introduction

Patients with end-stage renal disease (ESRD) are immunosuppressed, given that uremia reduces the expression of B7-2 costimulatory molecule on antigen-presenting cells; this alters the function of polymorphonuclear cells and interferes with phagocytic efficiency, migration efficiency, and chemotactic efficiency, reducing the ability of cells to kill intracellular microorganisms [1]. Kidney transplantation improves the quality of life and overall survival with a lower cost than dialysis and is, therefore, the treatment of choice for ESRD patients [2]. Transplant recipients are also at high risk of active tuberculosis (TB), related to post-transplantation immunosu-ppressive medications that specifically target T cell-mediated immunity, which is critical to maintaining latency in patients with *Mycobacterium Tuberculosis*-infection [3, 4]. Impaired immunity in people with ESRD is the main risk factor for the development of TB. Latent TB is characterized by the presence of bacilli in host tissues without clinical or radiological evidence of disease. Approximately 5% of the individuals carrying the tuberculosis bacillus will develop the active form of the disease, and 95% will present with latent TB [5].

TB in transplant recipients is more frequent than in the general population [6-8]. Like dialysis patients, most cases of TB in transplant recipients appear to be from latent TB reactivation. However, cases of transmission from donor organs, as well as nosocomial transmission in renal transplant programs, have been reported [6]. Active TB in transplant recipients can result from latent infection with *Mycobacterium Tuberculosis* in the transplant candidate, donor tissue, or de novo post-transplant infection. These scenarios prompt targeted pre-transplant screening of recipients and donors to allow focused management of recipients selected for preventive intervention in the pre-and/or post-transplant period.

The objective of this study was to find out the prevalence of latent TB in potential renal transplant recipients and live donors using *Mycobacterium Tuberculosis* specific interferon-gamma release assays (IGRAs) and tuberculin skin test (TST) in a tertiary-level transplant center.

Materials and Methods

This observational study was conducted at Tribhuvan University Teaching Hospital (TUTH), Kathmandu, Nepal, from July to October 2020. TUTH was selected purposively as this tertiary center has regularly been the pioneer institution in renal transplantation and post-transplant care in Nepal since 2008 [9]. Written informed consent was obtained from the patients, donors, and their parties. The study was approved by the Institutional Review Committee of the Institute of Medicine, Tribhuvan University (Ref. No. 426/ (6-11) E2/076/077) and adhered to the tenets of the Declaration of Helsinki. Convenience census sampling was applied. All ESRD patients and their potential live donors being worked up for kidney transplantation during the study period were included as study samples. There were 148 potential study participants, including potential-renal transplant recipients and their potential live donors. Baseline characteristics of donors and recipients were obtained. They were evaluated for the presence of a BCG vaccination scar, history of tuberulo-sis, and history of contact with a tuberculosis patient. A detailed history was taken, and a physical examination was done. Complete blood count, serum albumin, calcium, vitamin D, intact parathyroid, serum ferritin, transferrin saturation, liver function test, Mantoux test, IGRA test, chest x-ray, sputum culture, and acid-fast bacilli stain were done. The diagnosis of active TB infection was based on clinical symptoms that included fever, weight loss, and malaise,along with either a chest x-ray with typical active TB infection findings or the identification of *Mycobacterium Tuberculosis* in a cultured clinical specimen. Any ESRD patients or donors who had previously been treated for TB, had active TB infection, or were under TB medications were excluded from the sample.A latent TB infection was defined as a positive TST or IGRA test with no clinical indicators of an active infection.

A study proforma was developed from literature review and experts'advice. The data were entered and cleaned in MS Excel 2016 (Released 2020. Microsoft Corp., Redmond, Washington, United States) and analyzed using the statistical package for social sciences (SPSS) version 22.0 for windows (Released 2013. IBM Corp., Armonk, New York, United States). Mean and standard deviation was used for continuous variables, and proportion was used for categorical variables. The independent-samples t-test was considered to evaluate the difference between the means of two independent groups. Logistic regression analysis was used to find associations between variables that showed significant associations in bivariate analyses. All tests of significance were two-tailed, and a p-value less than 0.05 was considered significant.

