ORIGINAL ARTICLE INFECTIOUS DISEASES

Clinical features and outcomes of tuberculosis in transplant recipients as compared with the general population: a retrospective matched cohort study

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Abstract

There are no previous studies comparing tuberculosis in transplant recipients (TRs) with other hosts. We compared the characteristics and outcomes of tuberculosis in TRs and patients from the general population. Twenty-two TRs who developed tuberculosis from 1996 through 2010 at a tertiary hospital were included. Each TR was matched by age, gender and year of diagnosis with four controls selected from among non-TR non-human immunodeficiency virus patients with tuberculosis. TRs (21 patients, 96%) had more factors predisposing to tuberculosis than non-TRs (33, 38%) (p <0.001). Pulmonary tuberculosis was more common in non-TRs (77 (88%) vs. 12 TRs (55%); p 0.001); disseminated tuberculosis was more frequent in TRs (five (23%) vs. four non-TRs (5%); p 0.005). Time from clinical suspicion of tuberculosis to definitive diagnosis was longer in TRs (median of 14 days) than in non-TRs (median of 0 days) (p <0.001), and invasive procedures were more often required (12 (55%) TRs and 15 (17%) non-TRs, respectively; p 0.001). Tuberculosis was diagnosed post-mortem in three TRs (14%) and in no non-TRs (p <0.001). Rates of toxicity associated with antituberculous therapy were 38% in TRs (six patients) and 10% (seven patients) in non-TRs (p 0.014). Tuberculosis-related mortality rates in TRs and non-TRs were 18% and 6%, respectively (p 0.057). The adjusted Cox regression analysis showed that the only predictor of tuberculosis-related mortality was a higher number of organs with tuberculosis involvement (adjusted hazard ratio 8.6; 95% CI 1.2–63). In conclusion, manifestations of tuberculosis in TRs differ from those in normal hosts. Post-transplant tuberculosis resists timely diagnosis, and is associated with a higher risk of death before a diagnosis can be made.

Keywords: Haematopoietic stem cell transplant recipients, *Mycobacterium tuberculosis* infection, solid organ transplant recipients, transplantation, tuberculosis
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Introduction

Transplant recipients (TRs) are at increased risk of active tuberculosis, mainly through reactivation of a latent infection

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[1–6]. The incidence of tuberculosis in a geographical area correlates with its incidence in the general population; in immigrant populations, it is more reflective of the countries of origin. Either way, the incidence of tuberculosis in TRs is higher than in the general population, with differences by type of transplant [3,5–8]. One Spanish study showed an annual tuberculosis incidence of 512 cases per 100 000 TRs (lung transplant recipients showed the highest incidence (2072/100 000 patients)), as compared with 19 cases/100 000 persons in the general population [6].

Tuberculosis remains one of the most serious post-transplant infections, with mortality rates of 10–40% [1,2,5,7–11]. Despite recently published guidelines for the management of post-transplant tuberculosis [12–15], the diagnosis and treatment of tuberculosis after transplantation remain challenging, because of the potential side effects of antituberculous agents and interactions with immunosuppressive drugs [2,3,16–21].

No previous studies have compared tuberculosis in TRs with tuberculosis in other immunocompromised or immunocompetent hosts. Although tuberculosis in TRs is considered to have a different presentation and a worse outcome than tuberculosis in the general population, possible differences are not well characterized.

The aim of this study was to compare the characteristics and outcomes of tuberculosis in TRs and in patients from the general population.

Materials and methods

Setting, study design, and patients

This study was conducted at the Hospital Clínic Universitari, a tertiary-care university hospital in Barcelona with active organ transplantation programmes, including kidney, kidney–pancreas, liver, heart and haematopoietic stem cell transplantation.

We used a retrospective matched cohort study to compare clinical features and outcomes of tuberculosis in patients who had received (transplant cohort) or had not received (control cohort) a solid organ or stem cell transplant. All patients had a definitive tuberculosis diagnosis established by isolation of *Mycobacterium tuberculosis* (from any clinical sample).

Patients were identified from clinical microbiology laboratory and transplantation programme databases. We included all TRs who were culture-positive for tuberculosis diagnosed from January 1996 through December 2010. Non-TRs were selected from a list of all patients with culture-positive diagnoses of tuberculosis in our centre during the same period. For each year of the study, the order of the list of culture-positive tuberculosis diagnoses was randomized. Every TR with tuberculosis on the list was paired with the next four tuberculosis patients (the non-TRs) who fulfilled the matching criteria, namely, human immunodeficiency virus (HIV)-negative patients who had not received a transplant, matched further according to gender, age (±2 years), and year of tuberculosis diagnosis. HIV patients were excluded because of the specific characteristics of tuberculosis in this patient group as compared with HIV-negative patients [22].

