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Antibiotic Prophylaxis has no Advantage over Surveillance alone in Terms of the Incidence of Mycobacterium Tuberculosis Infection after Liver Transplantation

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Abstract

Screening for latent Mycobacterium tuberculosis (MTB) in liver transplant (LT) candidates and antibiotic prophylaxis in those who test positive is recommended, but its effectiveness remains unclear. This study compared the impact of antibiotic prophylaxis and active surveillance alone on the incidence of MTB infection following LT. Four hundred and ninety-six LT patients that were enrolled in two LT (LT-1 and LT-2) centres were screened for latent MTB infection via the Quantiferon (QTF) test. A total of 88/496 (17.7%) of the QFFs tested positive. Past MTB infection (p=0.030), older age (p<0.001) and hepatocellular carcinoma (p=0.003) were independent predictors of QTF positivity. After LT, 38/59 (64.4%) LT-2 patients and 29/29 (100%) LT-1 QTF-positive patients received antibiotic prophylaxis or active surveillance alone, respectively. MTB infections between LT-2 centres and LT-1 centres were comparable both in all populations (2/262 vs. 1/234, p=0.630) and in QFFs who tested positive (1/59 vs. 1/29, p=0.604). Predictors of MTB infection after LT were hepatitis B virus infection (p=0.004), QTF positivity (p=0.006) and treatment with mycophenolate (p=0.021). All MTB-infected patients were alive after receiving antitubercular treatment. Antibiotic prophylaxis in QTF-positive patients is not superior to observation alone in preventing and determining the clinical outcome of MTB infection following LT.

Keywords: Antibiotic prophylaxis; Surveillance; Mycobacterium tuberculosis; Liver transplantation; Quantiferon; Human immunodeficiency virus

Abbreviations: MTB: Mycobacterium Tuberculosis; LT: Liver Transplant; QTF: Quantiferon; TST: Tuberculin Skin Testing; QFT: QuantiFERON-TB; GESITRA: Group for the Study of Infection in Transplant Recipients; HIV: Human Immunodeficiency Virus; PCR: Polymerase Chain Reaction; IQRs: Interquartile Ranges; HCC: Hepatocellular Carcinoma; IS: Immunosuppressive; HBV: Hepatitis B Virus; CMV: Cytomegalovirus

Introduction

The World Health Organization estimates that approximately one-third of the world's population is infected with Mycobacterium tuberculosis (MTB) [1] and that up to 10% of infected individuals will develop the symptomatic MTB-related disease during their life [2]. Risk factors for developing MTB-related disease are living in low-income countries, close contact with people with active MTB infection, and impaired immunological function [3,4]. Compared with the general population, liver transplant (LT) recipients are at increased risk of developing MTB infection since their host defense against infections is compromised by immunosuppressive drugs [5]. The acquisition of infection is commonly due to the reactivation of latent infection in patients with previous exposure [4], although reinfection has been described in endemic areas [6]. Furthermore, donor-transmitted MTB accounts for approximately 4% of all cases [7].

Several clinical guidelines recommend systematic screening for latent MTB infection in LT candidates; this can be done by either tuberculin skin testing (TST) or interferon- γ release assays for the detection of the proliferative response of peripheral lymphocytes to specific MTB antigens including the QuantiFERON-TB Gold (QFT) test and chest X-ray findings [8-11]. In LT candidates who tested positive and after ruling out active MTB disease, the prophylactic antibiotic therapy against MTB reactivation/infection after LT was recommended [12-14]. Scientific societies suggest the use of isoniazid (INH) or rifampin (RIF) for a duration of 6-9 months for all LT recipients who test positive for TST or QFT and suspected latent MTB [13,15-18]. The optimal timing of therapy in relation to the time of LT and the risk of drug-induced hepatotoxicity of INH- and RIF-based regimens in LT recipients continues to be debated [19]. To overcome the potential hepatotoxicity of INH and RIF, a prophylactic regimen based on ethambutol plus either levofloxacin or moxifloxacin for at least 6 months has been suggested by the Group for the Study of Infection in Transplant Recipients (GESITRA) [18]. However, observational studies have shown that the MTB reactivation rate is inferior to the risk of drug-induced hepatotoxicity [20]; thus, some LT centres screen for but do not adopt antibiotic prophylaxis in patients with latent MTB infection [21,22]. Owing to the large variability of prophylactic strategies adopted in LT candidates with latent MTB infection, data regarding their efficacy and safety are still inconclusive. Furthermore, data showing a clear efficacy of antibiotic prophylaxis compared with surveillance alone in reducing the incidence of MTB reactivation/infection after LT are not available. This study evaluated the overall incidence of MTB reactivation/infection after LT to compare the efficacy of antibiotic prophylaxis with that of surveillance alone in preventing MTB reactivation after LT in patients who tested positive for TST or QTF. Furthermore, the safety of antibiotic prophylactic treatment in this population was assessed.

