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Treatment Outcomes and Loss to Follow-Up in Tuberculosis: A Real-World Cohort Study from Sicily, Italy

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Abstract

Background Tuberculosis (TB) remains a major cause of morbidity and mortality worldwide. Its management is frequently complicated by prolonged treatment, drug-related toxicity, antimicrobial resistance, and difficulties in maintaining long-term follow-up. We aimed to describe the clinical characteristics, management, and treatment outcomes of patients with TB treated at a tertiary referral center in Sicily, Italy.

Methods We conducted a retrospective observational study of consecutive patients with TB managed between January 2021 and December 2023. Demographic, clinical, microbiological,

treatment-related, and outcome data were collected. Outcomes included treatment completion, loss to follow-up (LTFU), transfer to another center, treatment failure, relapse, and death. Factors associated with treatment completion were evaluated using multivariable logistic regression.

Results Among 164 patients, 130 (79.2%) were male, and 105 (64.0%) were born outside Italy. Pulmonary TB was diagnosed in 141 patients (86.0%), including 82 (58.2%) with concomitant extrapulmonary involvement. Microbiological confirmation was obtained in 106 (64.6%). Phenotypic drug susceptibility testing was available for 50 patients, of whom 17 (34.0%) showed resistance to at least one drug tested. Adverse drug reactions occurred in 37 patients (22.6%), most commonly hepatotoxicity, and led to treatment modification in 35. By the end of follow-up, 95 patients (57.9%) had completed treatment, 53 (32.3%) were LTFU, 5 (3.0%) had been transferred to another center, and 11 (6.7%) had died. Treatment failure and relapse were each documented in one patient. Five deaths were directly attributable to TB, whereas six were related to underlying or concomitant comorbidities. Foreign-born status was independently associated with lower likelihood of treatment completion (adjusted OR, 0.260; 95% CI, 0.106–0.641; p=0.003).

Conclusions In this real-world cohort, TB management was characterized by substantial clinical complexity and a high rate of LTFU. Foreign-born patients were significantly less likely to complete treatment, underscoring the need for patient-centered strategies to strengthen long-term engagement and reduce LTFU.

Keywords

Tuberculosis, Italy, Migrants, Outcome, follow-up, lost, treatment

Background

Tuberculosis (TB), caused by organisms belonging to the *Mycobacterium tuberculosis* complex, remains the leading cause of death from a single infectious agent worldwide [1]. According to the

World Health Organization (WHO) Global Tuberculosis Report 2025, an estimated 10.7 million people developed TB worldwide in 2024, corresponding to a global incidence rate of approximately 131 cases per 100,000 population [1]. TB is primarily transmitted through the airborne route, with the risk of infection depending on the intensity and duration of exposure, particularly among household and other close contacts of individuals with pulmonary TB [2]. Although most infected individuals remain asymptomatic, a proportion develops active disease either through progression of a recent infection or through reactivation or reinfection. TB most commonly affects the lungs but may involve virtually any organ, with extrapulmonary disease often posing substantial diagnostic challenges [2]. Increasing recognition of incipient and subclinical TB has further supported the view of TB as a dynamic disease spectrum rather than a simple dichotomy between latent infection to active disease [3].

Microbiological testing, including smear microscopy, culture, and molecular assays, remains the cornerstone of TB diagnosis. WHO recommends the use of a rapid molecular assay as the initial diagnostic test in patients with signs and symptoms of pulmonary TB [1]. Nevertheless, negative microbiological findings do not exclude active disease, particularly in patients with paucibacillary or extrapulmonary TB. Immunological tests, such as interferon-gamma release assays (IGRAs), can provide evidence of *M. tuberculosis* infection but cannot distinguish latent infection from active disease [4].

Delayed diagnosis may result in more advanced disease, ongoing transmission, and an increased risk of long-term impairment and disability among TB survivors, particularly in patients with comorbidities or other conditions associated with poor health [3], [5].

Despite the availability of effective antimicrobial regimens, the management of active TB remains challenging because of the prolonged duration of treatment, the need for multidrug regimens, potential drug toxicity and interactions, antimicrobial resistance, and difficulties in maintaining adherence [2].

Although WHO targets call for treatment success rates of at least 90%, treatment outcomes remain suboptimal, particularly among patients with drug-resistant TB and other high-risk conditions [6]. Moreover, real-world data on treatment tolerance, adherence, and long-term outcomes remain limited, particularly in high-resource, low-incidence settings.

Italy is classified as a low-incidence country; nevertheless, TB remains a relevant public health concern, with a disproportionate burden among migrants from high-incidence countries [1], [7]. Sicily represents a distinctive epidemiological setting because of its geographical position, with sustained migration flows from Africa, Asia, and Eastern Europe, and a relatively high TB burden compared with other Italian regions.

In a previous study based on hospital discharge records, we identified 3,745 patients hospitalized with TB in Sicily between 2009 and 2021, accounting for 5,239 hospital admissions and 166 deaths [8]. However, that study was based exclusively on administrative hospitalization data and did not provide information on treatment regimens, adverse events, adherence, or treatment completion.

The aim of the present study was to describe the demographic and clinical characteristics, microbiological findings, treatment management, and outcomes of patients with TB treated at a tertiary university hospital in Palermo, Sicily. Particular attention was given to treatment adherence, adverse drug reactions, treatment completion, loss to follow-up, and mortality.

Methods

Study design and setting

We conducted a retrospective observational study of patients with TB managed from January 2021 to December 2023 at a tertiary-care university hospital in Palermo, Sicily, Italy. The hospital serves as a regional referral center for the diagnosis and management of TB and HIV/AIDS. Its activities include active surveillance for TB among hospitalized patients, outpatient evaluation of individuals with suspected TB, and respiratory isolation of patients with suspected or confirmed pulmonary TB.

This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies. The completed STROBE checklist is provided as Supplementary Table S1.

Study population

All consecutive patients hospitalized and/or receiving anti-TB treatment at our center during the study period were assessed for eligibility. Patients were included if they had a diagnosis of active TB and their medical records contained sufficient clinical information to characterize disease presentation, treatment and outcome. Both pulmonary and extrapulmonary TB were included. Because this was a retrospective cohort of all consecutive eligible patients during a predefined 3-year period, no a priori sample-size calculation was performed; the sample size was determined by the number of eligible patients identified during the study period.

Pulmonary TB was defined as TB involving the lungs and was further categorized as pulmonary TB limited to the lungs, with or without concomitant intrathoracic lymph node involvement, or pulmonary TB associated with extrapulmonary involvement. Extrapulmonary TB was defined as TB involving organs or anatomical sites outside the lungs in the absence of pulmonary involvement.

Cases were classified as microbiologically confirmed or clinically diagnosed. Microbiologically confirmed TB was defined by detection of *Mycobacterium tuberculosis* complex through culture and/or a positive nucleic acid amplification testing using the Xpert MTB/RIF assay. A positive acid-fast bacilli (AFB) smear was also considered microbiological evidence when accompanied by clinical and/or radiological findings consistent with TB. Patients with subclinical or paucisymptomatic disease were also included when they met the microbiological criteria for TB, despite having no or only mild symptoms.

Clinically diagnosed TB was defined as a disease diagnosed on the basis of compatible clinical and/or radiological findings in the absence of microbiological confirmation.

Diagnostic procedures and infection control

Diagnostic investigations were selected according to disease presentation and clinical judgment. In patients with suspected pulmonary TB, microbiological testing included AFB smear microscopy, mycobacterial culture, and nucleic acid amplification testing. In patients with a positive molecular test for *M. tuberculosis* complex, rifampicin resistance was assessed using the Xpert MTB/RIF assay.