Throughout the study period, any hospitalized or ambulatory patient with suspicion of tuberculosis was tested at our centre; most patients diagnosed with tuberculosis in primary-care centres in the area were also referred to our hospital, where *M. tuberculosis* cultures were repeated. Any patient with active tuberculosis was treated and followed up by tuberculosis experts in the Infectious Diseases Service for at least the duration of tuberculosis treatment.

Clinical data and definitions

Data were obtained from the patient's medical records with a standard case report form. Variables collected for all patients included: demographic features; underlying conditions; Charlson comorbidity score [23]; date of onset of tuberculosis symptoms; clinical presentation and radiographic findings; tuberculin skin test (TST) results; procedures used to obtain a definitive tuberculosis diagnosis; time to diagnosis; number of sites with tuberculosis involvement; type and number of antituberculous drugs prescribed; antituberculous drug-related toxicity; length of follow-up following tuberculosis diagnosis; date of last follow-up and status of the patient at that time; and date and cause of death during follow-up, if appropriate. For TRs, the following information was recorded: type of transplant and date; pre-transplant TST tests; clinical and/or radiological evidence of pre-transplant tuberculosis; treatment of latent infection; and time to tuberculosis diagnosis after transplantation.

Information collected about the presence of other well-known factors predisposing to tuberculosis (excluding transplantation) included: diabetes mellitus, chronic renal failure/haemodialysis, silicosis, gastrectomy, jejunoileal bypass, haematological malignancies, carcinoma of the head or neck, alcohol consumption, and therapy with corticosteroids (prednisone or prednisone equivalent administered at >15 mg/day for $\geq$1 month) or other immunosuppressive agents [24–26].

TST results were interpreted according to American Thoracic Society and CDC recommendations [27]. Organ involvement by tuberculosis was considered to be definite if *M. tuberculosis* was isolated from the organ, and probable when patients with a confirmed tuberculosis diagnosis had acid-fast bacilli smear and/or histopathological findings consistent with tuberculosis, and/or signs/symptoms highly suggestive of tuberculosis involvement (with no alternative diagnosis) that

resolved with antituberculous treatment. Tuberculosis was classified as pulmonary (definitive parenchymal pulmonary involvement), extrapulmonary (definitive involvement of other organs), or disseminated (*M. tuberculosis* was isolated from two or more non-contiguous organs or from blood) [1,6]. Hepatotoxicity of antituberculous drugs was established when alanine aminotransferase levels were ≥3 times the upper limit of normal in the presence of symptoms, or ≥5 times the upper limit of normal in the absence of symptoms [28,29]. Other drug toxicity was considered when a drug was discontinued because of adverse effects. Crude mortality was defined as all deaths occurring during tuberculosis treatment. Mortality was considered to be tuberculosis-related when death occurred during treatment with no other apparent cause, and/or investigators considered tuberculosis to be the main cause of death. A post-mortem diagnosis of tuberculosis was made when positive microbiology results became known after the patient died.

Statistical analysis

Continuous variables were described as means and standard deviations, or medians and interquartile ranges, depending on homogeneity. Categorical variables were expressed as absolute frequencies and percentages. Matching was taken into account in all statistical analyses. Mantel–Haenszel matched-pairs analysis and the Wilcoxon test were used to assess group differences for continuous and categorical variables, respectively. Kaplan–Meier curves were used for survival analysis, and the log-rank test was used to compare tuberculosis-related mortality in the transplant and control cohorts. The Cox proportional hazards model with stratification on matched pairs was used to calculate adjusted hazard ratios and determine whether tuberculosis-related mortality differed between the two groups, with adjustment for clinically relevant covariates. All statistical tests were two-tailed; p-values of <0.05 were considered to be significant. Data analyses were performed with SPSS for Windows version 16 (SPSS, Chicago, IL, USA).

Results

Baseline characteristics of TRs with tuberculosis

Twenty-two TRs (all from Spain) were diagnosed with culture-positive tuberculosis during the study period. Table 1 shows the characteristics of the patients. One patient received treatment for latent infection; no information was available on total length of treatment and/or degree of compliance. All transplanted organs were from cadaveric donors, with no identified or suspected cases of donor-transmitted tuberculosis [30].

