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ORIGINAL ARTICLE

Prevalence of latent *Mycobacterium tuberculosis* infection in renal transplant recipients

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ABSTRACT

Objective: To estimate the prevalence of latent *Mycobacterium tuberculosis* infection (LTBI) in renal transplant recipients and to assess sociodemographic, behavioral, and clinical associations with positive tuberculin skin test (TST) results. **Methods:** This was a cross-sectional study of patients aged ≥ 18 years who underwent renal transplantation at the Renal Transplant Center of the Federal University of Minas Gerais *Hospital das Clínicas*, located in the city of Belo Horizonte, Brazil. We included renal transplant recipients who underwent the TST between January 2011 and July 2013. If the result of the first TST was negative, a second TST was administered. Bivariate and multivariate analyses using logistic regression were used to determine factors associated with positive TST results. **Results:** The sample included 216 patients. The prevalence of LTBI was 18.5%. In the multivariate analysis, history of contact with a tuberculosis case and preserved graft function (estimated glomerular filtration rate ≥ 60 mL/min/1.73 m^2) were associated with positive TST results. TST induration increased by 5.8% from the first to the second test, which was considered significant ($p = 0.012$). **Conclusions:** The prevalence of LTBI was low in this sample of renal transplant recipients. The TST should be administered if renal graft function is preserved. A second TST should be administered if the first TST is negative.

Keywords: Tuberculosis; Tuberculin test; Immunocompromised host.

INTRODUCTION

According to the Brazilian Transplant Registry, the absolute number of renal transplantations from January to December 2016 was 5,492 in Brazil, 563 of which occurred in the state of Minas Gerais. There are 21,264 renal transplant candidates on the waiting list nationwide, 2,297 of whom are from the state of Minas Gerais.[1]

The incidence of tuberculosis in renal transplant recipients compared with that in the general population is approximately 20 to 74 times higher (0.5-15% among kidney recipients)[2] and varies according to the geographical area (0.5% to 1% in North America).[3]

Current immunosuppressive drugs have more specific and potent pharmacological activity to prevent graft rejection, especially in deceased donor recipients at high immunological risk, who require antibody therapy to prevent early humoral rejection.[4] However, these drugs may cause toxicity effects[5] and predispose patients to increased risk of infections,[6] such as tuberculosis and neoplasia.

The most common form of tuberculosis infection after transplantation is reactivation of latent *Mycobacterium tuberculosis* infection (LTBI). Disease development is favored by immunosuppression, and most cases of tuberculosis occur in the first year after transplantation.[2,6,7]

In most countries, the tuberculin skin test (TST) is used for diagnosing LTBI, having a sensitivity of approximately 70%, despite various factors that affect its result, such as immunosuppressant pharmacokinetics, induction therapy, previous therapy for cellular or humoral rejection, cytomegalovirus (CMV) infection, time elapsed since transplantation, retransplantation, chronic renal disease (CRD) stage after transplantation, diabetes mellitus (DM), etc.[8]

The TST for detection of LTBI is relevant as a diagnostic assessment test and, consequently, for the prescription of preventive therapy in positive cases, being able to contribute to reducing the rate of tuberculosis in renal transplant recipients.[9,10] However, the TST is not performed rigorously at transplant centers in Brazil.[11,12] It is of note that there are few published studies on this topic in the country.

Therefore, the objective of the present study was to estimate the prevalence of LTBI in renal transplant recipients and to assess sociodemographic, behavioral, and clinical associations with positive TST results.

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METHODS

This was a cross-sectional study conducted at the Renal Transplant Center of the *Universidade Federal de Minas Gerais* (UFMG, Federal University of Minas Gerais) *Hospital das Clínicas*, located in the city of Belo Horizonte, Brazil. All renal transplant recipients were screened for LTBI between January 2011 and July 2013 by using the TST. The study was approved by the UFMG Research Ethics Committee (Protocol no. 132/10).

