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Original Article

Latent Tuberculosis Infection Management in Solid Organ Transplantation Recipients: A National Snapshot

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Abstract

OBJECTIVE: Latent tuberculosis infection (LTBI) screening is strongly recommended in the pre-transplant evaluation of solid organ transplant (SOT) recipients, although it remains inadequate in many transplant centers. We decided to investigate pre-transplant TB risk assessment, LTBI treatment, and registry rates in Türkiye.

MATERIAL AND METHODS: Adult SOT recipients who underwent tuberculin skin test (TST) and/or interferon-gamma release test (IGRA) from 14 centers between 2015 and 2019 were included in the study. An induration of ≥5 mm on TST and/or probable/positive IGRA (QuantiFERON-TB) was considered positive for LTBI. Demographic features, LTBI screening and treatment, and pre-/post-transplant TB history were recorded from the electronic database of transplantation units across the country and pooled at a single center for a unified database.

RESULTS: TST and/or IGRA were performed in 766 (33.8%) of 2266 screened patients most of whom were kidney transplant recipients (n = 485, 63.4%). LTBI screening test was positive in 359 (46.9%) patients, and isoniazid was given to 203 (56.5%) patients. Of the patients treated for LTBI, 112 (55.2%) were registered in the national registry, and 82 (73.2%) completed the treatment. Tuberculosis developed in 6 (1.06%) of 563 patients who were not offered LTBI treatment.

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CONCLUSION: We determined that overall, only one-third of SOT recipients in our country were evaluated in terms of TB risk, only 1 of the 2 SOT recipients with LTBI received treatment, and half were registered. Therefore, we want to emphasize the critical importance of pretransplant TB risk stratification and registration, guided by revised national guidelines.

KEYWORDS: Solid organ transplantation, tuberculosis, latent tuberculosis infection, interferon-gamma release test, tuberculin skin test
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INTRODUCTION

Tuberculosis (TB) is still one of the world's most predominant infectious causes of morbidity and mortality since the 18th century when TB became epidemic in Western Europe.[1] According to the World Health Organization data, 20 million people developed TB and 1.5 million people died from TB in 2020, thus TB has become the second leading cause of infectious killer after COVID-19.[2]

Tuberculosis risk is increased in immunosuppressive conditions. Solid organ transplant (SOT) recipients have a 20-74 times increased risk of active TB.[3,4] The pooled prevalence of post-transplant active TB was estimated at 3%[5] and in cohort studies the overall median incidence has been reported as 2.37% (0.05%-13.27%) with higher incidences in endemic regions.[6] Tuberculosis incidence has been reported 15/100 000 for Türkiye in 2020[7] and TB prevalence in SOT was found to be 3.2% in a recent meta-analysis conducted in 4553 Turkish SOT recipients.[8] Since TB-related morbidity and mortality in SOT recipients are high, prevention and early recognition of TB infection is critical. There have been TB consensus guidelines for a long time; however, the diagnosis and management of LTBI have not been mentioned in a separate section detailed with brief recommendations.[9,10]

SOTprocedure, started in 1975 in Türkiye; however, routine pretransplant TB risk screening protocol has been established recently, therefore we aimed to investigate the practice in latent TB infection (LTBI) screening in SOT recipients and donors as well as posttransplant follow-up, registry rates, and TB prevalence in a given period in Türkiye.

MATERIAL AND METHODS

We conducted a retrospective descriptive study including 14 centers (36 clinics) from different regions of Türkiye and reviewed the data of all registered adult (age >18 years/old) SOT recipients. Patients who had undergone pretransplant LTBI screening with tuberculin skin test (TST) and/or interferon-gamma releasing assay (IGRA) between January 2015 and December 2018 were included in the study. The study was approved by the Ethics Cmmittee of Dokuz Eylül University (September 4, 2014, 2014/28-13). An informed consent form is not required due to the fact that it is a retrospective study.

Demographic characteristics and TB risk factors, pre/post-t ransplantation TB history, and LTBI screening procedure were recorded from the electronic database of each transplantation unit and combined for a nationwide united database. The findings were also checked with the national registry of the national "Ministry of Health, General Directorate of Public Health, and Department of Tuberculosis."

Latent Tuberculosis Infection Diagnosis

Tuberculin Skin Test

Tuberculin skin test was performed in standard procedure and interpreted 48/72 hours after the administration.

Interferon Gamma Releasing Assay

Interferon-gamma releasing assay was performed in registered laboratories nationwide with a commercial kit approved by the Ministry of Health.

