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Original article

Hospitalizations for tuberculosis in Sicily over the years 2009–2021: Clinical features, comorbidities, and predictors of mortality

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ABSTRACT

Background: Very few data are available in the literature regarding tuberculosis (TB) hospitalization, and few studies have reported the clinical characteristics and comorbidities of admitted patients and burden and cost of hospitalization. In our study, we described the occurrence of TB hospital admissions in the southern Italian region of Sicily over 13 years (2009–2021), explored the characteristics of patients with TB, and determined the comorbidities associated with mortality.

Method: Data on the hospital discharge of all patients with TB hospitalized in all Sicilian hospitals were retrospectively collected from hospital standard discharge forms. Age, sex, nationality, length of hospital stay, comorbidities, and TB localization were evaluated using univariate analysis according to in-hospital mortality. The factors associated with mortality were included in the logistic regression model.

Results: In Sicily, 3745 people were hospitalized for TB, with 5239 admissions and 166 deaths from 2009 to 2021. Most hospitalizations involved Italian-born people (46.3%), followed by African-born people (32.8%) and Eastern European-born people (14.1%). The average hospitalization cost was EUR 5259 ± 2592, with a median length of stay of 16 days (interquartile range, 8–30) days. Multivariate analysis showed that the development of acute kidney failure (adjusted odds ratio [aOR]=7.2, $p < 0.001$), alcohol consumption (aOR=8.9, $p = 0.001$), malignant tumors (aOR=2.1, $p = 0.022$), human immunodeficiency virus infection (aOR=3.4, $p < 0.001$), sepsis (aOR=15.2, $p < 0.001$), central nervous system involvement (aOR=9.9, $p < 0.001$), and miliary TB (aOR=2.5, $p = 0.004$) were independent predictors of mortality.

Conclusion: TB in Sicily remains an important cause of hospitalization. HIV infection and comorbidities may complicate patient management and worsen patient outcomes.

Introduction

With 10.6 million new cases estimated by the World Health Organization (WHO) and 1.6 million deaths in 2021, tuberculosis (TB) is a worldwide health issue. Along with coronavirus disease 2019 (COVID-19) and human immunodeficiency virus (HIV) infection, TB is one of the most influential infectious diseases worldwide, and the 13th most notable cause of death [1]. Low- and middle-income countries are the most affected by TB, although numerous cases have been observed in Western countries. In fact, due to the migration of people from areas with high TB incidence, average age increase in the autochthonous population with latent TB reactivation, and cases of immunosuppression, especially cases of acquired immune deficiency syndrome or rheumatologic diseases, TB remains a crucial public health issue. Italy is considered a low TB incidence country, with an estimated 4000 new cases per year (< 10 per 100,000 inhabitants) and 7.5 new cases per 100,000 inhabitants from 2011 to 4 new cases per 100,000 inhabitants in 2020 [2].

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The number of TB cases remained steady until 2019 (6 per 100,000 inhabitants), with an average value of 3643 ± 277 per year. In 2020, 2287 cases were reported, with a remarkable reduction compared to the preceding years and yearly estimates [2]. The COVID-19 pandemic may explain these data [3]. Few studies have reported the clinical features and comorbidities of patients hospitalized for TB [4,5]. Due to the continued shift from communicable to non-communicable diseases and from premature deaths to years lived with disability, studies on the relationship between TB and non-communicable diseases are needed [6].

Sicily is the largest region in Italy and the fifth most populous, with a population of 4801,468 inhabitants (8.1% of the 58,983,122 Italian inhabitants). Hospitalizations in Sicily represent approximately 7% of national hospitalizations. The current study aimed to describe the occurrence of TB hospital admissions in the south-Italian region of Sicily over 13 years (2009–2021), explore TB population characteristics, and determine the comorbidities associated with mortality.