Study population

For sample size calculation, we considered as potentially eligible 324 patients at the Renal Transplant Outpatient Clinic of the hospital. Assuming a confidence interval of 95%, an error of 5%, and an LTBI prevalence of 15% (according to a previous study),[6] we estimated the required sample size to be 160 patients. After adding a refusal rate of 30%, we determined that the minimum sample size was 208 patients. The inclusion criteria were as follows: being ≥ 18 years of age and having undergone transplantation at least three months previously. The exclusion criteria were as follows: 1) history of tuberculosis treated before or after transplantation; 2) preventive treatment with isoniazid before transplantation; 3) renal graft loss and return to dialysis therapy before the first TST (TST_1) or second TST (TST_2); 4) death; 5) nonadherence to immunosuppressive therapy; 6) having made fewer than two annual visits to the transplant outpatient clinic; or 7) not having given written informed consent (Figure 1).

Screening for LTBI

Participants were screened for LTBI by using the TST with purified protein derivative RT23 (PPD RT23; Statens Serum Institute, Copenhagen, Denmark). The TST was performed by the Mantoux method, which consists of intradermal administration of 0.1 mL (2 tuberculin units) of PPD RT23 on the volar aspect of the forearm. Test results were read within 72-96 h of administration and were recorded in millimeters of induration. TST_1 was administered after three months following renal transplantation, and TST_2 was administered three weeks later if TST_1 was negative, in order to assess reactivation of the immune response. All patients with a TST_1 induration ≥ 5 mm were considered to have a positive result; those with a negative result were referred for TST_2, which was considered positive if there was a > 10-mm increase in induration compared with the TST_1 reading.[13-15] The cumulative frequency of LTBI was also calculated (N = 216).

Variables and definitions

We investigated the following variables: (i) sociodemographic variables (gender, age, individual income, place of residence, and history of contact with tuberculosis); (ii) behavioral variables (smoking, alcoholism, and marital status); (iii) clinical variables (BCG vaccination scar, body mass index [BMI], DM, autoimmune disease, hepatitis B, hepatitis C, and neoplasms); (iv) transplant-related variables (living/deceased donor, double transplantation, retransplantation, immunosuppressive regimen, time