TABLE 1. Baseline characteristics of transplant recipients with active tuberculosis infection

Characteristic	Value
Mean age in years (SD)	47 (15)
Male gender, no. (%)	17 (77.3)
Transplant type, no. (%)	
Solid organ transplant	17 (77.3)
Kidney	10 (45.5)
Kidney–pancreas	4 (18.2)
Liver	2 (9.1)
Heart	1 (4.5)
Haematopoietic stem cell transplant	5 (22.7)
Allogenic stem cell transplant	2 (9.1)
Autologous stem cell transplant	3 (13.6)
Prior tuberculin skin test performed, no. (%)[a]	10 (50)
Exposure to tuberculosis before transplantation, no.(%)[b]	6 (27.3)
Prior positive tuberculin skin test result	2 (20)[c]
Clinical and/or radiological evidence of prior tuberculosis	5 (22.7)
Radiographic findings consistent with prior tuberculosis	2 (9.1)
History of prior tuberculosis	4 (18.2)
Treatment of latent tuberculosis infection, no. (%)[d]	1 (5.3)
Median duration (months) of follow-up (IQR)	50 (70)
Median time (months) from transplantation to diagnosis of tuberculosis (IQR)	15 (51)
Diagnosis of tuberculosis within 1 year of transplantation, no. (%)	11 (50)

IQR, interquartile range; SD, standard deviation.
[a]Data on tuberculin skin tests were available for 20 patients.
[b]One patient had a positive tuberculin test result and a previous history of tuberculosis.
[c]Percentage of positive results in patients with a tuberculin skin test.
[d]Data on treatment of latent tuberculosis infection were available for 19 patients.

Comorbid conditions and clinical characteristics of tuberculosis in TRs and non-TRs

Table 2 compares the underlying conditions of TRs and non-TRs. More TRs than non-TRs had Charlson scores of ≥2. Overall, most TRs (21, 95.5%) and a lower percentage of non-TRs (33, 37.5%; p <0.001) had factors predisposing to active tuberculosis (excluding transplantation and immunosuppressive drugs). Alcohol consumption was more common in non-TRs.

The most common presenting symptoms in both patient cohorts were fever, constitutional symptoms, and cough (Table 3), although more TRs had fever and symptoms/signs of extrapulmonary disease. Pulmonary tuberculosis was the commonest form of disease in both groups, although it was more common in non-TRs; disseminated tuberculosis was more common in TRs.

TRs had a higher percentage of normal chest radiographs than non-TRs. One-third of TRs with radiographic abnormalities and none of the non-TRs had diffuse infiltrates. Chest radiographs showing cavitary infiltrates were common in the non-TRs; no TR showed cavitary infiltrates.

Diagnosis and treatment of tuberculosis in TRs and non-TRs

The TST for suspected active tuberculosis was positive in 16 (84.2%) non-TRs and in none of the TRs (p 0.022) (Table 4).

A tuberculosis diagnosis was clinically suspected in 18 (90%) TRs and in 78 (89.7%) non-TRs (p 0.718). The time from clinical suspicion to diagnosis (positive acid-fast bacilli smear,

TABLE 2. Underlying conditions and risk factors for tuberculosis in transplant recipients and patients from the general population, matched by age, gender, and year of tuberculosis diagnosis

Variable	Transplant recipients (n = 22), no. (%)	Patients from the general population (n = 88), no. (%)	RR (95% CI)	p
Comorbid condition				
Chronic renal failure	13 (59.1)	2 (2.3)	51 (6.48–401.11)	<0.001
Diabetes mellitus	6 (27.3)	6 (6.8)	4 (1.25–12.84)	0.008
Haematological neoplasm	5 (22.7)	0 (0)	—	<0.001
Chronic hepatopathy	2 (9.1)	6 (6.8)	1.5 (0.22–10.08)	0.695
Alcohol consumption	1 (4.5)	26 (29.5)	0.08 (0.01–0.73)	0.043
Chronic pulmonary disease	0 (0)	10 (11.4)	—	0.216
Other diseases	3 (13.6)[a]	2 (2.3)[b]	6 (1.01–35.91)	0.025
Corticosteroid therapy[c]	17 (85.3)	3 (15)	96.33 (21–441.84)	<0.001
Other immunosuppressive therapy	22 (100)	0 (0)	—	<0.001
Any comorbid condition	22 (100)	43 (48.9)	—	<0.001
Charlson score ≥2	20 (90.9)	8 (9.1)	64.49 (8.60–483.67)	<0.001
Factors predisposing to tuberculosis (excluding transplantation and immunosuppressive drugs other than corticosteroids)[d]	21 (95.5)	33 (37.5)	34.8 (4.50–272.42)	<0.001