Methods

Data on the discharge forms of all patients with TB in all public and private Sicilian hospitals from January 2009 to September 2021 were retrospectively collected from hospital standard discharge forms (H-SDFs) and subsequently analyzed. H-SDF data was compiled by clinicians after discharge or patient death. All individuals with an International Classification of Diseases 9 (ICD-9) code identifying a TB diagnosis in the H-SDF were included in the study. Some patients were hospitalized for TB multiple times during the study period, and each hospitalization was considered separately. Whether the cause of hospitalization was related to a new tuberculosis episode or complications associated with the same tuberculosis episode was not available in the H-SDF.

The dataset includes up to six diagnoses. The following variables were assessed for each patient: age, sex, nationality, length of stay (LOS), death, main comorbidities, HIV, hepatitis B virus (HBV), and hepatitis C virus (HCV) coinfections, and TB organ involvement.

Admission costs were derived from reimbursements made by the Italian Health System to hospitals based on the diagnosis-related group.

As this computerized system is anonymous, according to the Italian Data Protection Authority, neither ethical committee approval nor informed consent was required. Regional health authorities routinely use anonymous data for epidemiological and administrative purposes. Demographic characteristics, comorbidities, coinfections, and organ localization were examined to evaluate their associations with mortality. Each repeated hospitalization was considered separately in the statistical analyses.

The hospitalization features of African and non-African patients were compared because Africans represent most non-Italian-born patients (NIBP) hospitalized for TB in Sicily. Sub-analyses of TB site involvement according to age (≤16 vs > 16 years), sex, and HIV infection were performed.

Statistical analysis

Continuous variables are summarized as mean ± standard deviation or median and interquartile range (IQR), whereas categorical variables are presented as absolute and relative frequencies. Annual trends for the number of TB cases among Italian-born (IBP) and NIBP were investigated using a linear regression model and estimates of unstandardized coefficients (ß) and their confidential intervals (95% CI).

Differences in means were evaluated using an unpaired Student's t-test or Mann-Whitney U test, and the χ^2 test was applied to categorical variables. Statistical significance was set at a p-value < 0.05.

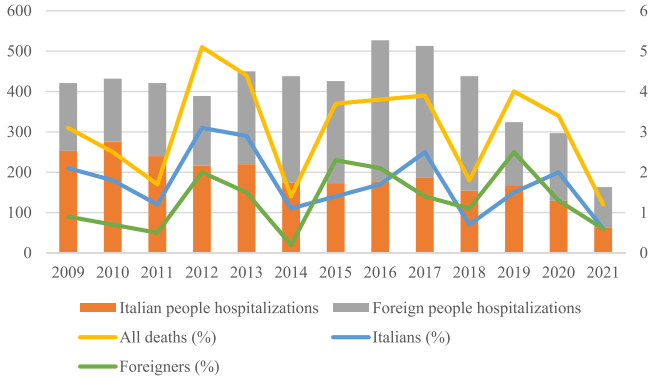

Fig. 1. Hospitalizations for TB (absolute frequency) and percentage of deaths among Italians and foreigners over the years (January 2009 to September 2021).

Crude odds ratios (cORs) and their 95% CI for the association between mortality and potential risk factors were calculated using univariate analysis. The adjusted OR (aOR) was calculated using logistic regression analysis to identify the factors independently associated with mortality. Only factors associated with mortality in the univariate analysis were included in the logistic regression analysis.

Spearman's correlation coefficient was computed to verify the existence of correlations among age, country of origin, positive microscopic examinations, and TB organ site involvement. Only statistically significant results were reported.

Results

In Sicily, 3745 patients were hospitalized for TB, with 5239 admissions and 166 deaths from 2009 to 2021 (Fig. 1).

The percentage of TB hospitalizations compared with hospitalizations for all causes (n = 5135,573) in Sicily did not show a statistically significant trend (p = 0.504) between 2011 and 2020 (Fig. 2). The TB hospitalization rate per 100,000 Sicily inhabitants presented an average of 8.4 ± 1.2 per 100,000 Sicily inhabitants (Fig. 2).