Materials and methods

Patients

All consecutive patients who received an LT from January 1st, 2010, to December 31st, 2018, at two LT centres in northern Italy (the Hepatology and Liver Transplantation Unit, University of Udine, LT-1, and the Gastroenterology and Medicine Departments, University of Padova, LT-2) were enrolled in this study. The inclusion criteria were age ≥18 years, pre-LT diagnostic work-up including TST or QFT, post-LT survival of at least 60 days, and post-LT follow-up of at least 1 year. The exclusion criteria were combined solid organ transplantation, active MTB infection for up to one year before LT, and Human Immunodeficiency Virus (HIV) infection. The patients' main demographic, clinical and laboratory characteristics, as well as the immunosuppressive treatment schedules adopted after LT, were extracted from the electronic medical records of each LT center. Informed consent to participate in the study was obtained from all participants while they agreed to be enlisted for LT. Furthermore, the study was approved by the local internal review boards and ethical committees of the two LT centers. This work was conducted in accordance with the Declaration of Helsinki.

Definition of latent MTB infection and antibiotic prophylactic strategy

Both LT-1 and LT-2 centers tested all LT candidates using TST (PPD skin test - Tubersol-Sanofi Pasteur) or QTF (Quantiferon-TB Gold, Cellestis, Inc.) during their pre-LT diagnostic work-up. The diagnosis of latent MTB infection was defined by one or more of the following conditions: positive TST (≥5 mm induration), positive QTF, chest radiography with high-risk abnormalities evaluated by a TB infectious disease and radiologist specialist physicians. Internal clinical policies were followed; in the LT-1 center, TST- or QTF-positive patients did not undergo antibiotic prophylaxis, whereas in the LT-2 center, antibiotic prophylaxis was proposed for all TST- or QTF-positive patients. The antibiotic prophylactic regimen was based on the combination of oral levofloxacin 500mg plus ethambutol 800-1200mg three times per day from Day 1 postsurgical operation to hospital discharge, and then three times a week for 1 year as previously reported [23]. Prophylaxis was discontinued at the discretion of patient's physicians if symptoms of liver or other significant drug-induced toxicity occurred.

Definition of MTB reactivation/infection

All patients, independent of the TST and QTF results, were followed after LT through regular visits and laboratory and radiological evaluations as determined by the LT centers' clinical policies. In the occurrence of fever episodes, unexplained graft dysfunction, or clinical deterioration, infections, including bacteria, fungi and MTB, were systematically detected via blood, urine and biological fluid cultures and through the MTB polymerase chain reaction (PCR) test. In cases of suspected respiratory infection, an MTB search was conducted on respiratory secretions or bronchoalveolar lavages obtained during bronchoscopy. Active MTB reactivation/infection was defined by positive microscopic evidence of MTB and MTB positivity of cultures or PCR in examined samples.

Statistical Analysis

Statistical analysis was performed via Stata 15.1 statistical software (StataCorp. 2017. Stata Statistical Software: Release 15.1 College Station, TX: StataCorp LLC). Categorical variables were compared via the Pearson chi-square test and data presented as frequencies (%); continuous variables were compared via the nonparametric rank-sum test (Mann-Whitney), and data are presented as medians and interquartile ranges (IQRs). In multivariate analyses, only univariate factors with a statistical significance determined by $p<0.10$ were re-evaluated in a stepwise regression model with a forward selection approach.

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Results

Four hundred ninety-six LT patients (370 males, median age 57 years) were enrolled in the study. Among them, 234 (47.2%) were enrolled in LT-1 and 262 (52.8%) were enrolled in LT-2. No significant differences in recipient age, sex, or the presence of hepatocellular carcinoma (HCC) were observed between the two LT groups. Compared with those in the LT-1 center, patients in the LT-2 center had significantly higher median Child–Pugh (10 vs. 8, p<0.001) and Model for End Stage Liver Disease (MELD and MELD-Na) scores (19 vs. 16, p<0.001 and 21 vs. 16, p<0.001). Patients enrolled in the LT-2 center presented a greater frequency of hepatitis B virus (HBV) or hepatitis D virus (HDV) infections (55/262 vs. 24/234, p<0.001) and metabolic dysfunction-associated steatosis liver disease (MASLD) (30/262 vs. 4/234, p<0.001) than those enrolled in the LT-1 center (Table 1).

Table 1: Comparisons of baseline demographic and clinical characteristics of patients enrolled in the two liver transplant centres (LT-1 and LT-2). Categorical parameters are presented as frequencies (%), and the Pearson chi-square test was used for statistical comparisons. Continuous variables are presented as medians (interquartile ranges), and the rank-sum test (Mann–Whitney) was used for statistical comparisons.

	LT-1 Center	LT-2 Center	
	(N=234)	(N=262)	p
Recipient male gender	173 (73.9)	197 (75.2)	0.748
Recipient age at transplant (years)	58 (51-63)	57 (49-63)	0.179
BMI (kg/m^2)	24.7 (22-28)	25.8 (23-28)	0.027
Child–Pugh score	8 (6-10)	10 (7-12)	<0.001
MELD score	16 (11-20)	19 (13-26)	<0.001
MELD-Na score	16 (12-22)	21 (15-28)	<0.001
KDIGO Stage III and IV renal insufficiency	44 (18.8)	40 (15.3)	0.295
Diabetes	51 (21.8)	61 (23.3)	0.692
Presence of ascites	137 (58.6)	166 (63.4)	0.273
Presence of esophageal varices	168 (71.8)	177 (67.6)	0.306
Etiologies liver diseases (primary or additional)			
HCV	93 (39.7)	86 (32.8)	0.109
HBV+HBV/HDV	24 (10.3)	55 (21.0)	0.001
ALD	102 (43.6)	112 (42.8)	0.85
MASLD	4 (1.7)	30 (11.5)	<0.001
Autoimmune	20 (8.6)	23 (8.8)	0.927
Inherited liver diseases	1 (0.4)	4 (1.5)	0.221
HCC	115 (49.2)	118 (45.0)	0.36
Other	11 (4.7)	15 (5.7)	0.609