RR, risk ratio.
[a]Other diseases included: systemic lupus erythematosus, amyloidosis, and ischaemic heart disease.
[b]Other diseases included: head and neck cancer and Crohn's disease.
[c]Prednisone (or prednisone equivalent) administered at >15 mg/day for ≥1 month.
[d]Well-known factors predisposing to tuberculosis included here are: diabetes mellitus, chronic renal failure/haemodialysis, silicosis, gastrectomy, jejunoileal bypass, haematological malignancies, head or neck carcinoma, alcohol consumption and therapy with corticosteroids (prednisone or equivalent administered at >15 mg/day for ≥1 month). Other established risk factors for tuberculosis not included here are: other immunosuppressive agents (different from corticosteroids), transplantation, and human immunodeficiency virus infection.

TABLE 3. Clinical characteristics of tuberculosis in transplant recipients and patients from the general population, matched by age, gender, and year of tuberculosis diagnosis

Characteristics	Transplant recipients (n = 22), no. (%)	Patients from the general population (n = 88), no. (%)	RR (95% CI)	p
Clinical manifestations				
Fever	17 (81)	42 (49.4)	8.5 (1.81–39.81)	0.002
Constitutional symptoms[a]	9 (45)	54 (63.5)	0.57 (0.22–1.48)	0.207
Cough	9 (45)	53 (62.4)	0.6 (0.21–1.49)	0.245
Dyspnoea	1 (5)	13 (15.3)	0.27 (0.03–2.41)	0.396
Pleuritic chest pain	1 (5)	15 (17.6)	0.4 (0.05–3.04)	0.287
Haemoptysis	1 (5)	23 (27.1)	0.11 (0.01–1.11)	0.070
Symptoms suggestive of epididymo-orchitis	3 (15)[b]	0 (0)	—	0.004
Monoarticular or oligoarticular pain	2 (10)	1 (1.2)	8 (1.01–88.22)	0.043
Dysphonia	1 (5)	4 (4.7)	1 (0.08–12.56)	1.000
Other clinical manifestations	5 (25)[c]	4 (4.7)[d]	9 (1.57–51.74)	0.004
Physical findings	13 (65)	27 (31.4)	5.33 (1.55–18.39)	0.007
Ascites	7 (35)[e]	0 (0)	—	<0.001
Findings consistent with epididymo-orchitis	3 (15)[b]	0 (0)	—	0.004
Monoarthritis or oligoarthritis	2 (10)	1 (1.2)	8 (1.01–88.22)	0.043
Rales on chest examination	1 (5)	14 (16.3)	0.29 (0.04–2.04)	0.346
Findings consistent with pleural effusion	1 (5)	3 (3.5)	2 (0.18–22.06)	0.564
Peripheral lymphadenopathy	1 (5)	8 (9.3)	0.43 (0.04–4.29)	0.861
Tuberculosis form				
Pulmonary	12 (54.5)	77 (87.5)	0.12 (0.03–0.44)	0.001
Extrapulmonary	5[f] (22.7)	7[g] (8)	3.17 (0.94–10.70)	0.055
Disseminated	5[h] (22.7)	4[i] (4.5)	6.33 (1.29–31.11)	0.005
Number of involved organs				
Two or more organs involved with a definitive diagnosis	4 (18.2)	3 (3.4)	6.30 (1.30–30.60)	0.045
Two or more organs involved with a probable diagnosis	8 (36.4)	10 (11.4)	5.40 (1.64–17.77)	0.003
Chest radiograph findings				
None	6 (28.6)	5 (5.7)	5.75 (1.57–21.02)	0.003
Unilateral vs. bilateral pulmonary infiltrates[j]	10 (66.7)	44 (56.4)	1.55 (0.48–4.95)	0.653
Cavitary infiltrates[j]	0 (0)	50 (64.1)	—	<0.001
Diffuse infiltrates vs. focal infiltrates[j]	5 (33.3)	0 (0)	—	<0.001
Pleural effusion	1 (5)	3 (3.5)	2 (0.181–22.156)	0.571