Patients with smear-positive pulmonary TB remained in respiratory isolation until three consecutive sputum specimens tested negative by Ziehl–Neelsen microscopy. For patients with negative AFB smear microscopy but a positive molecular test for *M. tuberculosis* complex, respiratory isolation was discontinued after at least 2 weeks of appropriate anti-TB treatment.

For extrapulmonary TB, diagnosis was based on clinical and radiological findings, supplemented, whenever possible, by microbiological and molecular investigations performed on specimens obtained from the affected site. Depending on the disease localization, specimens included cerebrospinal fluid, bone biopsy specimens, urine, stool, pleural fluid, and peritoneal fluid. QuantiFERON ® -TB Gold IGRA testing was used as an adjunctive diagnostic test when appropriate.

Follow-up and treatment monitoring

After completion of the respiratory isolation period, clinically stable patients were managed in the outpatient setting. During treatment, patients underwent periodic clinical assessments and laboratory testing to evaluate treatment response, detect adverse drug reactions, and identify clinical deterioration or other conditions requiring changes in management. Follow-up duration was not fixed because this was a retrospective real-world cohort and depended on treatment duration, treatment interruption or modification, transfer to another center, loss to follow-up, and clinical

circumstances. Consequently, outcomes were assessed at the end of the available follow-up rather than at a uniform prespecified time point, and no time-to-event analysis was performed.

The initial anti-TB regimen, treatment duration, subsequent treatment modifications, use of second-line anti-TB agents, and corticosteroid administration were recorded. When treatment was modified, the underlying indication and the drugs discontinued, added, or replaced were documented when available.

Microbiological testing at the end of treatment was not performed systematically, primarily because many patients were unable to provide adequate sputum specimens. Patients with suspected treatment failure or clinical worsening were rehospitalized when appropriate and underwent repeat microbiological and radiological assessment.

Data collection

Patient data were retrospectively extracted from medical records using a standardized data-collection form.

The following variables were collected:

- Demographic and epidemiological characteristics: age, sex, country of birth, and relevant epidemiological risk factors.
- Clinical characteristics: presenting symptoms, comorbidities, Charlson Comorbidity Index (CCI), HIV, HBV, and HCV status, and TB disease localization.
- Radiological characteristics: pulmonary and extrapulmonary imaging findings and specific manifestations of TB.
- Microbiological characteristics: AFB smear microscopy, mycobacterial culture, nucleic acid amplification testing, IGRA results, and drug susceptibility testing (DST), when available.

- Treatment-related characteristics: initial anti-TB regimen, estimated and observed treatment duration, treatment modifications, use of second-line anti-TB drugs, and corticosteroid therapy.

- Safety outcomes: occurrence and type of adverse drug reactions and treatment modifications related to toxicity. Adverse drug reactions were considered potentially related to antituberculosis therapy after exclusion of other plausible causes based on the patient's medical and medication history and clinical assessment. The assessment considered the main known adverse effects of first-line antituberculosis drugs, including hepatotoxicity, gastrointestinal symptoms, hypersensitivity reactions, cutaneous rash, peripheral neuropathy, visual disturbances, arthralgia, hyperuricemia, and hematological abnormalities. Furthermore, the temporal relationship between treatment initiation and the onset of symptoms or laboratory abnormalities, as well as their evolution after treatment modification or discontinuation, was also considered.

- Clinical outcomes: treatment completion, loss to follow-up (LTFU), transfer to another treatment center, rehospitalization, treatment failure, relapse, and death.

Drug susceptibility testing

Phenotypic DST results were recorded, when available, for rifampicin (RIF), isoniazid (INH), ethambutol (EMB), pyrazinamide (PZA), and streptomycin (SM). Phenotypic drug resistance was defined as resistance to at least one of the drugs tested.

The analysis of phenotypic resistance patterns was performed on patients for whom DST results were available. Resistance patterns were categorized according to the number and combination of drugs to which resistance was detected.

Definitions of treatment outcomes

Treatment outcomes were determined at the end of the available follow-up period. Because follow-up duration was not uniform across patients, particularly because of LTFU and transfers, outcome frequencies were reported using the available observation period and were not interpreted as fixed-time-point risks. Patients who were transferred to another healthcare facility were retained as a separate outcome category because their subsequent treatment course could not be verified in our records.

Treatment completion was defined as completion of the prescribed anti-TB treatment course without documented evidence of treatment failure.

LTFU was defined, for the purposes of this study, as failure to attend the outpatient clinic for more than 30 consecutive days after the scheduled follow-up visit, with no subsequent documented resumption of care at our center.

Treatment failure was defined as the persistence or reappearance of bacteriological positivity during treatment or at the end of the prescribed treatment course.

Relapse was defined as a new episode of active TB occurring after documented completion or cure of the initial TB episode, based on microbiological and/or clinical evidence of recurrent disease. Thus, recurrence occurring before completion of the initial treatment course was not classified as relapse but, when bacteriologically documented, was considered in the assessment of treatment failure. Because post-treatment surveillance was not standardized and was limited by the retrospective design, relapse could only be identified when a recurrent episode was documented in the available medical record.

Death was defined as death from any cause occurring during anti-TB treatment or follow-up. Among deceased patients, deaths were classified as TB-related or unrelated to TB when the available clinical documentation allowed the cause of death to be determined.

Patients transferred to another healthcare facility for continuation of treatment and follow-up were classified separately and were not considered LTFU.

Potential sources of bias were considered a priori. The retrospective single-center design may introduce selection and information bias, while the tertiary referral setting may preferentially capture more complex disease. Differential loss to follow-up may also introduce attrition bias, and incomplete ascertainment of treatment outside our center may lead to misclassification of LTFU and under-ascertainment of subsequent outcomes. These issues were considered when interpreting treatment outcomes and are described in the Limitations section.

Statistical analysis

Statistical analyses were performed using SPSS software (IBM Corp., Armonk, NY, USA; version 26.0). Categorical variables were summarized as absolute frequencies and percentages. Continuous variables were expressed as mean ± standard deviation (SD). Comparisons between categorical variables were performed using Pearson's chi-square test or Fisher's exact test, as appropriate. Continuous variables were compared using the Student's *t*-test for normally distributed variables or the Mann–Whitney *U* test when appropriate. A two-sided *P* value <0.05 was considered statistically significant. Missing data frequencies of selected diagnostic and laboratory variables were reported in supplementary Table 2. Analyses were performed using an available-case approach for each variable or analysis, without imputation.

Univariable analyses were performed to identify factors associated with treatment completion. Variables considered clinically relevant and/or associated with the outcome in univariable analysis were subsequently considered for inclusion in a multivariable logistic regression model. Adjusted odds ratios (AORs) and corresponding 95% confidence intervals (CIs) were calculated. Subgroup analyses were performed, where appropriate, according to TB disease localization (pulmonary versus extrapulmonary TB) and country of birth (Italian-born versus non-Italian-born patients).

Radiological findings were analyzed descriptively and, where relevant, compared between prespecified clinical groups by univariate analysis. Variables significantly associated with treatment completion in univariate analyses were considered for inclusion in the multivariable model. Radiological characteristics were therefore evaluated in relation to clinical outcomes but were not specifically investigated as independent radiological predictors of treatment response.

Ethics

The study was conducted in accordance with the principles of the Declaration of Helsinki. Given the retrospective observational design and the use of anonymized data extracted from medical records, the requirement for individual informed consent was waived by the Ethics Committee.