BMI: Body Mass Index; MELD: Model of End-Stage Liver Disease; MELD-Na: Model of End-Stage Liver Disease Sodium; HCV: Hepatitis C Virus; HBV: Hepatitis B Virus; HDV: Hepatitis D Virus; KDIGO: Kidney Disease Improving Global Outcomes; ALD: Alcohol-Related Liver Disease; MASLD: Metabolic Dysfunction-Associated Steatotic Liver Disease; HCC: Hepatocellular Carcinoma.

Prevalence of latent MTB infection before LT

All 496 patients underwent the QTF test, and 88 (17.7%), 378 (76.3%), and 30 (6%) tested positive, negative and indeterminate, respectively. Thirty-one (6.1%) patients underwent TST and 8 (25.8%) tested positive. Since all TST-positive patients were also QTF positive, in the following analyses, only the QTF test results were evaluated. Table 2 compares the frequencies of QTF test results and MTB-related past infection, proven source contact, and vaccination between patients enrolled in LT-1 and those enrolled in LT-2 centers. A significantly greater percentage of QTF-positive patients were observed in the LT-2 center than in the LT-1 center (59/262 vs. 29/234, p=0.001). The independent predictors for having a positive QTF test in the whole population studied are presented in Table 3. In the multivariate analysis, in addition to being enrolled in the LT-2 center (p=0.003), past MTB infection (p=0.030), older age at listing (p<0.001) and the presence of HCC (p=0.003) were selected as independent predictors for testing QTF-positivity compared with negative or indeterminate results.

Evaluation of patients after liver transplantation

Immunosuppression schedules adopted. Table 4 shows the immunosuppressive (IS) treatment regimens adopted in each LT center. Compared to those in the LT-2 center, patients in the LT-1 center received the following: more frequent IS treatment with

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cyclosporine (43/234 vs. 11/262, p<0.001) and less frequent treatment with tacrolimus (173/234 vs. 235/262, p<0.001), MMF (33/234 vs. 85/262, p<0.001) and mammalian target of rapamycin (mTOR) drugs (102/262 vs. 23/234, p<0.001).

Table 2: Comparisons of Quantiferon (QTF) test results, past MTB-related infection, source contact, and vaccination between patients enrolled in the LT-1 and LT-2 centres. Categorical parameters are presented as frequencies (%), and the Pearson chi-square test was used for statistical comparisons.

	LT-1 center	LT-2 center	
	(N=234)	(N=262)	p
QTF test results			
Negatives	196 (83.8)	182 (69.5)	
Indeterminates	9 (3.9)	21 (8.0)	0.001
Positives	29 (12.4)	59 (22.5)	
Past MTB infection	1 (0.4)	5 (1.9)	0.132
Proved MTB source contact	3 (1.3)	1 (0.4)	0.263
MTB vaccination	0 (0.0)	1 (0.4)	0.344

LT-1: Liver Transplant Centre 1; LT-2: Liver Transplant Centre 2; MTB: Mycobacterium Tuberculosis; QTF: QuantiFERON

Table 3: Results of the Quantiferon (QTF) test (negative or indeterminate vs. positive) in relation to the baseline demographic and clinical parameters of the whole study population (N=469). Categorical variables are presented as frequencies (%), and the Pearson chi-square test was used for statistical comparisons. Continuous variables are presented as medians (interquartile ranges), and the rank-sum test (Mann–Whitney) was used for statistical comparisons. Stepwise logistical regression with a forward approach was used to discriminate variables independently associated with the presence of a positive QTF test.

	Univariate Analysis			Multivariate Analysis		
	Negative or Indeterminate (N=408)	Positive (N=88)	p	O.R.	95% C.I.	p
Past MTB infection	2 (0.5)	4 (4.6)	0.002	7.483	1.220-45.90	0.03
Recipient age at transplant (years)	56.0 (49.5-62.6)	61.2 (54.4-65.5)	<0.001	1.067	1.034-1.102	<0.001
Recipient male gender	295(72.3)	75 (85.2)	0.012	-	-	-
Enrollment in LT-2 vs. LT-1 center	203 (49.8)	59 (67.1)	0.003	2.202	1.320-3.683	0.003
BMI (kg/m^2)	25.4 (22.8-28.1)	25.4 (23.2-27.9	0.552			
KDIGO Stage III and IV renal insufficiency	70 (17.2)	14 (15.9)	0.777			
Diabetes	84 (20.6)	28 (17.7)	0.022	-	-	-
Presence of ascites	256 (62.8)	47 (53.4)	0.103			
Presence of esophageal varices	288 (70.6)	57 (64.8)	0.288			
Child–Pugh score	9 (7-11)	8 (6-11)	0.082	-	-	-
MELD score	17 (12-24)	16 (11-22)	0.127			
MELD-Na score	19 (13-27)	16 (12-24)	0.012	-	-	-
Etiology of liver disease						
Viral	200 (49.0)	49 (55.7)	0.257			
ALD	161 (39.5)	29 (33.0)	0.255			
MASLD	26 (6.4)	8 (9.1)	0.36			
Autoimmune	38 (9.3)	5 (5.7)	0.272			
Inherited	5 (1.2)	0 (0.0)	0.297			
HCC	174 (42.7)	59 (67.1)	<0.001	2.173	1.295-3.645	0.003
Other	22 (5.4)	4 (4.6)	0.747			