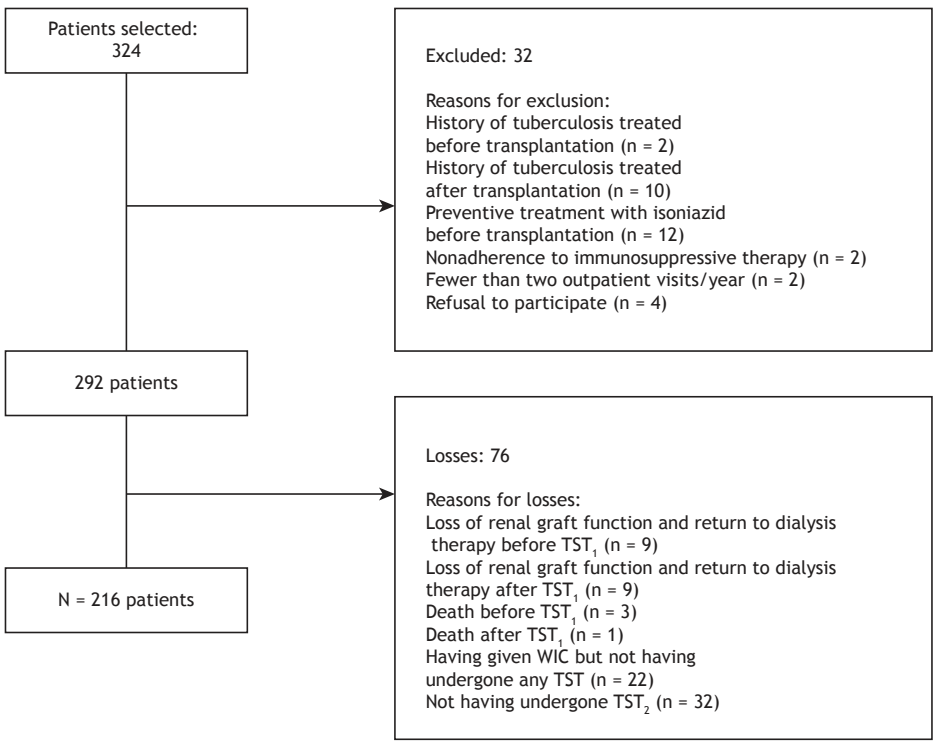

Figure 1. Study flow chart of renal transplant patient selection. TST_1: first tuberculin skin test; TST_2: second tuberculin skin test; and WIC: written informed consent.

interval between transplantation and TST, and renal graft function based on the glomerular filtration rate).

Patients were classified as "having individual income" (employed, retired, or away from work/medical leave) or as "having no income" (unemployed or never worked). Patients were screened for alcoholism with the Cut down, Annoyed, Guilty, and Eye-opener questionnaire, which was incorporated into the patient interview.[16] Patients were classified as "smokers" or "nonsmokers" (people who had never smoked or people who had quit smoking one year prior to the study).[17] BCG vaccination status was determined using the presence or absence of a BCG scar on the right arm. Renal transplant recipient age was categorized on the basis of the median age of the study population. BMI was calculated as recommended by the World Health Organization.[18] Patients were categorized as obese (BMI > 30 kg/m^2) or non-obese (18.5 < BMI ≤ 29.9 kg/m^2). A diagnosis of DM was made in accordance with the classification proposed by the American Diabetes Association[19] and the Brazilian Diabetes Society.[20] Renal graft function was assessed by means of the estimated glomerular filtration rate (eGFR), as calculated by the Modification of Diet in Renal Disease equation.[21] Renal graft function was categorized as "preserved renal function" (eGFR values ≥ 60 mL/min/1.73 m^2) or as "impaired renal function" (eGFR values < 59 mL/min/1.73 m^2).

Statistical analysis

Descriptive statistics (frequency distribution and measures of central tendency and dispersion) were used to analyze the characteristics of the study population. The mean differences for continuous variables were compared by using the Student's t-test for independent samples, and the proportions of categorical variables were compared by using Pearson's chi-square test or Fisher's exact test. For all tests, p values ≤ 0.05 were considered significant. The measure of association in the bivariate analysis was OR and 95% CI.

Explanatory variables with p values ≤ 0.20 in the bivariate analysis were selected for multivariate analysis via a logistic regression model. The level of significance required for inclusion in the final model was 0.05, with adjustment for confounding factors. The goodness of fit of the final model was assessed by using the Hosmer-Lemeshow test.

The data collected were entered into Microsoft® Excel spreadsheets. All statistical analyses were performed with the IBM SPSS Statistics software package, version 21.0 (IBM Corporation, Armonk, NY, USA), and the R software, version 2.15.1 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The characteristics of the study population (N = 216) and the causes of CRD are shown in Table 1. Age at the time of the test ranged from 18 to 75 years, with a median of 48 years and a mean of 46.5 ± 12.3 years. History of contact with tuberculosis was positive in 38 patients (17.6%), negative in 168 (77.8%), and unknown in 10 (4.6%). Obesity was present in 23 patients (10.6%), and 54 patients (25%) had diabetes, of whom 13 were diagnosed with type I DM before transplantation and 41 were diagnosed with type II DM or drug-induced diabetes after transplantation. Seven patients (3.2%) had a previous diagnosis of autoimmune disease. Post-transplant neoplasia, including skin cancer, was present in 23 (10.6%) of the patients.