Most hospitalizations involved IBP (46.3%), followed by African-born people (32.8%), Eastern European-born people (14.1%), and Asian-born people (5.9%). African hospitalizations were mainly of people from Somalia (18.6%), Gambia (14.1%), Eritrea (10.5%), Senegal (9.1%), Morocco (8.1%), and Nigeria (6.6%). Eastern Europeans were mainly from Romania (88.1%), while Asians from Sri Lanka (31.0%), Bangladesh (28.7%), and Philippines (14.8%). The yearly percentage of TB hospitalizations among NIBP presented a progressive increase from 2009, with a peak in 2016 (67%). The trend of Africans' hospitalization had a number increase (ß=0.216; 95% CI: 0,02576,

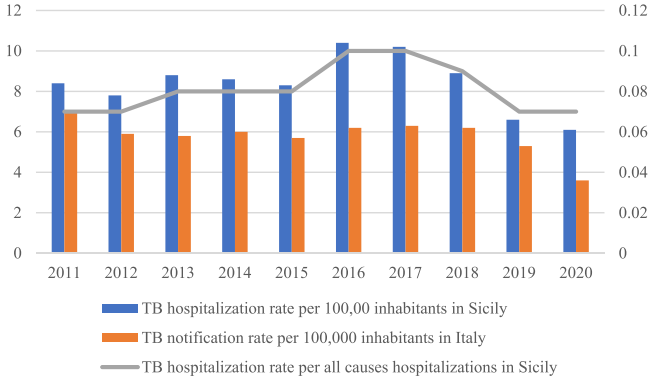

Fig. 2. TB hospitalization rate per 100,000 inhabitants in Sicily and TB notification rate in Italy (primary axis); TB hospitalization rate per all causes of hospitalization in Sicily (secondary axis) from 2011 to 2020.

Table 1
Demographic features, country of origin, comorbidities, coinfections, and TB localizations at univariate analysis for mortality.