MTB: Mycobacterium Tuberculosis; BMI: Body Mass Index; KDIGO: Kidney Disease Improving Global Outcomes; MELD: Model of End-Stage Liver Disease; MELD-Na: Model of End-Stage Liver Disease-Sodium; ALD: Alcohol-Related Liver Disease; MASLD: Metabolic Dysfunction-Associated Steatotic Liver Disease; HCC: Hepatocellular Carcinoma. Logistic Regression Model: pseudo-R2= 0.111 (p<0.001), Akaike's Information Criterion = 422.

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Table 4: Comparison of immunosuppressive (IS) drug regimens adopted in the two liver transplant centers (LT-1 and LT-2). Categorical parameters are presented as frequencies (%), and the Pearson chi-square test was used for statistical comparisons.

	LT-1 Center	LT-2 Center	
	(N=234)	(N=262)	p
IS drugs			
Prednisone >3 months	0	8 (3.1)	0.007
Tacrolimus	173 (73.9)	235 (89.7)	<0.001
Cyclosporine	43 (18.4)	11 (4.2)	<0.001
Mycophenolate mofetil	33 (14.1)	85 (32.4)	<0.001
mTOR (everolimus, sirolimus)	23 (9.8)	102 (38.9)	<0.001
Combination of IS drugs			
Tacrolimus + Mycophenolate mofetil	23 (9.8)	71 (27.1)	<0.001
Tacrolimus + mTOR	5 (2.1)	89 (34.0)	<0.001
Cyclosporine + Mycophenolate mofetil	8 (3.4)	6 (2.3)	0.449
Other combinations	2 (0.9)	12 (4.6)	0.012

IS: Immunosuppressive; MTB: Mycobacterium Tuberculosis; mTOR: Mammalian Target of Rapamycin

Duration and safety of antibiotic prophylaxis

Among the 59 QTF-positive patients enrolled in the LT-2 center, only 38 (64.4%) received antibiotic prophylaxis against MTB reactivation/infection. The reasons why twenty-one patients did not receive antibiotic prophylaxis were as follows: were judged too sick at the time of the LT operation (N=10), refused the indication to assume prophylaxis (N=7) and were positive for the Quantiferon test, which became available only after LT (N=4). Furthermore, in 5 patients, owing to a proven past allergy to fluoroquinolones, antibiotic prophylaxis included INH (300 mg/day) along with 25–50 mg of vitamin B6 starting from the first week after LT and then continuing for 6 months. The median duration of antibiotic prophylaxis was 12 months, and only 2 patients had levofloxacin and ethambutol suspended by their physicians who followed the patients within 3 months after LT for the appearance of fluroquinolone-related tendinopathy. No grade >1 hepatoxicity was recorded in either the 5 patients receiving INH or in those receiving levofloxacin and ethambutol.

Incidence and clinical characteristics of MTB reactivation/infection during follow-up

The median follow-up time was significantly longer in the LT-2 center than in the LT-1 center (78 vs. 71 months; p=0.027). During the follow-up period, the incidence of MTB reactivation/infection in the whole population was 3/496 (0.6%), and 2/88 (2.3%) of the QTFs tested positive while one patient experienced MTB reactivation/infection despite a negative QTF test. MTB reactivations/infections were comparable between LT-2 and LT-1 centers for both the whole population (2/262 vs. 1/234, p=0.630) and in QTFs that tested positive (1/59 vs. 1/29, p=0.622). In the periodical chest X-ray or computed tomography (CT) scan evaluations, a pulmonary suspected MTB-related picture was observed in 33 (6.6%) patients without significant differences between LT-1 and LT-2 centers (15/234 vs. 18/262, p=0.837; data not shown). MTB pulmonary reactivation/infection after LT was confirmed through a positive PCR for MTB in the bronchoalveolar lavage fluid of 1 patient at each LT center and at 46 and 10 months in LT-2 and LT-1, respectively. One additional patient, who experienced extrapulmonary (peritoneal) MTB reactivation, was observed at the LT-2 center 44 months after LT.

The diagnosis of MTB reactivation/infection in this patient was confirmed by microscopic detection of MTB in the ascitic fluid. These three patients did not have a history of past MTB-related infection, contact or vaccination before LT. Only one of the two QTF-positive patients enrolled in the LT-2 center received antibiotic prophylaxis with levofloxacin plus ethambutol since the second patient did not agree to receive prophylaxis. Immunosuppressive treatment in the three patients who experienced MTB reactivation/infection involved tacrolimus in combination with MMF in two patients and with everolimus in one patient. All LT recipients who developed MTB reactivation/infection received antitubercular treatment with the combination of RIF, INH, pyrazinamide, and ethambutol for two months, which was followed by 4 months of continuation therapy with daily INH and RIF since none of them presented with MTB drug-resistant strains. During this period, periodical and strict evaluation of the blood immunosuppressive drug levels as well as a liver function test was performed. All patients who experienced MTB reactivation were alive at the last follow-up visit with a preserved graft function (Table 5). According to the multivariate analysis, the independent predictors of MTB reactivation/infection following LT were hepatitis B virus (HBV) infection (p=0.004), a positive QTF test (p=0.006) and receipt of IS treatment with MMF (p=0.021) (Table 6).