An induration of ≥5 mm on TST and/or probable and positive IGRA (QuantiFERON TB) was considered positive for LTBI.

Diagnosis of Tuberculosis

Solid organ transplant recipients with posttransplant TB were identified, and posttransplant TB prevalence was calculated. Patients with symptoms, signs, and radiological findings (cavities, consolidation, bronchopneumonia, lymphadenopathy) suggestive of active TB infection whose microbiological specimens were positive for acid-fast bacilli and/or have a histopathological diagnosis of caseating granuloma were considered to have TB.

Latent Tuberculosis Infection Indications and Treatment Protocols

Either an induration of ≥5 mm on TST and/or probable and positive IGRA (QuantiFERON TB) was considered positive for LTBI. A standard LTBI treatment protocol with isoniazid given daily for 9 months was considered unless SOT recipients have received a prior adequate course of LTBI or active TB treatment.

Statistical Analysis

Data were analyzed with the Statistical Package for the Social Sciences version 24.0 (IBM Corp., Armonk, NY, USA). Data were expressed as mean and standard deviation or median and minimum–maximum values according to the distribution of the data. Nonparametric variables were compared by Mann–Whitney *U*-test, and categorical data were evaluated by chi-square or Fisher's exact test. A *P*-value of <.05 was considered significant.

Main Points

- Pretransplant tuberculosis (TB) screening is important to avoid post-transplant TB infection-related morbidity and mortality in solid organ transplant (SOT) recipients.
- There are efficient laboratory tests for determining latent tuberculosis infection (LTBI).
- Although guidelines recommend screening and treatment of LTBI, compliance rates to recommendations are not as desired depending on the pretransplant procedures of the transplantation center and transplanted organs.
- Latent tuberculosis infection screening and treatment in SOT recipients should be re-evaluated by national guidelines and tracked by registration.

Results

For the given period, 2266 SOT recipients from 14 centers and 2 participants from the Ministry of Health were included. Tuberculin skin test and/or IGRA were administered to 766 (33.8%) of them (Figure 1). The pretransplant LTBI screening rate ranged between 2.2% and 100% depending on the transplantation center. Within these 766 patients, most of them were kidney transplant recipients (n = 485, 63.4%). Males were predominant and mean ages ranged from 35.6 to 51.0 according to donated organs (P = .023) (Table 1). Among the factors associated with the likelihood of active TB risk, prior contact with an active TB patient was observed in 23 (3.0%), while fibrotic lesions compatible with LTBI were found in 84 (10.9%). Demographic and clinical features of the patients according to donated organs are shown in Table 1.

The pretransplant LTBI screening test positivity rate was 46.9% (minimum 31.1%–maximum 83.3%), and TST was the most preferred method for screening. Latent tuberculosis infection screening tests were most frequently applied in heart transplantation recipients (83.3%), although none were offered treatment (Table 2).

Isoniazid (INH) was the treatment choice for LTBI treatment and was given to more than half of the screened patients (60.8%). Half of them (n = 104, 51.2%) started treatment on the post-transplant first day. National registry notification for LTBI treatment was only performed for half of the patients (n = 112, 55.2%). Most of the patients to whom LTBI was offered completed the treatment (n = 82, 73.2%) (Table 3).

Among the study population, posttransplant TB was observed in 6 (1.06%) patients, 3 of these patients had risk factors for TB, and only two had LTBI screening but had not received LTBI treatment despite being positive.

DISCUSSION

The risk of TB infection as well as TB-related and SOT-related morbidity is increased in SOT recipients. There are existing guidelines for pretransplant screening in SOT recipients to reduce the risk of TB disease in SOT recipients and LTBI screening and treatment is recommended for transplant candidates and recipients considered at high risk of TB.[11-13] In Türkiye, a section for SOT recipients has recently been added to the national "Tuberculosis Diagnosis and Treatment Directory." Therefore, we aimed to investigate the practice for LTBI screening and treatment in SOT recipients and candidates across Türkiye.[14]

We evaluated 766 patients among 2666 SOT recipients to whom TST and/or IGRA were administered, representing one-third of the SOT recipients. Most of them were kidney

Table 1. Demographic and Clinical Features of the Study Population According to Donated Organ

Characteristics n (%)	Kidney (n = 485)	Liver (n = 206)	Lung (n = 45)	Heart (n = 30)	Total (n = 766)
Age (mean ± SD)	40.9 ± 13.1	51.0 ± 13.2	47.4 ± 12.1	35.6 ± 9.0	43.8 ± 13.7
Gender (male)	317 (65.4)	141 (68.4)	38 (84.4)	26 (86.7)	522 (68.1)
Donor source (living)	363 (74.8)	130 (63.1)	-	-	493 (64.4)
Prior tuberculosis exposure	11 (2.3)	8 (3.9)	4 (8.9)	-	23 (3.0)
LTBI radiological evidence	15 (3.1)	24 (11.7)	45 (100)	-	84 (10.9)

LTBI, latent tuberculosis infection.