Of the 216 patients included in the study, 167 (77.3%) reported having income from employment, retirement pension, or medical leave. A total of 152 (70.4%) resided in the greater metropolitan area of Belo Horizonte, close to the transplant center, 63 (29.2%) resided in other areas of the state of Minas Gerais, and 1 (0.4%) resided in the state of Amapá.

The time interval between renal transplantation and TST_1 ranged from 3.0 to 360.4 months, with a mean of 86.8 ± 75.6 months and a median of 68.2 months. The time interval between renal transplantation and TST_2 ranged from 3.5 to 376.1 months, with a mean of 99.0 ± 78.3 months and a median of 79 months.

The prevalence of LTBI was 18.5%, and 40 individuals had positive TST results. Twenty-nine patients (13.4%) had positive TST_1 results, and 11 (5.1%) had positive TST_2 results. TST induration increased by 5.8% from the first to the second test, which was significant (p = 0.012).

The cumulative frequency of LTBI in the study population (baseline, TST_1, and TST_2) was 42.5%, because, of the 216 patients included in the study, 40 had previous positive TST results (18.5%); of the remaining 176 patients, 29 had positive TST_1 results (16.5%); therefore, there remained 147 patients to undergo TST_2, 11 of whom tested positive (7.5%).

In the bivariate analysis (p ≤ 0.20), the following factors were associated with a diagnosis of LTBI: having a history of contact with a tuberculosis case; alcoholism; presence of a BCG vaccination scar; eGFR ≥ 60 mL/min/1.73 m^2; double organ transplantation; and preemptive transplantation (transplantation performed before the initiation of dialysis therapy). In the final logistic regression model, the following variables were statistically significantly associated (p ≤ 0.05) with a diagnosis of LTBI: having a history of contact with a tuberculosis case; presence of a BCG vaccination scar; and eGFR ≥ 60 mL/min/1.73 m^2 (Table 2).

DISCUSSION

Various studies have shown a higher prevalence of tuberculosis in patients undergoing renal transplantation in countries with a low, medium, or high prevalence of the disease if these patients are infected with *M. tuberculosis*.[4,12,22] Therefore, there is a need to diagnose LTBI, and prescribing preventive therapy is relevant to preventing the development of the disease,[13] although this is not routinely done in clinical practice in Brazil.

Table 1. Sociodemographic, clinical, and behavioral characteristics, immunosuppressive regimen, and transplant-related variables in renal transplant recipients (N = 216).

Characteristic	n (%)	N
Sociodemographic variables		
Male gender	134 (62.0)	216
History of contact with a tuberculosis case	38 (17.6)	206
Cause of chronic renal disease		
Unknown	108 (50)	216
Chronic glomerulopathy	48 (22.2)	216
Diabetic nephropathy	20 (9.3)	216
Adult polycystic kidney	13 (6.0)	216
Other	27 (12.5)	216
Clinical variables		
BCG vaccination scar	165 (76.4)	216
BMI from 18.5-29.9 kg/m^2	193 (89.4)	216
Diabetes mellitus	54 (25.0)	216
Type I	13 (24.1)	
Type II/NODAT	41 (75.9)	
Autoimmune disease	7 (3.2)	216
Hepatitis B	7 (3.2)	216
Hepatitis C	4 (1.9)	216
Neoplasms	23 (10.6)	216
Behavioral variables		
Smoking	55 (25.5)	216
Alcoholism	66 (30.6)	216
Immunosuppressants		
Induction therapy	62 (28.7)	216
Monoclonal antibody	50 (80.6)	62
Polyclonal antibody	10 (16.2)	
Monoclonal + polyclonal antibody	2 (3.2)	
Triple immunosuppressive regimen	179 (83.0)	216
CNI + antiproliferative agent + prednisone	119 (66.5)	
mTORi + antiproliferative agent + prednisone	43 (24.0)	
CNI + mTORi + prednisone	17 (9.5)	
Double immunosuppressive regimen	36 (16.5)	216
mTORi + antiproliferative agent	2 (5.6)	
Antiproliferative agent + prednisone	12 (33.3)	
mTORi + prednisone	6 (16.7)	
CNI + prednisone	11 (30.5)	
CNI + antiproliferative agent	5 (13.9)	
Single immunosuppressive regimen	1 (0.5)	216
mTORi	1 (100)	1
Transplantation		
Deceased donor	108 (50.0)	216
Living donor	108 (50.0)	216
Simultaneous double transplantation	14 (6.5)	216
Pancreas + kidney	13 (6.0)	
Liver + kidney	1 (0.5)	
Preemptive transplantation	8 (3.7)	216
Retransplantation	11 (5.1)	216