Results

Demographics characteristics, comorbidities, and coinfections

A total of 164 patients with TB (PWT) were included in the study. Their demographic and clinical characteristics, stratified by country of birth, are summarized in Table 1. The mean age was 41.0 ± 19.1 years, and 130 patients (79.2%) were male. Fifty-nine patients (36.0%) were born in Italy, whereas 105 (64.0%) were born outside Italy. Among non-Italian-born patients, 78 (74.3%) originated from Africa, 15 (14.3%) from Asia, and 12 (11.4%) from Eastern Europe.

Italian-born patients were older than non-Italian-borne patients (56.0 ± 18.5 vs. 34.0 ± 14.3 years; $p < 0.001$) and had a higher mean Charlson Comorbidity Index (CCI) score (2.5 ± 2.6 vs. 0.9 ± 1.7; $p < 0.001$), see Table 1. The proportion of male patients was higher in the non-Italian-born group, although the difference did not reach statistical significance (83.8% vs. 71.2%; $p = 0.056$).

At the time of TB diagnosis, 11 patients were managed entirely in the outpatient setting, whereas the remaining patients were diagnosed during hospitalization. The number of hospital admissions per patient ranged from 1 to 7. Readmission was required in 32 patients (19.5%), accounting for 35 readmissions overall, with no significant difference according to country of birth (p = 0.650). Of

these readmissions, 18 were directly related to TB, including TB-related complications and clinical deterioration following treatment interruption, whereas the remaining 17 were attributable to causes unrelated to TB. Overall, 201 hospital admissions occurred among PWT during the study period.

Overall, at least one comorbidity was present in 88 patients (53.6%). The most frequent comorbidity was cardiovascular disease (34/164, 20.7%), followed by diabetes mellitus (23/164, 14.0%), chronic lung disease (20/164, 12.2%), chronic liver disease (17/164, 10.4%), autoinflammatory disorders (12/164, 7.3%), malignancy (10/164, 6.1%), chronic kidney disease (7/164, 4.3%), and previous transplantation (2/164, 1.2%). Cardiovascular disease, malignancy, and chronic lung disease were significantly more frequent among Italian-born patients, whereas chronic liver disease, particularly chronic hepatitis B, was more frequently observed among non-Italian-born patients.

Table 1. Demographic and clinical characteristics of patients with tuberculosis according to country of origin

Variables	Frequency (n = 164)	Italian-borne (n = 59)	Non-Italian-borne (n = 105)	P value
Mean age ± SD (years)	41 ± 19.1	56 ± 18.5	34 ± 14.3	< 0.001
Male (%)	130 (79.2%)	42 (71.2%)	88 (83.8%)	0.056
Mean ± SD CCI	1.4 ± 2.2	2.5 ± 2.6	0.9 ± 1.7	< 0.001
Comorbidities (at least one)	88 (53.6%)	41 (69.4%)	47 (44.8%)	0.002
Cardiovascular diseases	34 (20.7%)	24 (40.7%)	10 (9.5%)	< 0.001
Diabetes	23 (14.0%)	11 (18.6%)	12 (11.4%)	0.202
Chronic lung diseases	20 (12.2%)	13 (22.0%)	7 (6.7%)	0.004
Chronic liver disorders	17 (10.4%)	3 (5.1%)	14 (13.3%)	0.096
Autoinflammatory disorders	12 (7.3%)	6 (10.2%)	6 (5.7%)	0.293

Malignant neoplasm	10 (6.1%)	10 (16.9%)	0	< 0.001
Chronic kidney disease	7 (4.3%)	4 (6.8%)	3 (2.8%)	0.253
Transplants	2 (1.2%)	2 (3.4%)	0	0.128
Chronic coinfections				
HIV	8 (4.9%)	2 (3.3%)	6 (5.7%)	0.712
HBV	12 (7.3%)	0	12 (11.4%)	0.004
HCV	2 (1.2%)	1 (1.7%)	1 (0.9%)	1.000

SD: standard deviation; CCI: Charlson Comorbidity Index.

HIV infection was documented in 8 patients (4.9%), chronic HBV infection in 12 (7.3%), and HCV infection in 2 (1.2%). All patients with HBV infection were born outside Italy ($p = 0.004$). Absolute CD4+ T-cell counts were available for 64 patients. Among the 8 people with HIV (PWH), CD4+ T-cell counts ranged from 2 to 535 cells/μL.

Among the 56 PWT without HIV infection for whom CD4+ T-cell counts were available, 27 (48.2%) had CD4+ T-cell counts below 500 cells/μL, including 7 (12.5%) with severe CD4+ T-cell depletion (<200 cells/μL). The prevalence of CD4+ T-cell depletion did not differ significantly according to country of birth (p = 0.558).

Clinical characteristics and sites of tuberculosis

The most frequently reported symptoms were cough (51.2%), fever (48.9%), weight loss (33.0%), fatigue (21.3%), dyspnea (18.9%), chest pain (14.0%), hemoptysis (10.4%), night sweats (9.7%), and abdominal pain (7.9%). Other symptoms were reported in 15.2% of patients.

A subclinical or paucisymptomatic presentation was documented in 16 patients (9.8%). TB was microbiologically confirmed in 8 of these patients, whereas the remaining 8 were diagnosed based on clinical and radiological findings. Subclinical presentations were significantly more frequent among Italian-born than non-Italian-born patients (16.9% vs. 5.7%, p = 0.020). After adjustment for

microbiological confirmation of TB, non-Italian birth remained independently associated with a lower likelihood of subclinical or paucisymptomatic presentation (AOR 0.310; 95% CI, 0.106–0.906; p = 0.032).

Subclinical or paucisymptomatic disease was less frequent among male than female PWT (6.9% vs. 20.6%, p = 0.017). After adjustment for microbiological confirmation of TB, male sex remained associated with a lower likelihood of subclinical presentation (AOR, 0.627; 95% CI, 0.214–1.836; p = 0.040).

Pulmonary TB was the predominant disease presentation, occurring in 141/164 patients (86.0%). Among patients with pulmonary TB, 82/141 (58.2%) also had extrapulmonary involvement, most commonly in the lymph nodes. Isolated extrapulmonary TB was diagnosed in 23 patients (14.0%), with lymph node and osteoarticular disease being the most frequent extrapulmonary localizations. With one exception, osteoarticular involvement consisted of vertebral TB (Pott disease). The distribution of pulmonary and extrapulmonary TB sites is shown in Figure 1.