Table 2. Latent Tuberculosis Infection Screening Test Application and Positivity Rates According to Donated Organ

	Positive Test/Applied Test				
LTBI Screening Test n (%)	Kidney (n = 485)	Liver (n = 206)	Lung (n = 45)	Heart (n = 30)	Total (n = 766)
TST	181/400 (45.3)	103/147 (70.1)	-	24/29 (82.7)	308/576 (53.9)
QuantiFERON-TB	12/55 (21.8)	8/17 (47.1)	14/45 (31.1)	-	34/117 (29.0)
TST and QuantiFERON-TB	7/30 (23.3)	9/42 (21.4)	-	1/1 (100)	17/73 (23.3)
Total	200/485 (41.2)	120/206 (58.3)	14/45 (31.1)	25/30 (83.3)	359/766 (46.9)

LTBI, latent tuberculosis infection; SOT, solid organ transplantation; TB, tuberculosis; TST, tuberculin skin test.

Table 3. Latent Tuberculosis Infection Treatment Offer, Registration, and Completion Rates According to the Donated Organs

LTBI Treatment	Kidney (n = 485)	Liver (n = 206)	Lung (n = 45)	Heart (n = 30)	Total (n = 766)
Recommendation	159/200 (79.5)	36/120 (30.0)	8/14 (57.1)	-	203/334 (60.8)
Notification to national registry	94/159 (59.1)	12/36 (33.3)	6/8 (75.0)	-	112/203 (55.2)
Completion	70/159 (44.0)	7/36 (19.4)	5/8 (62.5)	-	82/203 (40.4)

LTBI, latent tuberculosis infection.

transplant recipients due to more kidney transplantations than others. Males were predominant and the mean age was 43.8 ± 13.7, heart and kidney transplant recipients were the youngest. In a review that evaluated a total of 187 studies from 1998 to 2016, 2082 cases of TB after SOT have been identified. The median age was 45, males, and kidney transplantations were predominant.[6] In another systematic review and meta-analysis examined the pooled prevalence of active TB after transplantation, no difference between the mean/median age of transplant recipients across the countries.[5]

Among the factors associated with the likelihood of active TB risk, prior contact with an active TB patient was observed in 23 (3.0%), while fibrotic lesions compatible with LTBI were found in 84 (10.9%). In a study of 1097 kidney transplant patients, post-transplant TB incidence was reported as 2.1%, and previously healed TB on chest radiograph Relative rate 8.71, 95% CI 1.00-75.84, $P = .05$) was found as a significant pre-transplant risk factor for post-transplant TB on multivariate analysis.[15] Documentation of a detailed history including exposure to individuals with active TB in the household or workplace, prior TST results, and prior active TB is strongly recommended in the consensus reports.[13]

Post-transplant TB mostly develops from reactivation of latent TB infection, acquired primary infection has been reported in a small number of cases and donor-derived TB constitutes <5% of all TB cases.[6,13] Therefore, LTBI screening has critical importance and all transplant candidates including those with a history of vaccination with Bacillus Calmette–Guerin (BCG) should be screened. Tuberculin skin test and IGRAs have been used for this procedure; TST is the main diagnostic method recommended, however, IGRA tests may be the choice especially in countries endemic for TB and prior history of BCG vaccination as IGRA results are specific to M. tuberculosis antigens. Interferon-gamma releasing assay tests also have been shown to be more sensitive than end-stage renal disease or advanced liver disease, due to their high specificity.[16,17] Both tests may have false–negative or indeterminate results due to immunosuppressive drugs and some experts recommend using both TST and IGRA in high risk to maximize the sensitivity.[18,19] False negative results for TST are partly due to anergy related to end-stage organ disease and only 20% to 50% of active TB disease have been reported to have a positive TST before transplantation.[15,20] False–positive TST is mostly associated with prior vaccination with BCG or infection with other non-tuberculous mycobacteria.[21] In our study, the LTBI screening rate was in a wide range, however, it was relatively low overall (33.8%). Tuberculin skin test was the most frequently applied method due to cost and feasibility issues. The patients who developed posttransplant TB had not been given LTBI treatment despite two of them being positive.