BMI: body mass index; NODAT: new-onset diabetes after transplantation; CNI: calcineurin inhibitor; and mTORi: mammalian target of rapamycin inhibitor.

Although it is recommended that transplant candidates be referred for TST,[13] there have been no studies on this practice. In the present study, the frequency of LTBI in our population was found to be high (42.5%). To our knowledge, this is the first time that LTBI and its associations with sociodemographic, behavioral, and clinical characteristics have been assessed in renal transplant recipients at a transplant center in Brazil.

Table 2. Bivariate and multivariate analysis of factors associated with tuberculin skin test results (N= 216)

Variables	Tuberculin skin test result[a]		Analysis			
	Positive (n = 40)	Negative (n = 176)	Bivariate OR	p*	Multivariate OR	p*
Sociodemographic						
Age > 46 years	21 (19.4)	87 (80.6)	1.13 (0.57-2.25)	0.73		
Male gender	30 (22.4)	104 (77.6)	2.08 (0.96-4.5.1)	0.60		
History of contact with tuberculosis	18 (47.4)	20 (52.6)	6.66 (0.07-0.33)	0.001	7.16 (3.11-16.49)	0.001
Clinical						
BCG vaccination scar	34 (20.6)	131 (79.4)	1.95 (0.77-4.94)	0.16	3.07 (1.03-9.19)	0.45
BMI from 18.5-29.9 kg/m^2	35 (18.1)	158 (81.9)	1.25 (0.44-3.61)	0.67		
Diabetes mellitus	12 (22.2)	042 (77.8)	1.37 (0.64-2.92)	0.42		
Autoimmune disease	1 (14.3)	6 (85.7)	0.73 (0.85-6.21)	0.77		
Hepatitis B	1.40(0.0)	7 (100.0)	1.04 (1.00-1.01)	0.35*		
Hepatitis C	1 (25.0)	3 (75.0)	0.74 (0.15-14.6)	0.74		
Neoplasms	3 (13.0)	20 (87.0)	0.63 (0.18-2.24)	0.48		
Behavioral						
Smoking	11 (20.0)	44(80.0)	1.14 (0.53-2.47)	0.74		
Alcoholism	16 (24.2)	50 (75.8)	1.68 (0.82-3.43)	0.15		
Immunosuppressants						
Induction therapy	13 (21.0)	49 (79.0)	0.80 (0.38-1.68)	0.56		
CNI + antiproliferative agent + prednisone	21 (17.6)	98 (82.4)	1.14 (0.57-2.26)	0.72		
CNI + mTORi + prednisone	5 (29.4)	12 (70.6)	0.51 (0.17-1.55)	0.23		
mTORi + antiproliferative agent + prednisone	1 (50.0)	1 (50.0)	0.22 (0.01-3.64)	0.25		
Antiproliferative agent + prednisone	1 (8.3)	11 (91.7)	2.60 (0.33-20.7)	0.35		
CNI + prednisone	2 (18.2)	9 (81.8)	1.02 (0.21-4.93)	0.97		
mTORi+ prednisone	0 (0.00)	6 (100.0)	0.81 (0.76-0.86)	0.24*		
Renal graft function (MDRD) at the time of TST_1 (N = 216)						
≥ 60 mL/min/1.73 m^2	19 (18.6)	83 (81.4)	2.14 (1.06-4.34)	0.03	2.14 (0.98 - 4.69)	0.056
< 60 mL/min/1.73 m^2	10 (8.8)	104 (91.2)	1			
Renal graft function (MDRD) at the time of TST_2 (N = 187)						
≥ 60 mL/min/1.73 m^2	5 (18.6)	78 (94.0)	1.05 (0.31-3.56)	0.94		
< 60 mL/min/1.73 m^2	19 (18.6)	83 (81.4)	1			
Transplantation						
Deceased donor	17 (15.7)	91 (84.3)	0.70 (0.35-1.38)	0.29		
Simultaneous double transplantation	5 (35.7)	9 (64.3)	2.65 (0.84-8.40)	0.09		
Preemptive transplantation	3 (37.5)	5 (62.5)	2.77 (0.08-1.58)	0.18		
Retransplantation	1 (9.1)	10 (90.9)	0.43 (0.05-3.42)	0.41		
Time interval between renal transplantation and TST_1						
3-68 months	13 (12.0)	95 (88.0)	1.27 (0.58-2.79)	0.55		
> 68 months	16 (14.8)	92 (85.2)	1			
Time interval between renal transplantation and TST_2						
3,5-79 months	6 (6.4)	88 (93.6)	0.83 (0.25-2.83)	0.77		
> 79 months	5 (5.4)	88 (94.6)	1			