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Table 5: Demographic and clinical characteristics of patients who presented with MTB reactivation/infection following liver transplantation.

Patient No.	LT-Center	Sex	Age at LT (years)	Etiology of Liver Disease	Past MTB Infection/ Contact/ Vaccination	QTF Test Result	IS Therapy	Antibiotic prophylaxis	Months from LT to MTB Reactivation/ Infection	MTB Infection Site	Clinical Outcome
1	2	M	26	HBV	No	Neg	TAC+EVR	No	46	Lung	Alive
2	1	M	65	HCV	No	Pos	TAC+MMF	No	10	Lung	Alive
3	2	M	57	HBV+HCV	No	Pos	TAC+MMF	LVF+ETH	44	Peritoneum	Alive

LT: Liver Transplantation; MTB: Mycobacterium Tuberculosis; QTF: Quantiferon; IS: Immunosuppressive; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; TAC: Tacrolimus; EVR: Everolimus; MMF: Mycophenolate Mofetil; LVF: Levofloxacin; ETH: Ethambutol

Table 6: Comparisons of pre- and post-liver transplant clinical parameters between patients who developed or did not develop liver transplant MTB reactivation/infection. Categorical parameters are presented as frequencies (%), and the Pearson chi-square test was used for statistical comparisons. Continuous variables are presented as medians (interquartile ranges), and the rank-sum test (Mann–Whitney) was used for statistical comparisons. Stepwise logistical regression with a forward approach was used to discriminate variables independently associated with patients experiencing post-transplant MTB reactivation.

	Univariate Analysis			Multivariate Analysis		
	Patients with MTB Reactivation/Infection N=3	Patients without MTB Reactivation/Infection N=493	p	O.R.	95% C.I.	p
Pre-transplant parameters						
Past MTB infection	0 (0.0)	6 (1.2)	0.848			
MTB prophylaxis	1 (33.3)	37 (7.5)	0.094	-	-	-
QTF positive test	2 (66.7)	86 (17.4)	0.026	9.95	1.96-50.7	0.006
Recipient male gender	3 (100)	367 (74.4)	0.311			
Recipient age at transplant (years)	57 (26-65)	57 (50-63)	0.868			
Enrollment in the LT-1 center	1 (33.3)	233 (47.4)	0.63			
BMI (kg/m^2)	28 (26-31)	25 (23-28)	0.168			
KDIGO Stage III and IV renal insufficiency	0 (0.0)	84 (17.0)	0.433			
Diabetes	1 (33.3)	140 (28.4)	0.85			
Presence of ascites	3 (100)	110 (22.4)	0.166			
Presence of esophageal varices	3 (100)	342 (69.3)	0.25			
Child–Pugh score	10 (8-11)	9 (7-11)	0.59			
MELD score	26 (13-30)	17 (12-24)	0.315			
MELD-Na score	28 (15-28)	19 (13-26)	0.381			
Etiology of liver disease						
HCV	2 (66.7)	177 (35.9)	0.269			
HBV/HDV	2 (66.7)	77 (15.6)	0.016	13.11	2.31-74.2	0.004
ALD	0 (0.0)	190 (38.5)	0.171			
MASLD	0 (0.0)	34 (6.9)	0.637			
Autoimmune	0 (0.0)	43 (8.7)	0.592			
Inherited	0 (0.0)	5 (1.0)	0.861			
HCC	1 (33.3)	232 (47.1)	0.635			
Other	0 (0.0)	26 (5.3)	0.683			
Post-transplant IS treatments						

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Prednisone (>3 months)	0 (0.0)	8 (1.6)	0.824			
Tacrolimus	3 (100)	405 (99.3)	0.42			
Cyclosporine	0 (0.0)	54 (11.0)	0.544			
Mycophenolate mofetil	2 (66.7)	116 (23.5)	0.08	7.25	1.35-38.9	0.021
mTOR (everolimus, sirolimus)	1 (33.3)	124 (25.2)	0.745			

MTB: Mycobacterium tuberculosis; QTF: quantiferon; BMI: body mass index; KDIGO: Kidney Disease Improving Global Outcomes; MELD: model of end-stage liver disease; MELD-Na: model of end-stage liver disease-Sodium; HCV: hepatitis C virus; HBV/HDV; hepatitis B/hepatitis D; ALD: alcohol-related liver disease; MASLD: metabolic dysfunction-associated steatotic liver disease; HCC: hepatocellular carcinoma; IS: immunosuppressive; mTOR: mammalian target of rapamycin. Logistic regression model: pseudo-R2= 0.267 (p=0.013), Akaike's information criterion = 34.8

Overall clinical outcomes at the post LT follow-up

No significant differences between LT centers were observed regarding post-LT survival rates, the incidence of chronic rejection, cytomegalovirus (CMV) infection, or the development of de novo cancers. Among the well-known metabolic complications present after LT, KDIGO stage III or IV renal insufficiency was more frequently observed in patients enrolled in the LT-2 center than those in the LT-1 center (25/262 vs. 1/234; p<0.001) (Table 7).