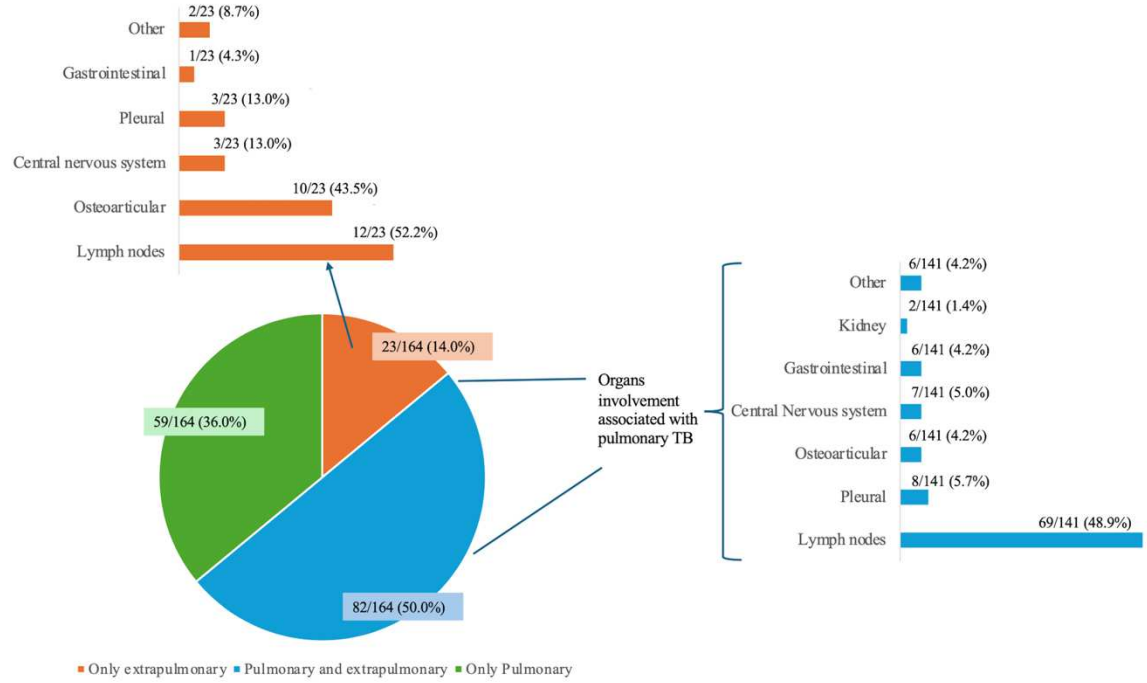


Figure 1. Pulmonary and extrapulmonary sites of tuberculosis in 164 patients included in the study.

Chest CT was performed in all 141 patients with pulmonary TB. The most frequent radiological findings were nodular coalescence and consolidation, observed in 112/141 patients (79.4%), followed by cavitary lesions in 63/141 (44.7%), tree-in-bud abnormalities in 29/141 (20.6%), ground-glass opacities in 22/141 (15.6%), and pulmonary abscesses in 5/141 (3.5%). Miliary TB was identified in 49/141 patients (34.8%), 18 of whom (36.7%) also had extrapulmonary involvement. Representative radiological imaging findings are shown in Figure 2.

No statistically significant differences were observed between Italian-born and non-Italian-born patients in terms of clinical presentation or radiological findings among those with overtly symptomatic TB. Similarly, the distribution of TB sites did not differ significantly between the two groups, except for osteoarticular TB, which was significantly more frequent among non-Italian-born than among Italian-born patients (14.3% vs. 3.4%, p = 0.032).

Female PWT showed a significantly higher prevalence of extrapulmonary TB compared with male PWT (29.4% vs. 10.8%, p = 0.006), while cavitary pulmonary lesions were less frequent (20.6% vs. 43.1%, p = 0.016).

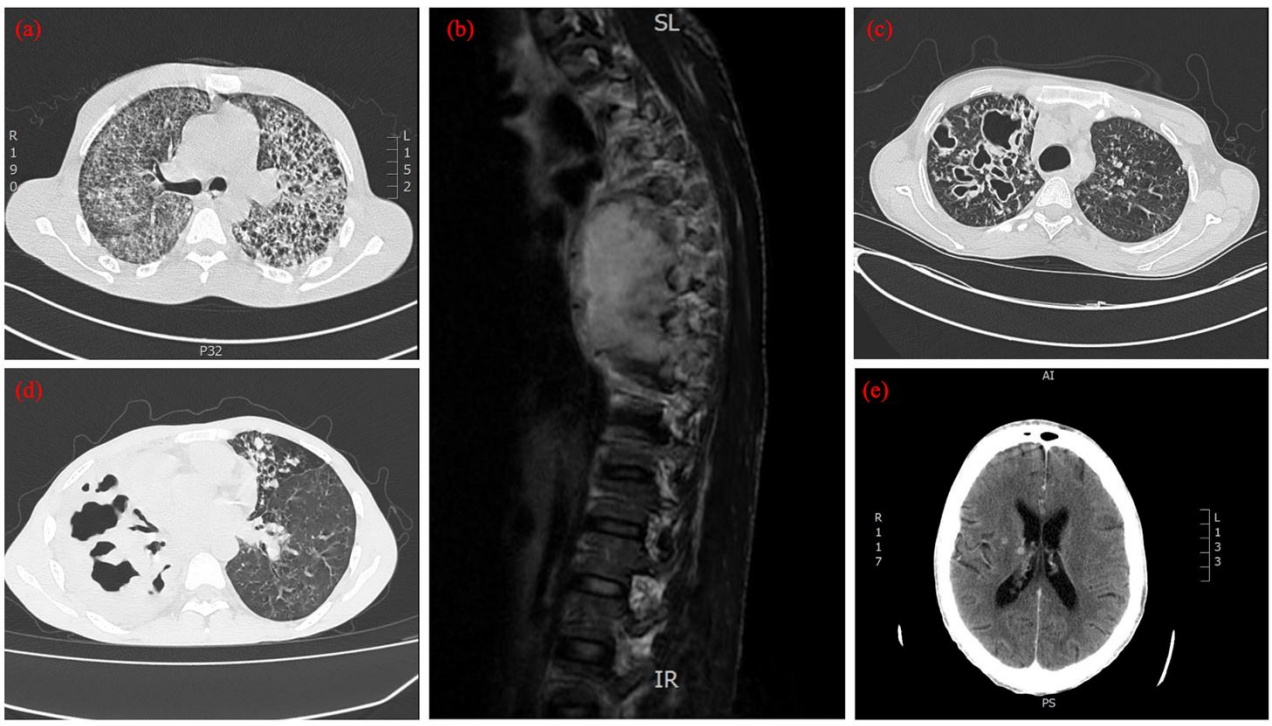


Figure 2. Multimodal imaging findings in patients with tuberculosis : (a) Chest CT demonstrating diffuse bilateral miliary nodules with areas of nodular coalescence and consolidation, predominantly involving the upper and middle lung fields, consistent with miliary pulmonary tuberculosis; (b) sagittal MRI showing tuberculous spondylodiscitis involving D5–D8, with extensive D6–D7 vertebral destruction, anterior wedge collapse of D7 with focal kyphotic deformity, and a large anterior/right paravertebral inflammatory collection extending from D4 to D9; (c) chest CT showing cavitary pulmonary tuberculosis, with multiple irregular cavitary lesions predominantly involving the right upper lobe, associated with bilateral nodular and consolidative parenchymal abnormalities; (d) Chest CT showing extensive exudative and consolidative cavitary tuberculosis of the right upper lobe, with multiple irregular thick-walled cavities, associated with nodular and interstitial abnormalities in the left lung; (e) contrast-enhanced brain CT showing multiple millimetric enhancing nodular lesions, involving both supratentorial and infratentorial regions, consistent with intracranial tuberculomas.

Diagnosis of Tuberculosis

TB was microbiologically confirmed in 106 patients (64.6%), whereas the remaining cases were diagnosed based on clinical and/or radiological findings without microbiological confirmation.

An IGRA was performed in 142 patients: 111 (78.2%) had a positive result, and 6 (4.2%) an indeterminate result. Among the 25 patients with a negative QuantiFERON ® -TB Gold result, 16 (64.0%) had microbiologically confirmed TB. In the remaining 9 patients, the diagnosis was not supported by either microbiological confirmation or a positive IGRA and was therefore based exclusively on clinical and radiological findings.

Microbiological results according to specimen type and diagnostic assay are presented in Figure 3.