BMI: body mass index; CNI: calcineurin inhibitor; mTORi: mammalian target of rapamycin inhibitor; MDRD: Modification of Diet in Renal Disease (equation); TST_1: first tuberculin skin test; TST_2: second tuberculin skin test. Values expressed as n (%). *Fisher's exact test.

The use of the TST to detect LTBI in pre-renal transplant evaluation is recommended in various countries,[4] including Brazil, where interferon-gamma release assays (IGRAs) have not been validated for routine use.[13,14] Some factors, such as DM, immunosuppressant pharmacokinetics, induction therapy, previous therapy for humoral rejection, CMV infection, etc., may cause false-negative TST results.[10,13] In 2015, the World Health Organization stated that the IGRAs or the TST can be used to detect LTBI, their use being strongly recommended, but with a low level of evidence.[14]

The predominant etiology of CRD before transplantation was indeterminate, because most patients in the present study did not undergo renal biopsy for histological confirmation of CRD. It is of note that, in the present study, glomerulopathies were important, as previously mentioned in another study.[7] Alcoholism and smoking are risk factors for LTBI and for the development of tuberculosis.[23-26] Since, in our study, most patients did not drink alcohol or smoke, there was no statistical association of alcoholism or smoking (they were not risk factors) with positive TST results.

Patients undergoing organ transplantation are more susceptible to infections because of immunosuppressant use. However, in our study, we found no such association with immunosuppressant use. Therefore, the best strategy is to screen for LTBI before organ transplantation. The World Health Organization recommends that high- and medium-income countries with a low incidence of tuberculosis (< 100 cases per 100,000 population) test for and treat LTBI in patients preparing for organ or hematologic transplantation.[14]

Use of tacrolimus and/or mycophenolate in young recipients, DM,[27] age of recipients,[8] time elapsed since transplantation,[7,12] hepatitis C,[28] CMV infection, cancer, and autoimmune diseases[8] have been reported as factors for reactivation of tuberculosis and development of severe tuberculosis, especially during the first six months after solid organ transplantation.[6] If LTBI is detected, as occurred in our study, prevention with isoniazid is recommended.[29]

Transplantation of deceased-donor kidneys with increased ischemia times and retransplantation are situations perceived as being of high immunological risk. In these situations, it is recommended that induction therapy consist of higher potency drugs, such as basiliximab, thymoglobulin, or other polyclonal antibodies, in order to prevent acute rejection and reduce the effects of delayed graft function both in the short and long term. This therapy increases the risk of developing tuberculosis after transplantation and may cause negative TST results,[4,6] thereby compromising the diagnosis of LTBI.[4,7] However, in our study, such an association with deceased-donor kidneys and retransplantation was not observed. Preemptive renal transplantation and double organ transplantation showed a trend toward higher TST positivity. Nevertheless, it should be taken into consideration that these transplant types represent a small sample, which would lead to an underestimated analysis.