Table 7: Comparisons of post-liver transplantation clinical outcomes between patients enrolled in LT-1 and LT-2 centres. Categorical parameters are presented as frequencies (%), and the Pearson chi-square test was used for statistical comparisons. Continuous variables are presented as medians (interquartile ranges), and the rank-sum test (Mann–Whitney) was used for statistical comparisons.

	LT-1 Center	LT-2 Center	
	(N=234)	(N=262)	p
Median follow-up (months)	71 (38-112)	78 (58-112)	0.027
Chronic rejection	1 (0.4)	5 (2.2)	0.098
CMV disease	2 (0.9)	1 (0.4)	0.498
Diabetes	76 (32.5)	65 (24.8)	0.059
KDIGO Stage III and IV renal insufficiency	1 (0.43)	25 (9.5)	<0.001
Myocardial infarction	3 (1.3)	4 (1.5)	0.818
De novo cancer	0 (0.0)	1 (0.4)	0.344
Patients alive at the last follow-up visit	157 (67.1)	192 (73.3)	0.132

LT: Liver Transplant; CMV: Cytomegalovirus; KDIGO: Kidney Disease Improving Global Outcomes.

Discussion

The prevalence of latent MTB infection in LT candidates ranges from 11% to 44% in several studies adopting the QTF test [11,24,25], which was similar to the 17.7% reported in our study. A significantly greater number of LT patients that were enrolled in the LT-2 center compared to the LT-1 center tested QTF positive and this difference was confirmed by multivariate analysis in addition to past MTB infection, older age, and the presence of HCC. The higher prevalence of latent MTB infection in older patients and in those with past MTB infection is not unexpected since it has been previously demonstrated [26]. More interestingly, latent MTB infection appeared to be more common in patients with HCC and more severe liver disease. MTB infection may play a role in carcinogenesis [27], and simultaneous MTB infection and HCC can occur [28]. These features could explain the increased prevalence of HCC in QTF-positive patients as previously reported [25]. In contrast with our findings, some reports indicate that patients with liver cirrhosis harbor systemic immunodepression, which leads to a lower detection rate of latent MTB infection [25]. However, these results have been obtained via the TST instead of the QTF test and have not been confirmed by analysing the severity of liver disease via the CPT score.

The overall MTB reactivation rate we observed was 0.6%, which was similar to that reported in LT patients in developed countries where MTB endemicity is low [12,29,30]. Only 2/88 QTF-positive patients developed MTB reactivation/infection, which confirms the suboptimal accuracy of pretransplant positive QTF tests in selecting patients with a greater risk of MTB reactivation after LT [31,32]. The positive and negative predictive values of the QTF test for identifying patients with latent MTB infection are <3% and 97%, respectively [8]. This implies that a positive and negative QTF test indicates a nearly 3% risk of MTB reactivation/infection as shown in our study. Pulmonary MTB reactivation was detected in only 2/3 of our patients, which supports data reported in other LT centres where extrapulmonary MTB reactivation was described [7,30].

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A novel and interesting observation is that among QTF-positive patients, the incidence of MTB reactivation/infection in our series was similar in patients regardless of whether they did or did not receive antibiotic prophylaxis (1/38 vs. 1/50, p=0.844). This finding contrasts with a systematic literature review demonstrating that antibiotic prophylaxis versus no treatment was associated with a significant reduction in MTB reactivation after LT [7]. However, these data referred to INH prophylaxis, which was used in our series in only a limited number of patients owing to its potentially severe hepatotoxicity in LT recipients [11,19]. Our data seem to confirm previous results obtained in Japan, which showed that no MTB reactivations after LT were observed despite the absence of antibiotic prophylaxis in patients considered at the highest risk of MTB reactivation such as those treated for active MTB infection several years before LT [22]. In our experience, no grade >1 hepatotoxicity was recorded in either the few patients receiving INH or in patients receiving levofloxacin, which confirms the reported good safety profile of fluroquinolone-based prophylaxis in LT patients [23,33-35]. In two of our patients, levofloxacin was prematurely discontinued due to the development of tendinopathy, which has been reported as a more frequent side effect in other studies [33,34].

A further novel feature of our study is its identification of an independent predictor of MTB reactivation/infection, which included not only being positive for QTF but also being positive for HBV infection and receiving immunosuppressive treatment with MMF. With respect to HBV infection, 2/3 of patients who experienced MTB reactivation/infection after LT were positive for HBV. This finding agrees with a recent large epidemiological study conducted in the U.S. in HBV-positive patients showing that the prevalence of latent MTB infection was 23.1% and was highest among persons born in high-incidence countries [36]. The increased risk of MTB reactivation in patients treated with MMF, to our knowledge has only been previously described in kidney transplant recipients [37]. MMF inhibits de novo purine synthesis, which leads to profound selective lymphocyte inhibition, and its use in LT recipients has increased in recent years due to its negative impact on renal, glucose and lipid parameters [38]. However, despite these favourable properties, MMF has been recently reported to be the main factor involved in reducing the immune response for coronavirus disease (COVID-19) after LT [39]. Furthermore, it has been demonstrated that the restoration of humoral and cellular immune responses to COVID-19 vaccination were achieved only after the interruption of MMF [40]. Thus, MMF may reduce the ability of lymphocytes to maintain immunological control of latent MTB infection and increase the probability of reactivation after LT.