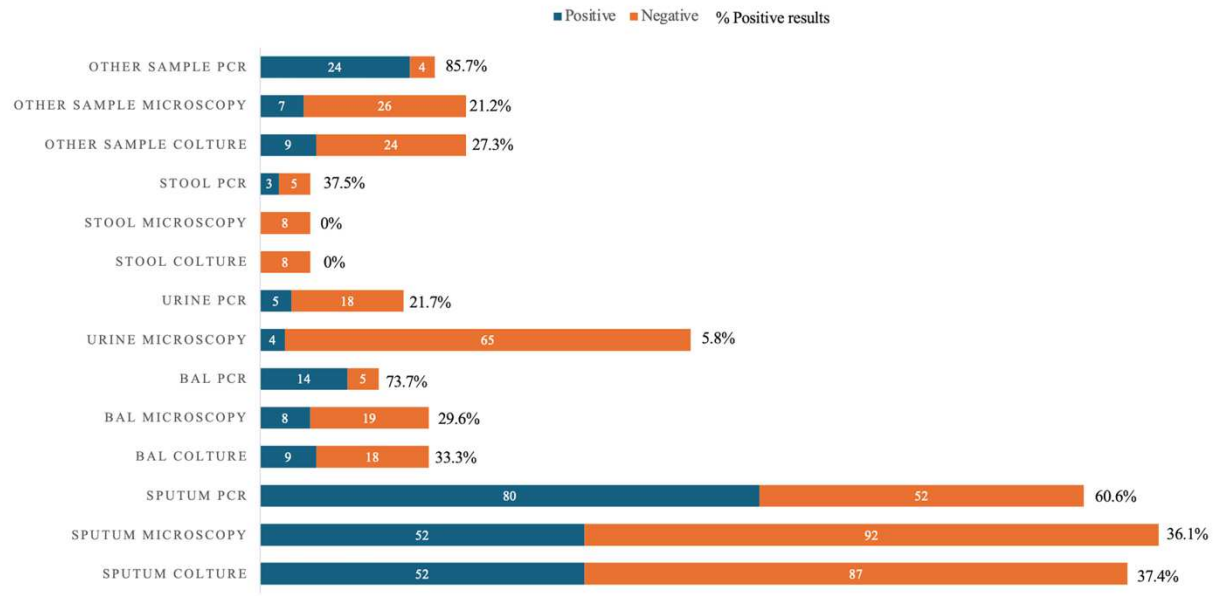


Figure 3. Microbiological diagnostic results according to specimen type and diagnostic assay. Absolute frequency of positive and negative microbiological results according to the type of clinical specimen and diagnostic examination, with the corresponding proportion of positive results.

Rifampicin resistance was detected by GeneXpert in 11/145 patients (7.6%). No discordance was observed between molecular and phenotypic RIF susceptibility results when both were available. Phenotypic DST results were available for 50/164 patients (30.5%). Resistance to at least one of the tested drugs, RIF, INH, EMB, PZA, or SM, was detected in 17/50 patients (34.0%). The prevalence of resistance did not differ significantly between Italian-born and non-Italian-born PWT (5/15 [33.3%] vs. 12/35 [34.3%], respectively; p = 0.948). Resistance to two, three, and four drugs was detected in 2 (4.0%), 1 (2.0%), and 3 patients (6.0%), respectively (Table 2). Monoresistance was observed in 11/50 patients (22.0% of those with available DST), including resistance to INH in 3 patients (6.0%), PZA in 4 (8.0%), and SM in 4 (8.0%). No cases of isolated RIF or EMB resistance were identified. Double resistance was observed in 2 patients (4.0%), triple resistance in

1 (2.0%), and quadruple resistance in 3 (6.0%). Phenotypic resistance patterns are summarized in Table 2.

Table 2. Phenotypic drug resistance patterns among patients with tuberculosis with available drug susceptibility testing for rifampicin (RIF), isoniazid (INH), ethambutol (EMB), pyrazinamide (PZA), and SM (streptomycin).

Resistance pattern	n	% (n=50)
Monoresistance	11	
RIF	0	0
INH	3	6.0%
EMB	0	0
PZA	4	8.0%
SM	4	8.0%
Double resistance	2	4.0%
RIF + INH	1	2.0%
INH + PZA	1	2.0%
Triple resistance	1	2.0%
INH + PZA + SM	1	2.0%
Fourth resistance	3	6.0%
RIF + INH + ETB + SM	1	2.0%
RIF + INH + PZA + SM	1	2.0%
RIF + INH + ETB + PZA	1	2.0%

Anti-TB treatment and adverse events

A first-line anti-TB regimen was initiated in 160/164 patients (97.6%). Pyridoxine (vitamin B6) was routinely prescribed at a dose of 150 mg three times weekly throughout isoniazid-containing treatment. In four patients, standard first-line therapy was not administered because of drug–drug interactions (n=3) or a previous history of extensively drug-resistant (XDR) TB (n=1).

The mean planned duration of anti-TB therapy was 8.4 ± 2.4 months, whereas the mean observed duration of treatment was 6.1 ± 4.0 months, $p < 0.001$. Observed treatment duration was influenced by LTFU, adverse drug reactions, or disease severity.

Adverse drug reactions were reported in 37/164 patients (22.6%). Hepatotoxicity was the most frequent adverse event (n=31), followed by peripheral neuropathy (n=3), acute kidney injury (n=2),

and other adverse events (n=4). Treatment was temporarily interrupted or modified because of toxicity in 35 patients.

Adverse drug reactions were significantly more frequent among Italian-born than among non-Italian-born PWT (20/59 [33.9%] vs. 17/105 [16.2%], respectively; p = 0.009). This association did not remain statistically significant after adjustment for LTFU and CCI.

Second-line anti-TB drugs were administered to 29/164 patients (17.7%). Reported indications included hepatotoxicity in 11 patients, clinically significant nausea and vomiting in 1 patient, temporary unavailability of rifampicin in 3 patients, antimicrobial resistance in 7 patients, and treatment intensification because of the clinical severity of TB in 6 patients. One patient with drug-resistant TB also developed hepatotoxicity. Levofloxacin, amikacin, and linezolid were the most frequently used second-line agents, followed by moxifloxacin and clofazimine (Figure 4).

In addition, in 10 patients, an anti-mycobacterial agent, most commonly linezolid, was temporarily administered for a confirmed or suspected concomitant infection rather than specifically for TB treatment.

Systemic corticosteroids were administered to 34/164 patients (20.7%) for a median duration of 30 days (IQR, 20–48 days). The reported indications included paradoxical TB reactions, central nervous system involvement, pleural or pericardial involvement, and non-TB-related conditions.

Six patients required surgery as part of TB management. Four underwent spinal stabilization for tuberculous spondylodiscitis, one underwent bowel resection for TB-associated peritonitis and intestinal ulcerative lesions, and one underwent drainage of an abdominal abscess.