Results

A total of 148 patients were eligible to participate in the study. Of those, 4 were excluded because

they reported a history of tuberculosis. Therefore, the final study sample consisted of 144 patients, among which 72 were potential renal transplant recipients, and the remaining 72 were their living donors. The mean age of the potential recipients and donor groups were 37.01±10.7 and 45.5 ±11.6 years, respectively. Fifty-seven (79.2%) potential recipients were male, and fifty-three (73.6%) potential donors were female.An equal number of potentialrecipients (n=55, 76.4%) were non-smokers and non-alcohol drinkers. Fifty-nine (81.9%) potential donors were non-smokers, and 62 (86.1%) were non-alcohol drinkers.

Though primary causes of chronic kidney diseases (CKD) were undetermined in more than half of the potential recipients, 26.4% had chronic glomerulonephritis, 12.5% had diabetic kidney disease, and 4.2% had obstructive nephropathy. More than one-third (34.7%) of potential recipients were doing maintenance hemodialysis for less than six months, exactly half had been under hemodialysis for 7-12 months, and the remaining had been doing it for more than a year.

The TB blood tests or IGRAs results showed that the prevalence of latent TB infection was 20.8% in the potential recipients and 16.6% in donors. In the TST or Mantoux test, TB was diagnosed among 9.7% of potential recipients and 33.3% of donors. In the potential recipient group, 64 had BCG scars, one less than the donor group, as presented in Table 1.

Table 1: IGRA, TST, and BCG scar status in potential recipients and donors

	Recipient (n=72)	Donor (n=72)
IGRA		
Positive	15 (20.8%)	12 (16.6%)
Negative	57 (79.2%)	60 (83.4%)
TST		
Positive	7 (9.7%)	24 (33.3%)
Negative	65 (90.3%)	48 (66.7%)
BCG scar		
Positive	64 (88.9%)	65 (90.3%)
Negative	8 (11.1%)	7 (9.7%)

The IGRA and TST results showed that four pairs and two pairs of potential recipients and donors had positive test results, respectively. Forty-nine pairs and 43 pairs of potential recipients and donors hadnegative results for IGRA and TST tests, respectively. Eleven pairs and five pairs of potential recipientswith positive results, and donors with negative results for IGRA and TST tests, respectively. Likewise, there were eight pairs and 22 pairs of potential recipients with negative results and potential donors with positive results for IGRA and TST tests, respectively.

The IGRA test result showed that 31-40 years old potential recipients and 51-60 years old potential donors had higher positive results than other age groups. The IGRA positive was seen more among males (58.3%) in potential donors andeven higher (86.7%) in potential recipients. In terms of gender, the association was statistically significant among potential donors, even after adjusting for confounding variables. The positive results were higher in non-smokers and non-alcohol drinkers than in their counterparts. Patients who were doing maintenance hemodialysis for more than six months also had higher IGRA positive results than those who had hemodialysis for six months or less,as shown in Table 2.

Table 2: Association of different variables with IGRA tests among recipients and donors

Characteristics	Recipients			Donors			
	Positive (%)	Negative (%)	p-value	Positive (%)	Negative (%)	p-value	p-value#
Age group							
18 – 30 years	3 (20.0)	15 (26.3)	0.867	1 (8.3)	6 (10.0)	0.857	
31 – 40 years	5 (33.3)	22 (38.6)		2 (16.7)	16 (26.7)		
41 – 50 years	4 (26.7)	12 (21.1)		3 (25.0)	15 (25.0)		
51 - 60 years	3 (20.0)	8 (14.0)		6 (50.0)	23 (38.3)		
Gender							
Male	13 (86.7)	44 (77.2)	0.421	7 (58.3)	12 (20.0)	0.006*	0.033*
Female	2 (13.3)	13 (22.8)		5 (41.7)	48 (80.0)		
Smoking status							
Non- smoker	9 (60.0)	46 (80.7)	0.093	8 (66.7)	51 (85.0)	0.132	
Ex smoking	6 (40.0)	11 (19.3)		4 (33.3)	9 (15.0)		
Alcohol drinking status							
No alcohol	10 (66.7)	45 (79.0)	0.319	8 (66.7)	54 (90.0)	0.003*	0.216
Ex alcoholic	5 (33.3)	12 (21.0)		4 (33.3)	6 (10.0)		
Hemodialysis duration							
0 – 6 months	6 (40.0)	20 (35.1)	0.725				
More than 6 months	9 (60.0)	37 (64.9)					