RR, risk ratio.
[a]Constitutional symptoms include weight loss, fatigue and/or night sweats.
[b]Tuberculous epididymitis was evaluated and confirmed in two of these patients.
[c]Three patients with ascites reported progressive abdominal distension; one patient with a psoas abscess reported back pain; and one patient with a brain abscess presented with neurological symptoms.
[d]Two patients with central nervous system disease reported neurological symptoms; one patient with tuberculous spondylitis (Pott's disease) reported back pain; and one patient with tuberculosis of the urinary tract reported symptoms of cystitis.
[e]Tuberculous peritonitis was confirmed in two of these patients.
[f]Organs involved: urinary tract (two patients), lymph nodes (one patient), brain (one patient), and peritoneum (one patient).
[g]Organs involved: lymph nodes (two patients), urinary tract (one patient), larynx (one patient), vertebral bones (one patient), psoas (one patient), and meninges (one patient).
[h]Organs involved: lung and blood (one patient), joint and peritoneum (one patient), lung, liver and bone marrow (one patient), lung and psoas (one patient), and lung and testicle (one patient).
[i]Organs involved: lung and peripheral lymph nodes (three patients), and lung and meninges (one patient).
[j]All 15 cases (100%) and 78 of 82 controls (95.1%) with radiographic abnormalities had pulmonary infiltrates (p 0.868).

TABLE 4. Diagnosis and treatment of tuberculosis in transplant recipients and patients from the general population, matched by age, gender, and year of tuberculosis diagnosis

Variable	Transplant recipients (n = 22)	Patients from the general population (n = 88)	RR (95% CI)	p
Diagnosis of tuberculosis				
Median time (days) from onset of symptoms to diagnosis (IQR)	70 (48)	46 (70)	—	0.076
Median time (days) from clinical suspicion of tuberculosis to definitive diagnosis (IQR)	14 (51.5)	0 (1.25)	—	0.001
Sputum culture performed, no. (%)	12 (54.5)	77 (87.5)	0.17 (0.06–0.49)	<0.001
Positive sputum culture, no. (%)	10 (83.3)	70 (90.9)	0.5 (0.09–2.75)	0.769
Invasive procedures required, no. (%)	12 (54.5)[a]	15 (17)[b]	5.84 (2.14–15.98)	0.001
Post-mortem diagnosis, no. (%)	3 (13.6)[c]	0 (0)	—	<0.001
Positive tuberculin skin test result when tuberculosis was suspected, no. (%)[d]	0 (0)	16 (84.2)	—	0.022
Treatment of tuberculosis				
Initial isoniazid-containing regimen, no. (%)	19 (100)	88 (100)	—	—
Initial rifampin-containing regimen, no. (%)	14 (73.7)	88 (100)	—	<0.001
Initial pyrazinamide-containing regimen, no. (%)	14 (73.7)	85 (93.1)	0.21 (0.06–0.77)	0.037
Initial ethambutol-containing regimen, no. (%)	16 (88.9)	69 (79.3)	2.09 (0.44–9.92)	0.542
Initial quinolone-containing regimen, no. (%)	2 (10.5)	7 (8)	1.35 (0.26–7.05)	0.918
Initial regimen of three drugs, no. (%)	12 (63.2)	22 (25.3)	5.07 (1.77–14.48)	0.004
Initial regimen of four or more drugs	7 (36.8)	65 (74.7)	0.30 (0.07–0.56)	0.004
Median duration (months) of tuberculosis treatment (IQR)[e]	18 (8.5)	6 (3)	—	0.012
Drug toxicity, no. (%)	6 (37.5)[f]	7 (9.6)[g]	5.66 (1.58–20.29)	0.014
Hepatotoxicity	4 (25)	6 (8.2)	3.72 (0.91–15.19)	0.139