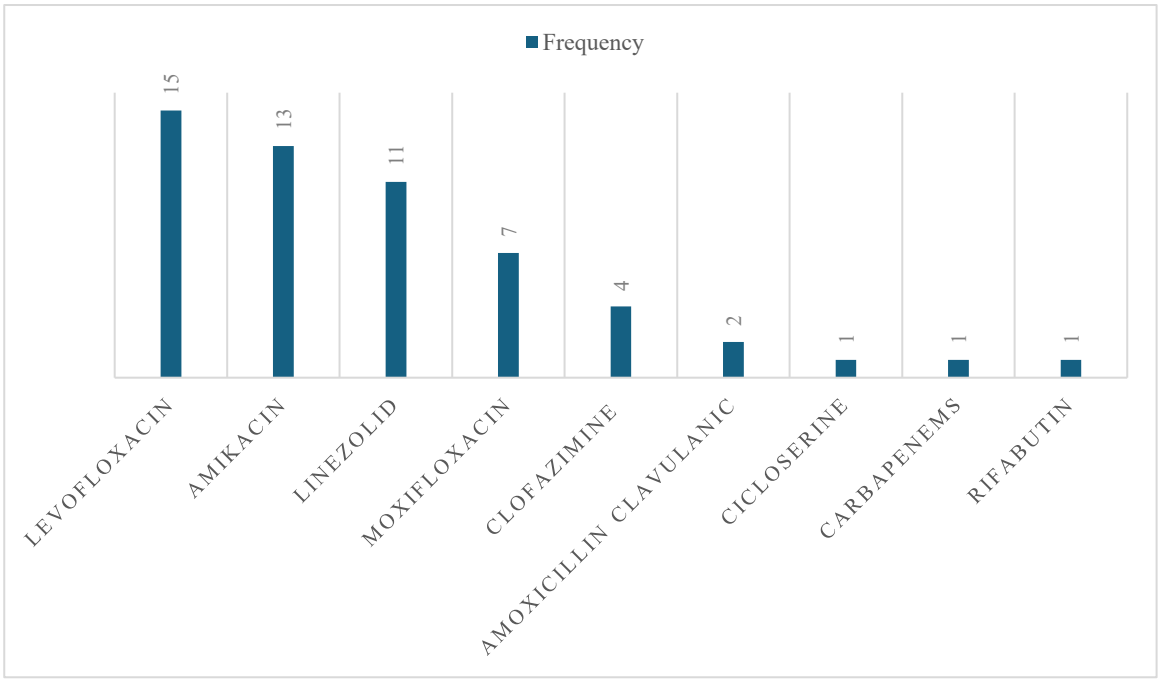


Figure 4. Use of second-line anti-tuberculosis drugs during treatment. Bars indicate the number of patients who received each agent.

Clinical outcomes

At the end of follow-up, 95 patients (57.9%) had completed anti-TB treatment, 53 (32.3%) were LTFU, 5 (3.0%) had been transferred to another center to continue treatment and follow-up, and 11 (6.7%) had died. Treatment failure occurred in one patient with XDR-TB who had poor treatment adherence and subsequently died. Relapse occurred in one patient with drug-susceptible TB and anti-TB treatment was reinitiated after completion of an initial 6-month regimen. The retreatment course was extended to 18 months, with amikacin added to the regimen during the first 2 months after treatment reinitiation. Among the 11 deceased patients, death was directly attributable to TB in 5 cases (45.5%), whereas in the remaining 6 cases (54.5%) it was attributed to underlying or concomitant conditions. Treatment outcomes according to TB disease site are shown in Figure 5.

Determinants of antituberculosis treatment completion

For the analysis of treatment completion, the five patients transferred to another center were excluded because their final outcomes were unavailable. Treatment was completed by 41/56 Italian-

born PWT (73.2%) and 54/103 non-Italian-born PWT (52.4%; $p = 0.011$). In univariable analyses, treatment completion was less frequent among patients with chronic liver disease (p = 0.007), particularly among those with chronic HBV infection (p = 0.004). Patients with pulmonary TB, with or without lymph node involvement, also had a lower probability of treatment completion (p = 0.008), particularly those with radiological evidence of pulmonary consolidation (p = 0.041) or cavitation (p = 0.012).

Conversely, treatment completion was more frequent among patients with autoimmune or autoinflammatory diseases (p = 0.028) and among those with osteoarticular TB (p = 0.017).

In a multivariable model adjusted for death and for the variables showing significant associations with treatment completion in univariable analyses, only non-Italian birth was independently associated with a lower likelihood of antituberculosis treatment completion (AOR 0.260; 95% CI, 0.106–0.641; p = 0.003).

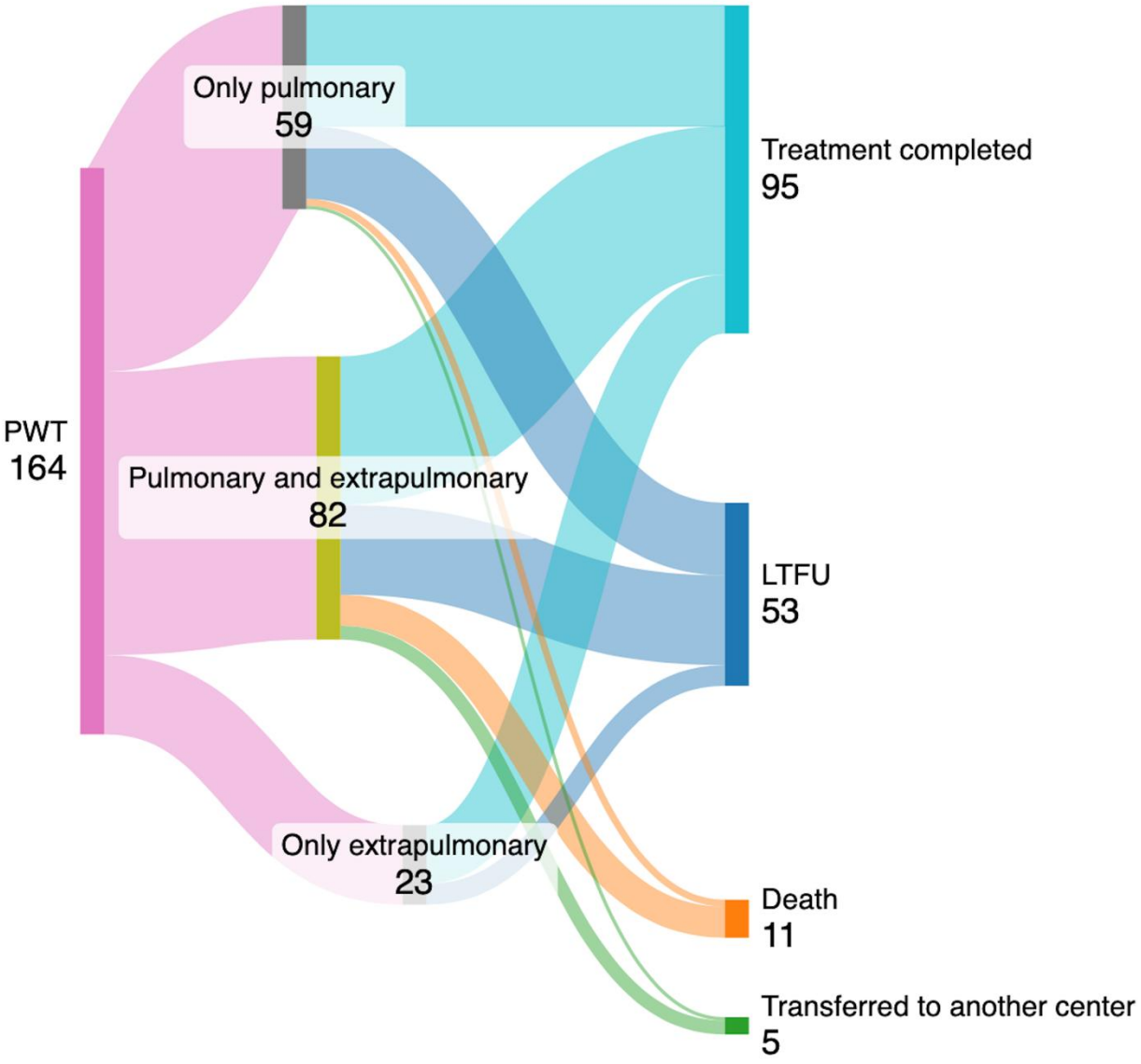


Figure 5. Distribution of treatment outcomes among patients with pulmonary, extrapulmonary, and combined pulmonary and extrapulmonary TB, including treatment completion, loss to follow-up, transfer to another treatment center, and death.