*: statistically significant at p<0.05; #: Multivariate analysis

The TST test results showed that potential participants between 41-50 years old and 51-60 years oldpotential donors had higher positive test results. The potential male recipients and potential female donors had higher TST positivity than their counterparts. This study showed that smoking (p=0.028) was significantly associated with the development of latent TB infection with TST positivity among potential recipients and no other variables showed any association, as depicted in Table 3.

Table 3: Association of different variables with TST test among recipients and donors

Characteristics	Recipients			Donors		
	Positive (%)	Negative (%)	p-value	Positive (%)	Negative (%)	p-value
Age group						
18 – 30 years	1 (14.3)	16 (24.7)	0.574	2 (8.3)	3 (6.2)	0.484
31 – 40 years	2 (28.6)	26 (40.0)		5 (20.8)	15 (31.2)	
41 – 50 years	3 (42.8)	13 (20.0)		6 (25.0)	12 (25.0)	
51 - 60 years	1 (14.3)	10 (15.3)		11 (45.9)	18 (37.6)	
Gender						
Male	6 (85.7)	51 (78.5)	0.653	5 (20.8)	14 (29.2)	0.449
Female	1 (14.3)	14 (21.5)		19 (79.2)	34 (70.8)	
Smoking status						
Non- smoker	3 (42.9)	52 (80.0)	0.028*	19 (79.2)	40 (83.3)	0.665
Ex smoking	4 (57.1)	13 (20.0)		5 (20.8)	8 (16.7)	
Alcohol drinking status						
No alcohol	4 (57.1)	51 (78.5)	0.207	20 (83.3)	42 (87.5)	0.630
Ex alcoholic	3 (42.9)	14 (21.5)		4 (16.7)	6 (12.5)	
BCG scar						
Present	6 (85.7)	58 (89.2)	0.778	21 (87.5)	44 (91.7)	0.574
Absent	1 (14.3)	7 (10.8)		3 (12.5%)	4 (8.3%)	
Hemodialysis duration						
0 – 6 months	2 (28.6)	23 (35.4)	0.719			
More than 6 months	5 (81.4)	42 (64.6)				

*: statistically significant at p<0.05.

Among different biochemical parameters, serum calcium was significantly associated with IGRA outcome (p-value=0.016) among potential recipients, as presented in Table 4. There was no significant difference in the mean biochemical parameter among potential donors and IGRA outcome.

Table 4: Assessment of biochemical parameters with IGRA among recipients and donors

Parameters	Potential Recipients						Potential Donors				
	IGRA outcome	N	Mean	SD	p-value	p-value#	IGRA outcome	N	Mean	SD	p-value
Hemoglobin	Positive	15	9.14	1.21	0.038*	0.089	Positive	12	14.92	1.97	0.084
	Negative	57	10.02	1.48			Negative	60	13.91	1.80	
Calcium	Positive	15	1.82	0.16	0.005*	0.016*	Positive	12	2.12	0.07	0.972
	Negative	57	2.00	0.23			Negative	60	2.12	0.16	
Albumin	Positive	15	36.53	5.15	0.214		Positive	12	40.33	4.99	0.107
	Negative	57	39.36	8.31			Negative	60	44.50	8.51	
Phosphorus	Positive	15	6.01	1.42	0.631		Positive	12	3.73	0.74	0.603
	Negative	57	5.80	1.52			Negative	60	3.62	0.67	
Total bilirubin	Positive	15	8.99	1.68	0.811		Positive	12	10.87	3.81	0.967
	Negative	57	9.22	3.55			Negative	60	10.96	7.21	
Vitamin D	Positive	15	37.04	13.32	0.545		Positive				
	Negative	57	34.15	17.02			Negative				
IPTH	Positive	15	257.61	164.94	0.301		Positive				
	Negative	57	396.93	508.03			Negative				
Ferritin level	Positive	15	393.63	205.26	0.100		Positive				
	Negative	57	559.95	370.91			Negative				
Transferrin saturation	Positive	15	26.40	6.15	0.100		Positive				
	Negative	57	33.38	20.37			Negative				