RR, risk ratio.
[a]The most common procedure performed was bronchoscopy with bronchoalveolar lavage (six patients); in the other six patients, biopsy specimens were obtained from different organs.
[b]The most common procedures performed were bronchoscopy with bronchoalveolar lavage (seven patients), biopsy of the lung (two patients), and biopsy of the lymph nodes (two patients); in the remaining four patients, biopsy specimens were obtained from different organs.
[c]A positive *Mycobacterium tuberculosis* culture result was obtained after death in three patients, and one patient was diagnosed only at necropsy (brain abscess culture).
[d]The tuberculin skin test was performed when tuberculosis was suspected in three of 19 transplant recipients (15.8%) (information was unavailable in three cases), and in 19 of 86 patients from the control cohort (22.1%) (information was unavailable for two controls) (p 0.766).
[e]Patients who did not die before the end of the planned treatment.
[f]Four patients had hepatotoxicity leading to discontinuation of rifampin; in addition, one of these patients also had hyperuricaemia that led to discontinuation of pyrazinamide, one patient had severe arthralgia and myalgia that led to discontinuation of pyrazinamide, and one patient developed optic neuritis secondarily to ethambutol treatment.
[g]Six patients developed hepatotoxicity that led to discontinuation of rifampin, isoniazid, or both; one patient had drug fever that led to discontinuation of rifampin.

histopathological pattern of tuberculosis, nucleic acid amplification test, or *M. tuberculosis* culture) was longer in TRs, who more often required invasive procedures. Three TRs (13.6%) and no non-TRs were diagnosed post-mortem (p <0.05).

Differences in tuberculosis treatment between the cohorts included the following: TRs were less likely to receive an initial rifampin-containing or pyrazinamide-containing regimen, and had a longer duration of antituberculous therapy. TRs had a higher rate of antituberculous drug toxicity.

Antituberculous drug resistance was observed in three non-TRs: two with isoniazid-resistant strains of *M. tuberculosis*, and the other with a strain resistant to isoniazid and rifampin. After the initial therapy had been changed, the patients were cured. The initial antituberculous regimen was appropriate in all other patients.

Outcomes and risk factors for tuberculosis-related mortality

No statistically significant differences in crude mortality were found within 30 days (three TRs (13.6%) vs. seven non-TRs (8%); p 0.411) or 90 days (four TRs (18.2%) vs. eight non-TRs (9.1%); p 0.217) of tuberculosis diagnosis. Tuberculosis-related mortality was higher among TRs (four patients, 18.2%) than among non-TRs (five patients, 5.7%), but the difference was not statistically significant (p 0.057).

No TRs and two non-TRs with tuberculosis relapsed (2.5%; p 0.68); one patient diagnosed with pulmonary tuberculosis did not complete the initial 6-month regimen, and relapsed 5 years later; the other had Pott's disease, and relapsed 10 months after completing a 12-month period of treatment. All other patients were considered to be cured.

After adjustment for previous transplantation, age, Charlson comorbidity score, and number of organs with probable tuberculosis involvement, the only independent predictor of tuberculosis-related mortality was having more organs with tuberculosis involvement (Table 5).

Discussion

The characteristics and outcomes of tuberculosis in TRs and non-TRs have not been directly compared before. We compared TRs and patients from the general population, and found that the factors predisposing to tuberculosis (other than

TABLE 5. Multivariate risk factors for tuberculosis-related death in transplant recipients and patients from the general population with tuberculosis

Risk factor	Adjusted hazard ratio (95% CI)	p
Transplantation	1.11 (0.06–21.43)	0.943
Age (years)	1.58 (0.38–6.51)	0.529
Charlson comorbidity score ≥2	8.03 (0.32–203.41)	0.206
Number of organs with tuberculosis involvement	10.14 (1.06–97.16)	0.045

transplantation), diagnosis and manifestations differed between the cohorts. Having more organs with tuberculosis involvement—which was more common in TRs—was associated with higher tuberculosis-related mortality.

The risk of tuberculosis in TRs depends mainly on the endemicity in the geographical area, the transplanted organ (lung transplant recipients are at highest risk), and the level of immunosuppression [13]. We additionally found that well-established risk factors for active tuberculosis in other populations [12,24,26], except for alcohol abuse, were much more common in TRs than in the general population.

In previous reports, extrapulmonary or disseminated tuberculosis accounted for almost half of post-transplant tuberculosis cases [1,2,5,9]. Remarkably, we found that the incidence of disseminated tuberculosis was six times higher in TRs than in non-TRs. Consequently, more TRs had fever and diverse manifestations of extrapulmonary disease. To improve early diagnosis and help prevent mortality in TRs, we think that tuberculosis should be considered in any TR with fever of unknown origin [3]. Mycobacterial cultures should also be routinely considered when any infectious complication or atypical finding is evaluated in this population [3].