Discussion

This retrospective study provides a real-world overview of the clinical presentation, diagnosis, treatment, and outcomes of patients with TB managed at a tertiary referral center in Sicily. Among 164 patients managed at our tertiary referral center, TB accounted for more than 200 hospital admissions during the study period, underscoring its substantial healthcare burden.

Most patients were born outside Italy, predominantly in Africa, and were younger and had fewer comorbidities than Italian-born PWT, reflecting the changing epidemiology of TB in low-incidence European countries [9].

The cohort was characterized by substantial clinical and diagnostic complexity, including frequent extrapulmonary involvement, treatment-related toxicity, and use of second-line agents. Comorbidities and coinfections further complicated TB management. More than half of patients had at least one comorbidity, with cardiovascular disease, diabetes, chronic lung disease, and chronic kidney disease more frequent among Italian-born PWT, whereas HBV infection was more common among non-Italian-born patients. HBV coinfection is particularly relevant because prolonged exposure to potentially hepatotoxic antituberculosis drugs may increase the risk of treatment interruption or regimen modification.

HIV infection was identified in 4.9% of patients, without differences according to country of birth.

In the Italian TUBHIVIT study 1105 PWH were screened for latent TB infection using the QuantiFERON ® -TB Gold plus test, revealing a prevalence of 3.4% of positive results [10].

TB remains a major opportunistic infection in people with advanced HIV and is strongly influenced by cellular immunosuppression. Interestingly, among HIV-negative patients with available CD4+ T-cell counts, almost half had fewer than 500 cells/µL, and 12.5% had fewer than 200 cells/µL. This finding should be interpreted cautiously but it raises the possibility of clinically relevant CD4+ lymphopenia in a subset of patients with active TB. Larger prospective studies with serial CD4+ measurements would be required to determine whether this reflects disease-related immune dysregulation, disease severity, or pre-existing susceptibility.

Microbiological confirmation was obtained in approximately two-thirds of the cohort (64.6%), while the remaining cases were diagnosed on clinical and radiological grounds. This finding illustrates the diagnostic challenges encountered in routine practice, particularly in patients with

paucibacillary or extrapulmonary disease or in those unable to provide adequate respiratory specimens. The diagnostic yield varied according to specimen type and testing method, supporting the use of multiple complementary approaches and targeted sampling. Even in sputum, the principal respiratory specimen for pulmonary TB diagnosis, molecular testing was positive in only 60.6% of cases, favoring molecular testing of targeted biopsies and bronchoalveolar lavage, when initial investigations are negative. The absence of microbiological confirmation introduces diagnostic uncertainty and limits the ability to perform comprehensive drug susceptibility testing.

IGRA testing provided useful diagnostic support but could not replace microbiological assessment. Notably, 16 patients with a negative QuantiFERON ® -TB Gold result had microbiologically confirmed TB, reinforcing that IGRA positivity indicates *M. tuberculosis* infection rather than active disease, whereas a negative result does not exclude active TB, particularly in patients with severe disease or impaired cellular immunity. The CD4+ lymphopenia observed in some HIV-negative patients provides an intriguing potential biological context, although this hypothesis requires confirmation.

Nevertheless, detecting active disease before the development of typical symptoms may have important implications for both individual outcomes and TB control. Subclinical or paucisymptomatic TB was identified in 9.8% of patients and was more frequent among Italian-born patients and women, but only half of these cases were microbiologically confirmed. This observations are consistent with the increasingly recognized concept of TB as a spectrum extending from infection through incipient and subclinical disease to overt symptomatic TB [3]. A multicenter Italian study reported asymptomatic TB in 36.4 % of 510 patients with microbiologically confirmed TB diagnosed between 2018 and 2023 [11]. The lower proportion observed in our cohort may reflect differences in case definitions, referral pathways, screening practices, and study populations.

Microbiologically confirmed disease in minimally symptomatic individuals is epidemiologically relevant because these patients may remain undetected for prolonged periods, although their contribution to transmission could not be assessed in our study.

Pulmonary TB was the predominant presentation, but extrapulmonary involvement was also common. Women had a higher prevalence of extrapulmonary disease and fewer cavitary pulmonary lesions, suggesting possible sex-related differences in disease phenotype. Non-Italian-born patients significantly more frequently had osteoarticular involvement, predominantly vertebral disease. In our cohort, four patients required spinal surgery, illustrating the substantial morbidity, prolonged management, and multidisciplinary care that may be required for advanced osteoarticular TB.

Drug resistance represented an additional relevant concern. Molecular RIF resistance was detected in 7.6% of tested patients. Resistance to at least one tested drug (RIF, INH, EMB, PZA, or SM) was found in 34.0% of the 50 patients with available phenotypic drug susceptibility results, while six had resistance to multiple first-line agents. Although DST was available only for a subset of patients, these findings underscore the importance of rapid molecular resistance testing and comprehensive susceptibility assessment. No association between resistance patterns and country of birth was observed, suggesting that drug resistance in our population cannot be attributed exclusively to migration-related epidemiological factors.

Treatment was frequently complex: 17.7% of patients received second-line agents because of resistance, drug–drug interactions, toxicity, or disease severity. Adverse drug reactions occurred in 22.6%, predominantly hepatotoxicity, and required treatment interruption or modification in 35 patients. Adverse drug reactions were more frequent among Italian-born patients, likely reflecting their older age and greater comorbidity burden; in fact, this association was no longer significant after adjustment for LTFU and CCI.

Corticosteroids were administered to approximately one-fifth of patients, mainly for central nervous system involvement and paradoxical TB reactions. The latter are clinically relevant because disease

worsening during effective treatment may occur even in HIV-negative patients and should not automatically be interpreted as treatment failure. Corticosteroids were also used in a small number of patients with pleural or pericardial involvement, although evidence supporting their routine use in these settings remains limited.

The most concerning finding of our study was the high proportion of patients classified as LTFU. Although mortality was 6.7%, only 57.9% completed treatment, whereas 32.3% were LTFU. This treatment-completion rate is considerably lower than both the global treatment success reported for drug-susceptible TB (88% in 2024) and the treatment success reported through European surveillance [12]. In the European treatment cohort for 2024, treatment success was 64.2% in the EU/EEA, while 3.5% were reported as LTFU, although substantial inter-country variability existed [9].

The magnitude of LTFU in our cohort therefore represents a major programmatic concern. Treatment interruption may lead to clinical deterioration, preventable complications, continued transmission, and potentially the selection or amplification of drug resistance. The fact that 18 readmissions were directly related to TB, including complications and clinical deterioration following treatment interruption, further illustrates the clinical consequences of inadequate continuity of care.

The strongest finding of our study was that being born outside Italy was the only independent predictor of treatment non-completion. Non-Italian PWT had a markedly lower probability of completing treatment, and this association persisted after adjustment for death and other variables associated with treatment completion in univariable analysis (AOR, 0.260; 95% CI, 0.106–0.641; p = 0.003).

Our findings are consistent with previous Italian evidence suggesting that treatment outcomes remain particularly challenging among foreign-born populations in Italy [13], [14], [15]. In these studies, treatment success ranged from 49% to 57%, and elevated LTFU prevalence was observed.

In particular, Faustini et al. showed that LTFU was more frequent among foreign-born patients, while foreign birth was also associated with treatment failure [13]. Data from Milan similarly reported higher rates of LTFU and MDR-TB among migrants, whereas Italian-born patients had higher mortality and extrapulmonary disease [14]. More recently, Di Gennaro et al. reported that younger age, non-Italian nationality, homelessness, and diagnostic delay were associated with unsuccessful TB treatment outcomes in a cohort of 206 patients treated in Italy between 2013 and 2021 [15]. In another Italian study including 669 PWT, migrants face longer patient-related diagnostic delays (median 90 vs 10 days, $P < 0.0001$), suggesting that barriers may occur to healthcare access [16].