All patients who experienced MTB reactivation completed antitubercular treatment without significant drug-induced side effects or amenable interactions and all of them were alive at the last follow-up. This excellent survival rate seems to confirm data reported in other studies with post-LT mortality ranging from 9% [21] to 30% [4]. The absence of MTB exposure was identified as the only factor associated with longer survival in patients who experienced reactivated MTB infection after solid organ transplantation [30]. This observation can explain why our patients, who did not have MTB contact, had excellent clinical outcomes.

Our study has several limitations. First, it was retrospective and not randomized. Second, we cannot rule out that some QTF-positive patients were not included because their data were missing or incomplete in the electronic records. However, the present study also presents several strengths since, to our knowledge, this is the first study to compare the impact of antibiotic prophylaxis with that of observation alone in conditioning the incidence of MTB reactivation/infection in LT patients from two large series.

In summary, MTB reactivation after LT is rare. The QTF test remains a suboptimal tool for selecting patients with latent MTB who should be considered at increased risk of MTB reactivation after LT. Moreover, antibiotic prophylaxis in QTF-positive patients does not seem superior to observation alone for both preventing and determining the clinical outcome of MTB reactivation/infection after LT.

References

1. Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC (1999) Consensus statement. Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. WHO Global Surveillance and Monitoring Project. JAMA 282(7): 677-686.
2. Sutherland I, Svandova E, Radhakrishna S (1976) Alternative models for the development of tuberculosis disease following infection with tubercle bacilli. Bull Int Union Tuberc 51(1): 171-179.
3. Rashid HU, Begum NAS, Kashem TS (2021) Mycobacterial infections in solid organ transplant recipients. Korean J Transplant 35(4): 208-217.
4. Singh N, Paterson DL (1998) Mycobacterium tuberculosis infection in solid-organ transplant recipients: impact and implications for management. Clin Infect Dis 27(5): 1266-1277.
5. Rao VK, Iademarco EP, Fraser VJ, Kollef MH (1998) The impact of comorbidity on mortality following in-hospital diagnosis of tuberculosis. Chest 114(5): 1244-1252.
6. Rajagopala S, Olithselvan A, Varghese J, Shanmugam N, Rela M (2011) Latent Mycobacterium tuberculosis Infection in Liver Transplant Recipients-Controversies in Current Diagnosis and Management. J Clin Exp Hepatol 1(1): 34-37.
7. Holty JE, Gould MK, Meinke L, Keeffe EB, Ruoss SJ (2009) Tuberculosis in liver transplant recipients: a systematic review and meta-analysis of individual patient data. Liver Transpl 15(8): 894-906.
8. Yahav D, Gitman MR, Margalit I, Avni T, Leeflang MMG (2023) Screening for Latent Tuberculosis Infection in Solid Organ Transplant Recipients to Predict Active Disease: A Systematic Review and Meta-Analysis of Diagnostic Studies. Open Forum Infect Dis 10(8): ofad324.
9. Pai M, Zwerling A, Menzies D (2008) Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: an update. Ann Intern Med 149(3): 177-184.
10. Mazurek GH, Jereb J, Vernon A, LoBue P, Goldberg S (2010) Updated guidelines for using Interferon Gamma Release Assays to detect Mycobacterium tuberculosis infection - United States, 2010. MMWR Recomm Rep 59(RR-5): 1-25.

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11. Jafri SM, Singal AG, Kaul D, Fontana RJ (2011) Detection and management of latent tuberculosis in liver transplant patients. Liver Transpl 17(3): 306-314.

12. Subramanian AK, Theodoropoulos NM, Infectious Diseases Community of Practice of the American Society of T (2019) Mycobacterium tuberculosis infections in solid organ transplantation: Guidelines from the infectious disease's community of practice of the American Society of Transplantation. Clin Transplant 33(9): e13513.

13. European Association for the Study of the Liver. Electronic address eee (2016) EASL Clinical Practice Guidelines: Liver transplantation. J Hepatol 64(2): 433-485.

14. Fagiuoli S, Colli A, Bruno R, Craxi A, Gaeta GB (2014) Management of infections pre- and post-liver transplantation: report of an AISF consensus conference. J Hepatol 60(5): 1075-1089.

15. Jahng AW, Tran T, Bui L, Joyner JL (2007) Safety of treatment of latent tuberculosis infection in compensated cirrhotic patients during transplant candidacy period. Transplantation 83(12): 1557-1562.

16. Murray KF, Carithers RL, Aasld (2005) AASLD practice guidelines: Evaluation of the patient for liver transplantation. Hepatology 41(6): 1407-1432.

17. Bumbacea D, Arend SM, Eyuboglu F, Fishman JA, Goletti D (2012) The risk of tuberculosis in transplant candidates and recipients: a TBNET consensus statement. Eur Respir J 40(4): 990-1013.

18. Aguado JM, Torre-Cisneros J, Fortun J, Benito N, Meije Y (2009) Tuberculosis in solid-organ transplant recipients: consensus statement of the group for the study of infection in transplant recipients (GESITRA) of the Spanish Society of Infectious Diseases and Clinical Microbiology. Clin Infect Dis 48(9): 1276-1284.