*: statistically significant at p<0.05; #: Multivariate analysis;IPTH: intact parathyroid

The mean biochemical parameters like albumin (p=0.013) and vitamin D (p=0.022) were significantly different in the development of latent TB infection,as shown from TST tests among potential recipients. Meanwhile, the assessment of biochemical parameters with TST among potential donors was not statistically significant (Table 5).

Table 5: Assessment of biochemical parameters with TST among recipients and donors

Parameters	Potential Recipients						Potential Donors				
	TST outcome	N	Mean	SD	p-value	p-value#	TST outcome	N	Mean	SD	p-value
Hemoglobin	Positive	7	9.89	1.04	0.916		Positive	24	13.89	2.07	0.549
	Negative	65	9.83	1.51			Negative	48	14.17	1.75	
Calcium	Positive	7	2.04	0.29	0.391		Positive	24	2.11	0.19	0.580
	Negative	65	1.96	0.23			Negative	48	2.13	0.12	
Albumin	Positive	7	31.28	13.00	0.007*	0.013*	Positive	24	44.29	4.37	0.723
	Negative	65	39.58	6.72			Negative	48	43.56	9.53	
Phosphorus	Positive	7	6.25	1.73	0.449		Positive	24	3.74	0.65	0.370
	Negative	65	5.80	1.48			Negative	48	3.58	0.69	
Total bilirubin	Positive	7	7.91	1.11	0.284		Positive	24	10.63	6.23	0.783
	Negative	65	9.30	3.37			Negative	48	11.10	7.04	
Vitamin D	Positive	7	47.80	17.82	0.025*	0.022*	Positive				
	Negative	65	33.35	15.60			Negative				
IPTH	Positive	7	343.91	429.76	0.886		Positive				
	Negative	65	370.49	466.90			Negative				
Ferritin level	Positive	7	416.31	244.69	0.388		Positive				
	Negative	65	537.04	357.31			Negative				
Transferrin saturation	Positive	7	41.71	41.81	0.142		Positive				
	Negative	65	30.87	14.31			Negative				

*: statistically significant at p<0.05; #: Multivariate analysis; IPTH intact parathyroid

Discussion

Our study showed that the prevalence of latent TB infection was 20.8% in the potential recipients and 16.6% in donors from IGRA tests, whereas TST diagnosed TB among 9.7% of potential recipients and 33.3% of donors. Our study showed that the prevalence of latent TB in potential recipients from the IGRA test was20.8%. The prevalence of IGRA positivity declined in patients aged > 50 years which was compatible with previous studies done in Taiwan, where the prevalence of IGRA positivity declined in patients aged >70 years[10]. The decrease in prevalence observed in older age groups is also consistent with previous studies[11, 12].

In our study, the prevalence of latent TB among recipients was found to be higher in males (86.7%), which was supported by the study conducted in Iran, where male recipients (59.4%) were higher than females[13]. Similarly, a cross-sectional study conducted among hemodialysis

patients in Kaohsiung Medical University Hospital, Taiwan, had a similar finding where 53.0% of the study population were male[10].

One of the retrospective studies conducted among 79 dialysis patients at 13 hemodialysis centers in five different cities in Southeast Turkey reported that a high frequency of latent TB cases was discovered in the first year of dialysis [14]. Similarly, several studies had reported that a high frequency of latent TB cases was discovered in the first year of dialysis[15, 16], which was attributed to poor general health and compromised host immunity during that stage. Consistent with these previous studies, the majority of latent TB infection prevalence was positive in recipients who have been on hemodialysis for ≤12 months in our study. There was no statistically significant difference between age, BCG scar, and alcoholic status with IGRA positivity in our study, consistent with the study conducted in Taiwan[10]. Also, another study conducted in Brazil had a similar finding that showed no significant association between the presence of latent TB infection and the measured variable (i.e., age, BCG vaccination scar, and hemodialysis duration)[17].