These observations, together with our findings, suggest that the challenges associated with migrant TB care have persisted despite substantial changes in TB diagnosis and treatment over time.

Importantly, foreign birth should not be interpreted as a biological determinant of treatment adherence. Rather, it is likely to act as a marker of a complex combination of social, economic, and healthcare-system factors.

Previous studies have identified socioeconomic vulnerability, limited education, homelessness, substance use, inadequate social support, difficulties accessing healthcare, undernutrition, and treatment-related adverse events among important determinants of unfavorable TB outcomes and LTFU [17], [18], [19], [20], [21], [22], [23].

In a large Brazilian cohort, Peetluk et al. developed a prediction model for unsuccessful TB treatment outcomes incorporating seven readily available baseline factors, including HIV infection, diabetes, drug use, age, education, tobacco use, and hemoglobin level [17]. Similarly, large observational cohorts have demonstrated that the determinants of LTFU differ from those associated with mortality, emphasizing the need to identify patients at risk of treatment discontinuation early during care [17], [18], [19], [20], [21], [22].

In our setting, some foreign-born patients referred to a tertiary center for diagnosis or treatment may have subsequently moved to other regions within Italy or to other European countries. Thus, some cases classified as LTFU may have continued treatment elsewhere without information being communicated and may represent failures in information continuity rather than definitive discontinuation of treatment. Nevertheless, from a clinical and public health perspective, the inability to document continued care remains a critical gap.

These findings support the development of dedicated networks for migrant TB care involving hospital-based TB units, territorial healthcare services, migrant health centers, public health authorities, and, when necessary, healthcare facilities in other regions or countries. Interventions should begin at treatment initiation and include systematic assessment of social vulnerability, culturally and linguistically appropriate counseling, active tracing after missed appointments, facilitation of medication access, and coordination of care when patients relocate. Housing and transportation support, social workers, community health workers, and digital systems allowing secure transfer of treatment information between healthcare facilities could further reduce LTFU. Such interventions should aim not only to improve adherence but also to ensure continuity of care across geographical and organizational boundaries.

More broadly, our findings support the concept of early risk stratification for unfavorable treatment outcomes. Prediction models and large observational cohorts have shown that clinical, hematological, behavioral, and socioeconomic variables can identify individuals at increased risk of LTFU, treatment failure, or death [17], [18], [19], [20], [21], [22], [24]. Rather than waiting for treatment interruption to occur, TB programs should use these characteristics to intensify follow-up and provide tailored adherence support from the beginning of therapy.

Overall, our study highlights that the major challenge of TB management in a low-incidence country is not limited to diagnosis and selection of an effective regimen.

Ensuring that patients remain engaged with healthcare services throughout treatment is equally important. The combination of a predominantly young and foreign-born population, substantial disease complexity, drug resistance, treatment-related toxicity, and particularly high LTFU highlights the need for a multidisciplinary and patient-centered model of TB care. In this context, strengthening continuity of care for migrant and socially vulnerable populations should be considered a central component of TB control strategies in Italy.

Limitations

This study has several limitations that should be acknowledged. First, its retrospective, single-center observational design limits the ability to establish causal relationships and may have introduced selection and information biases. Second, the study was conducted at a tertiary referral center, which may preferentially manage patients with more complex, severe, or disseminated forms of TB; therefore, our findings may not be fully generalizable to other healthcare settings or to the broader TB population in Italy. Third, microbiological confirmation was not available for all patients, as 58 cases were diagnosed on the basis of clinical and radiological findings, potentially limiting the microbiological characterization of the cohort. Similarly, phenotypic drug-susceptibility testing was available for only 50 patients, which may have resulted in an underestimation of the prevalence and patterns of drug resistance.

The substantial proportion of patients LTFU may have affected the assessment of treatment outcomes and introduced attrition bias, particularly because the clinical status and treatment completion of patients after loss to follow-up could not always be ascertained. Finally, the retrospective collection of treatment and follow-up data may have resulted in incomplete documentation of adherence, adverse events, and other potentially relevant clinical variables. Despite these limitations, the study provides a real-world description of TB epidemiology, clinical presentation, drug resistance, treatment management, and outcomes in a tertiary referral setting in

Sicily. In addition, follow-up duration was not uniform across participants, so the reported outcome frequencies should not be interpreted as estimates at a common fixed time point.

Conclusions

In this real-world cohort of patients with TB managed at a tertiary referral center in Sicily, disease presentation was heterogeneous and frequently complex, with a high proportion of patients showing concomitant pulmonary and extrapulmonary involvement, including a substantial burden of miliary and vertebral disease. Subclinical or paucisymptomatic TB accounted for nearly 10% of cases and was more frequently observed among Italian-born patients and women, highlighting the heterogeneous clinical spectrum of TB in this setting. Diagnosis was not always supported by microbiological confirmation, while drug resistance and treatment-related toxicity further contributed to the complexity of management.

The most relevant finding of this study was the high frequency of treatment non-completion: nearly one-third of patients were classified as LTFU, and only 57.9% completed treatment. Notably, non-Italian birth was independently associated with a lower likelihood of treatment completion, despite non-Italian-born patients being younger and having fewer comorbidities. This finding identifies continuity of care as a major challenge in this population and supports the need to better characterize and address the factors underlying LTFU among foreign-born patients with TB. In our setting, improving treatment completion may therefore be as important as optimizing diagnosis and antimicrobial management for achieving effective TB control.

Author contributions

LP: Conceptualization, Investigation, Data curation, Formal analysis, Writing – original draft, Writing – review & editing, Coordination of data collection. CVM: Investigation, Data curation. CC: Investigation, Data curation. DG: Investigation, Data curation. EB: Investigation, Data

curation. CG: Investigation, Data curation. AV: Investigation, Data curation. GD: Investigation, Data curation. LC: Investigation, Data curation. SU: Investigation, Data curation. RI: Investigation, Data curation. SDS: Investigation, Data curation. AB: Investigation, Data curation. FDF: Investigation, Data curation. SC: Investigation, Data curation. EM: Investigation, Data curation. GDA: Investigation, Data curation. SB: Visualization. PDC: Investigation, Data curation. GMG: Supervision, Writing – review & editing. AC: Conceptualization, Supervision, Writing – review & editing. CB: Conceptualization, Supervision, Writing – review & editing.

Clinical trial number: not applicable

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Ethics approval and consent to participate The study was approved by the the Ethics Committee "Palermo 1", Palermo Italy (Verbal n.11 – 22 December 2022). The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was waived because of the retrospective nature of the study and the anonymous of the data.

Consent for publication Not applicable.

Data availability Data will be made available upon request to corresponding author.

Conflict of interest The authors have no competing interests to declare that are relevant to the content of this article.

Abbreviation

AFB	Acid-fast bacilli
AOR	Adjusted odds ratio
CCI	Charlson Comorbidity Index
CI	Confidence interval
DST	Drug susceptibility testing
EMB	Ethambutol
EPTB	Extrapulmonary tuberculosis
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IGRA	Interferon-gamma release assay
INH	Isoniazid
IQR	Interquartile range
LTFU	Loss to follow-up
PZA	Pyrazinamide
RIF	Rifampicin
SD	Standard deviation
SM	Streptomycin
TB	Tuberculosis
XDR-TB	Extensively drug-resistant tuberculosis

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