Lung transplantation candidates were the ones with the lowest LTBI laboratory test positivity rates (31.1%) to whom 57.1% were offered LTBI treatment, while heart transplantation recipients were the most (83.3%), although none were offered treatment. Lung transplant recipients have been reported to have a greater risk of active TB, compared to other SOT recipients,[5,22] therefore LTBI treatment should be strictly administered in lung transplantation. More than half of the liver transplant candidates also had positive test results, however only one-third were offered LTBI treatment. Overall, LTBI screening test positivity was relatively high (46.9%) due to the heterogeneity of donated organs and the multicenter design. In another single-center study conducted on liver transplant recipients in Türkiye, a lower rate of 25.9% was reported.[23]

A positive TST and/or IGRA test demonstrates the presence of LTBI; however, a negative test does not exclude LTBI. Therefore, guidelines recommend screening all transplant candidates for TB by careful epidemiologic history, physical exam, and chest X-ray or thorax computed tomography, as well as TST or IGRA testing. A positive TST or IGRA should be considered for LTBI treatment after excluding active TB. Transplant candidates who have had recent exposure to a case of active TB and/or radiographic evidence of untreated TB are also recommended to be considered for LTBI treatment even in the case of indeterminate or negative TST or IGRA tests. Since donor-derived TB cases have been reported, all living donors should be screened, and transplant recipients who have received an organ from a donor with a positive TST should be offered.[13]

Although some cohorts defined that TB could still develop after treatment[24,25] recent evidence supports that LTBI treatment significantly reduces the incidence of TB reactivation in transplant recipients.[26] Isoniazid is the first-choice drug used for LTBI treatment; however, isoniazid-related hepatotoxicity is the main factor restricting the widespread use of INH, and only a quarter of SOT recipients have been reported to undergo LTBI treatment. There are studies reporting the safety of LTBI treatment with INH in liver transplant recipients; however, hepatotoxicity, drug interactions, and relatively low compliance rates of liver transplant recipients restrict implementation.[27,28] Recent guidelines recommend starting LTBI treatment after transplantation in decompensated cirrhosis.[13] In our study, the overall LTBI treatment recommendation was 60.8%, with the least (30.0%) in liver transplant recipients. Considering the risks of LTBI treatment might outweigh the benefits may be the reason for the low LTBI treatment recommendation rates in our study. Compliance of the liver transplant recipients was the lowest (19.4%), compatible with previous studies, and was the best in lung transplant recipients (62.5%) in our study. The compliance in lung transplant recipients may be better due to strict pulmonary disease follow-ups. Overall, LTBI treatment was completed in less than half of the patients, with a low compliance rate compatible with previous studies from different countries.[22,29] The reasons for these low completion rates might be listed as lost to follow-up, LTBI treatment-related adverse events, not applying to the dispensaries, etc. Latent tuberculosis infection treatment notification rates to the national registry were also lower than expected.

A separate section has been prepared for SOT recipients in the national TB diagnosis and treatment guidelines recommending LTBI screening for SOT recipients and donors after this study was terminated.[30]

One of the limitations of the study was that IGRAs had been studied in different centers with different commercial tests, but all the commercial kits were approved by national authorities.

Another limitation is that TST was applied and evaluated by different practitioners in different centers. However, when we look at the results in the national data network, we think that both TST and IGRA applications comply with the standards. The lack of LTBI screening or registration for donors was also a limitation. Routine administration of the BCG vaccine may also have influenced some TST results.

CONCLUSION

We found that approximately one-third of SOT recipients have been screened for LTBI depending on the pretransplant procedures of the transplantation center and transplanted organs. Laboratory tests were positive in half of the patients; however, LTBI treatment rates were different according to the donated organ between 30.0%-79.5%, and half of them were not registered. LTBI treatment completion rates were also relatively low, which might also be related to untracked processes caused by unregistered applications. All these findings indicate that LTBI screening and treatment in SOT recipients are inadequate and should be re-evaluated considering national recommendations.

Ethics Committee Approval: This study was approved by the Non-Invasive Research Ethics Committee of Dokuz Eylül University (approval number: 2014/28-13; date: September 4, 2014).

Informed Consent: An informed consent form is not required due to the fact that it is a retrospective study.

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