19. Sidhu A, Verma G, Humar A, Kumar D (2014) Outcome of latent tuberculosis infection in solid organ transplant recipients over a 10-year period. Transplantation 98(6): 671-675.

20. Fabrega E, Sampedro B, Cabezas J, Casafont F, Mieses MA (2012) Chemoprophylaxis with isoniazid in liver transplant recipients. Liver Transpl 18(9): 1110-1117.

21. Torre-Cisneros J, Doblas A, Aguado JM, San Juan R, Blanes M (2009) Tuberculosis after solid-organ transplant: incidence, risk factors, and clinical characteristics in the RESITRA (Spanish Network of Infection in Transplantation) cohort. Clin Infect Dis 48(12): 1657-1665.

22. Nagai S, Fujimoto Y, Taira K, Egawa H, Takada Y (2007) Liver transplantation without isoniazid prophylaxis for recipients with a history of tuberculosis. Clin Transplant 21(2): 229-234.

23. Sgarabotto D, Fasolato S, Vianello F, Vittadello F, Boccagni P (2017) Antibiotic prophylaxis for preventing postorthotopic liver transplant tuberculosis: is there a safe alternative to isoniazid? Transpl Int 30(7): 734-736.

24. Moon HH, Park SY, Kim JM, Park JB, Kwon CHD (2017) Isoniazid Prophylaxis for Latent Tuberculosis Infections in Liver Transplant Recipients in a Tuberculosis-Endemic Area. Ann Transplant 22: 338-345.

25. Lauar ID, Faria LC, Romanelli RMC, Clemente WT (2021) Latent tuberculosis: Risk factors, screening and treatment in liver transplantation recipients from an endemic area. World J Transplant 11(12): 512-522.

26. Getahun H, Matteelli A, Chaisson RE, Raviglione M (2015) Latent Mycobacterium tuberculosis infection. N Engl J Med 372(22): 2127-2135.

27. Falagas ME, Kouranos VD, Athanassa Z, Kopterides P (2010) Tuberculosis and malignancy. QJM 103(7): 461-487.

28. Alsaif HS, Hassan A, Refai O, Awary K, Kussaibi H (2021) Concomitant hepatic tuberculosis and hepatocellular carcinoma: a case report and review of the literature. BMC Surg 21(1): 2.

29. Hsu MS, Wang JL, Ko WJ, Lee PH, Chou NK (2007) Clinical features and outcome of tuberculosis in solid organ transplant recipients. Am J Med Sci 334(2): 106-110.

30. Abad CLR and Razonable RR (2018) Mycobacterium tuberculosis after solid organ transplantation: A review of more than 2000 cases. Clin Transplant 32(6): e13259.

31. Rangaka MX, Wilkinson KA, Glynn JR, Ling D, Menzies D (2012) Predictive value of interferon-gamma release assays for incident active tuberculosis: a systematic review and meta-analysis. Lancet Infect Dis 12(1): 45-55.

32. Lee YW, Chung H, Kim SH, Sung H, Ha SM (2024) Safety and outcome of treatment of latent tuberculosis infection in liver transplant recipients. Infection 52(3): 1055-1061.

33. Torre-Cisneros J, San-Juan R, Rosso-Fernandez CM, Silva JT, Munoz-Sanz A (2015) Tuberculosis prophylaxis with levofloxacin in liver transplant patients is associated with a high incidence of tenosynovitis: safety analysis of a multicentre randomized trial. Clin Infect Dis 60(11): 1642-1649.

34. Tien V, Robilotti E, Callister D, Subramanian A, Lutchman G (2015) Tolerability of Fluoroquinolones in Management of Latent Tuberculosis in Liver Transplant Candidates. Clin Infect Dis 61(10): 1631-1632.

35. Grim SA, Layden JE, Roth P, Gallitano S, Adams W (2015) Latent tuberculosis in kidney and liver transplant patients: a review of treatment practices and outcomes. Transpl Infect Dis 17(5): 768-777.

36. Malden DE, Wong RJ, Chitnis AS, Im TM, Tartof SY (2024) Screening Practices and Risk Factors for Co-Infection with Latent Tuberculosis and Hepatitis B Virus in an Integrated Healthcare System – California. Am J Med 137(3): 258-265.

37. Viana LA, Cristelli MP, Santos DW, Tavares MG, Dantas MTC (2019) Influence of epidemiology, immunosuppressive regimens, clinical presentation, and treatment on kidney transplant outcomes of patients diagnosed with tuberculosis: A retrospective cohort analysis. Am J Transplant 19(5): 1421-1431.

38. Kaltenborn A, Schrem H (2013) Mycophenolate mofetil in liver transplantation: a review. Ann Transplant 18: 685-696.

39. Toniutto P, Falleti E, Cmet S, Cussigh A, Veneto L (2022) Past COVID-19 and immunosuppressive regimens affect the long-term response to anti-SARS-CoV-2 vaccination in liver transplant recipients. J Hepatol 77(1): 152-162.

40. Toniutto P, Cussigh A, Cmet S, Fabris M, Curcio F (2023) Mycophenolate Interruption Restores Anti-SARS-CoV-2 Vaccine Immunogenicity in Unresponsive Liver Transplant Recipients. Vaccines (Basel) 11(7): 1165.

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