Most active tuberculosis infections in adult patients, including TRs, are due to reactivation of latent infections. Most patients show chest radiograph abnormalities, which are characteristically parenchymal opacities in upper lobes, often with cavitation [27,31]. This was the most common radiographic pattern in patients from the general population, whereas almost 30% of TRs had no radiographic abnormalities and none had cavitary lesions. However, tuberculosis should be suspected in TRs with diffuse infiltrates, as one-third had this radiographic pattern.

Along with its atypical presentation, post-transplant tuberculosis resists early recognition and diagnosis, because invasive procedures are often necessary for a definitive diagnosis to be made [2,3,14]. We also observed that the definitive diagnosis took longer to reach in TRs than in the general population, supporting the importance of an early, aggressive approach to diagnosis.

Measurement of the cell-mediated immune response to *M. tuberculosis* is the accepted indirect method of detecting possible infection [13]; the TST is the standard measurement method. Like previous studies, we found that the TST was an imperfect identifier of tuberculosis infection in transplant candidates and TRs [1,2,32]. Moreover, the TST failed to detect tuberculosis in any TR with active infection, although it was positive in >80% of patients from the general population. Some studies have suggested that interferon-γ release assays are more sensitive than the TST in transplant candidates and TRs [33–36]. Unfortunately, neither of the tests is infallible in diagnosing *M. tuberculosis* infection, or distinguishes between active and latent tuberculosis [13,14,19,37].

Current guidelines recommend similar tuberculosis treatment in TRs and immunocompetent hosts [12–14]. Spanish guidelines, however, recommend the avoidance of rifamycins in non-severe cases, because they reduce the levels of some immunosuppressive drugs, increasing the risk of graft rejection [12]. Probably because of this, our TRs more often received a three-drug rifampin-sparing regimen and had lengthier treatments than patients from the general population. The recommendations concerning rifampin as a part of tuberculosis treatment are controversial, although most of the current guidelines favour a rifamycin-containing regimen [11,13,14].

In this series, antituberculous drug-induced toxicity was more frequent in TRs. There were no significant differences in the percentage of hepatotoxicity between the two groups, possibly because the definition of hepatotoxicity was stricter than in previous reports, the small number of liver transplant recipients (in whom hepatotoxicity is more common), or the use of rifampin-free regimens.

Having more organs with tuberculosis involvement, rather than patient characteristics related to age, Charlson score, or transplantation, was a predictor of tuberculosis-related mortality. The risk of disseminated tuberculosis is higher among patients with underlying conditions and impaired immunity; accordingly, in our study, TRs had more organs with tuberculosis involvement. We hypothesize that the delay in diagnosing tuberculosis in TRs means that more organs are involved by the time when the final diagnosis is made, which is associated with greater tuberculosis-related mortality.

The first limitation of this study is its retrospective design. Also, although this is one of the largest single-centre series of TRs with culture-positive tuberculosis to date [3,7–9], comparisons were made on a small sample, with a high risk of beta error (leading to no differences between the compared populations). The absence of significant differences between the populations (for drug-related hepatotoxicity or mortality) should therefore be interpreted with caution. The non-homogeneity of the transplanted population, including all types of organ and haematopoietic stem cell transplantation, is a limitation. Although most patients diagnosed with tuberculosis in the area were referred to our centre for treatment, we cannot completely exclude a referral bias in the control cohort. Additionally, our findings may not be generalizable to countries with different incidence rates of tuberculosis.

Our study demonstrates that the manifestations of tuberculosis in TRs differ from those in normal hosts. Post-transplant tuberculosis resists timely diagnosis, and is associated with a higher risk of death before a diagnosis is reached. The higher tuberculosis-related mortality among TRs may be a result of

more organs having tuberculosis involvement at diagnosis, and not transplantation itself, which was not associated with increased tuberculosis-related mortality. A high index of suspicion for tuberculosis and performing diagnosis early and aggressively could prevent death in TRs.

Author contributions

N. Benito takes responsibility for the content of the manuscript, including the data and analysis. N. Benito had full access to all of the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis. E. García-Vázquez, J. P. Horcajada, J. González, F. Oppenheimer, F. Cofán, M. J. Ricart, A. Rimola, M. Navasa, M. Rovira, E. Roig, F Pérez-Villa, C. Cervera and A. Moreno contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript, or had substantial involvement in its revision prior to submission.

Transparency declaration

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