We found that history of contact with a tuberculosis case, presence of a BCG vaccination scar, and preserved renal graft function were associated with positive TST results.

The likelihood of having a positive TST result is 7.16 times higher in patients reporting a history of contact with a tuberculosis case. A history of contact with tuberculosis has long been described as being associated with positive TST results and, therefore, has a direct relationship with a diagnosis of LTBI.[3,9,13] In the present study, having a history of contact with tuberculosis showed a significant association with positive TST results.

The presence of a BCG vaccination scar increases by 3.07 times the likelihood of a patient having a positive TST result. In contrast, recent BCG vaccination may cause a false-positive TST result.[30] However, studies have shown that TST results are unaffected if the TST is administered many years after vaccination,[13,31] given that the response to the TST is almost null and void 8-10 years after vaccination.[15,32] In the present study, we found a significant relationship between BCG vaccination and TST positivity. All patients in our study who had a BCG vaccination scar had been vaccinated more than 15 years previously (mean age, 46 years). A history of BCG vaccination[13,15,32] is commonly considered a confounding factor rather than a causal factor.

In our study, a six-month course of isoniazid was used to prevent tuberculosis; some studies recommend that a careful evaluation be made in order to arrive at a decision regarding the use of other drugs to prevent the disease.[2,6,8,33]

In the present study, preserved renal graft function (eGFR ≥ 60 mL/min/1.73 m^2) was the only dependent variable that was associated with positive TST results. The immunological effects resulting from uremia, such as changes in phagocytosis, bacterial lability, and lymphocyte transformation, may lead to negative TST results.[2,34] Therefore, in cases of reduced renal graft function, we observed negative TST results, as reported in another study.[28]

The prevalence of LTBI among the renal transplant recipients in our study (18.5%) was lower than that found by Sester et al.,[35] who obtained positive TST results in 52.14%, but similar to that reported in the study by Atasever et al. (13.6%).[6] This is probably due to the fact that the state of Minas Gerais has registered low tuberculosis incidence rates in recent years.[36]

The increase in induration from TST_1 to TST_2 (significant response) shows that it is advisable to administer a second test if the first one is negative, given that most patients failed to respond to TST_1 (81%). Similar results have been reported in other studies in which a TST_2 was administered,[5,13] with the administration of the second test favoring the detection of LTBI in patients receiving immunosuppressants.[8] Although the Brazilian National Tuberculosis Control Program recommends that the TST be administered to transplant recipients, we find that, given the significant increase in TST induration from the first to the second test, further studies including other populations should be conducted in order to assess reactivation of the immune response and inform the recommendation of the second test in clinical practice, because, if the second test is positive, preventive medications should be initiated, thus preventing the development of tuberculosis.

The limitation of our study is the use of the TST, which may not reflect the reality of LTBI because of lymphocyte immunodeficiency and variation in the prescribed immunosuppressive regimens. Some authors have studied the possibility of new markers for the diagnosis of LTBI and tuberculosis in order to overcome this limitation, but there is still no evidence of the use of new tests in solid organ transplantation.[37,38]

In conclusion, the risk factors observed for positive TST results in screening for LTBI in renal transplant recipients are history of contact with tuberculosis cases and preserved renal graft function. The prevalence of LTBI was low in renal transplant recipients. A TST_2 should be administered to these patients if TST_1 is negative. The TST should be administered if renal function is improved.

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