The current study reported that comparing the hematology and biochemical parameters like hemoglobin, calcium albumin, phosphorus, vitamin D, total bilirubin, and TSAT level, only hemoglobin and serum calcium was significantly associated with the development of latent tuberculosis. This study data was compatible with a study conducted in Taiwan where IGRA results were influenced by hemoglobin and serum calcium level[10].These parameters association demonstrates that poor nutritional status was associated with the development oflatent TB. In our study, the prevalence of LTBI estimated by TST was 9.7% in potential renal transplant recipients. In our study, smoking (p=0.028) was significantly associated with the development of latent tuberculosis with TST among potential recipients, but there was no significant association in variables like age, gender, hemodialysis duration, BCG scar, and alcohol consumption. A study in Brazilalso showed similar results, where variables like gender, age, hemodialysis duration, or alcoholic behavior were not significantly associated with TST-positive results [17]. Similarly, the finding is consistent with Turkey's finding, where variables like gender and BCG vaccination were not significant in developing latent tuberculosis with TST [14]. Our study did not find a significant relationship between BCG scar and TST positivity. Studies have shown that TST results are unaffected if the TST is administered many years after vaccination, given that the response to the TST is almost null and void 8-10 years after vaccination [18]. Also, a BCG vaccination is commonly considered a confounding factor rather than a causal factor, supported by the retrospective study conducted in Southeast Turkey[14]. However, in contrast, the study conducted in Brazil showed a significant association between the presence of BCG vaccination scar with positive TST results [18].

In our study, TST-positive recipients with low vitamin D levels were at 1.09 times higher risk of developing latent TB than those TST-negative recipients. Other studies also have reported that vitamin D deficiency was associated with an increased risk of latent TB[19-21].In our study, low serum albumin was associated with a 1.06 times higher risk of developing latent tuberculosis with TST, consistent with the study done in Taiwan[10]. In our study, TST-positive recipient who did not smoke was 93% more protective than those who were ex-smoker. This result was supported by the study conducted in Taiwan, where smoking was associated with an increased risk of latent TB[10]. When we compared the prevalence of latent TBwith the results of IGRA, the prevalence of latent TB was 16.6% in the prospective live donors.The prevalence of latent TB in prospective renal transplant live donors by the TST method was 33.3%. Similarly, different variables such as hemoglobin, albumin, total bilirubin, calcium, and phosphorus were not significantly associated with the IGRA positivity in donors in our study. But the study from the University of Washington showed that the combination of anemia and hypoalbuminemia was an independent risk factor for IGRA positivity [22]. Anemia and hypoalbuminemia in combination may represent an overall inflammatory state contributing to an impaired immune response resulting in IGRA positivity. However, this association was not found in our study among potential donors.

In our study, donors who do not consume alcohol were 64% protective of developing latent tuberculosis. This study was similar to that observed in a prospective cohort study from Singapore, where alcohol consumption increases the risk of latent tuberculosis infection[23]. This study was a single center with a small number of participants. A multicenter longitudinal study is recommend-ed for the management and to find outthe outcome of latent tuberculosis in renal transplant recipients and donors.

Conclusion

Potential renal transplant recipients and donors have a significant burden of latent tuberculosis in the pre-transplantation phase. Diagnosis and treatment of latent tuberculosis before transplan-

tation can prevent ominous complications. The biochemical parameters like hemoglobin, serum calcium, serum albumin, and Vitamin D were associated with the development of latent TB infection signifies that the nutritional status of potential recipients should be prioritized in pre-transplant time. The smoking and alcohol drinking habits of recipients and donors were also associated with the development of latent TB, implying the importance of promoting healthy habits among them.

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