Variables	All hospitalizations	Vital status at discharge		P value
		Alive	Dead	
	n: 5239	n: 5073	n: 166	
Demographics				
Age (average ± SD)	41.3 ± 21.3	40.8 ± 21.1	57.3 ± 20.6	**< 0.001**
Gender				
Male	3723 (71.1%)	3595 (70.9%)	128 (77.1%)	0.081
Female	1516 (28.9%)	1478 (29.1%)	38 (22.9%)	
Country (%)				
Africa	1719 (32.8%)	1690 (33.3%)	29 (17.5%)	**< 0.001**
Asia	310 (5.9%)	295 (5.8%)	15 (9.0%)	0.083
Eastern Europe	739 (14.1%)	718 (14.1%)	21 (12.6%)	0.584
North America	2 (< 0.1%)	2 (< 0.1%)	0 (0.0%)	0.798
Oceania	1 (< 0.1%)	1 (< 0.1%)	0 (0.0%)	0.856
Italy	2427 (46.3%)	2332 (46.0%)	95 (57.2%)	**0.004**
South and central America	16 (0.3%)	14 (0.3%)	2 (1.2%)	**0.033**
Western Europe (non-Italians)	24 (0.4%)	21 (0.4%)	3 (1.8%)	**0.009**
Comorbidities (%)				
Acute kidney failure	32 (0.6%)	23 (0.4%)	9 (5.4%)	**< 0.001**
Alcohol consumption	22 (0.4%)	18 (0.3%)	4 (2.4%)	**< 0.001**
Asma	12 (0.2%)	12 (0.2%)	0 (0.0%)	0.530
Cirrhosis	69 (1.3%)	66 (1.3%)	3 (1.8%)	0.573
Chronic obstructive pulmonary disease	316 (6.0%)	302 (5.9%)	14 (8.4%)	0.186
Chronic kidney disease	68 (1.3%)	64 (1.3%)	4 (2.4%)	0.198
Diabetes	326 (6.2%)	311 (6.1%)	15 (9.0%)	0.127
Dialysis	8 (0.15%)	7 (0.1%)	1 (0.6%)	0.132
Erythema nodosum	7 (0.1%)	7 (0.1%)	0 (0.0%)	0.632
Hematologic malignancies	55 (1.0%)	50 (1.0%)	5 (3.0%)	**0.011**
Intestinal bowel diseases	32 (0.6%)	30 (0.6%)	2 (1.2%)	0.318
Malign tumours	133 (2.5%)	120 (2.4%)	13 (7.8%)	**< 0.001**
Obesity	8 (0.15%)	8 (0.1%)	0 (0.0%)	0.609
Rheumatologic diseases	108 (2.1%)	104 (2.0%)	4 (2.4%)	0.748
Thrombosis	56 (1.1%)	50 (1.0%)	6 (3.6%)	**0.001**
Infections (%)				
HBV	77 (1.5%)	76 (1.5%)	1 (0.6%)	0.345
HCV	88 (1.7%)	84 (1.6%)	4 (2.4%)	0.457
HIV	150 (2.9%)	137 (2.7%)	13 (7.8%)	**< 0.001**
Sepsis	71 (1.3%)	48 (0.9%)	23 (13.8%)	**< 0.001**
TB Localizations (%)				
Bones and Joints	236 (4.5%)	229 (4.5%)	7 (4.2%)	0.856
CNS	123 (2.3%)	103 (2.0%)	20 (12.0%)	**< 0.001**
Digestive system	163 (3.1%)	156 (3.1%)	7 (4.2%)	0.404
Endocrine glands	4 (0.1%)	4 (0.1%)	0 (0.0%)	0.717
Eye	3 (< 0.1%)	3 (< 0.1%)	0 (0.0%)	0.754
Genitals	21 (0.4%)	21 (0.4%)	0 (0.0%)	0.406
Kidney	68 (1.3%)	67 (1.3%)	1 (0.6%)	0.421
Lungs	3926 (75.0%)	3800 (75.0%)	126 (76.0%)	0.770
Lymph nodes	426 (8.1%)	425 (8.4%)	1 (0.6%)	**< 0.001**
Miliary form	209 (4.0%)	194 (3.8%)	15 (9.0%)	**< 0.001**
Pleura	449 (8.6%)	444 (8.7%)	5 (3.0%)	**0.009**
Respiratory tract	112 (2.1%)	110 (2.2%)	2 (0.6%)	0.398
Skin	30 (0.6%)	30 (0.6%)	0 (0.0%)	0.320
Urinary tract	35 (0.7%)	34 (0.7%)	1 (0.6%)	0.916
Others	71 (1.3%)	69 (1.4%)	2 (1.2%)	0.865

0,03294; p < 0.001), while a reduction was observed among IBP (ß=−0.152; 95% CI: −0.02585, −0,01814; p < 0.001).

The median hospital LOS was 16 days (IQR, 8–30 days), without a statistically significant difference between surviving and deceased patients. A statistically significant difference was observed between the IBP and NIBP average LOSs (19 vs. 26 days, p < 0.001). A patient could be admitted up to eight times, with a total length of stay ranging from 2 to 348 days (median, 20 days; IQR, 10–37), and repeated hospitalizations were 1088, without significant statistical difference between IBP and NIBP (505 vs. 583, OR=1; 95% CI: 0.88–1.15; p = 0.360). The average hospitalization cost was EUR 5259±2592. Higher charges were observed in HIV patient hospitalizations (EUR, 8818±4224; p < 0.001), central nervous system (CNS) involvement (EUR, 8425±6022; p < 0.001), miliary form (EUR 5996±4010; p < 0.001), digestive system localization (EUR 5860±3786; p = 0.002), and osteoarticular localization (EUR 5660±3261; p = 0.0154).

Demographic characteristics, comorbidities, HBV, HCV, and HIV coinfections, and TB localization are reported in Table 1.

Spondylodiscitis was the common osteoarticular clinical presentation (80.5%, n = 190), and lung cavitary form was reported in 38.0% (n = 1493) of cases (n = 3926).

Eight admissions were related to childbirth, with the mothers demonstrating non-fatal events. Univariate analysis showed higher mortality in older patients and in patients with acute kidney failure, alcohol consumption, hematologic malignancies, malignant tumors, thrombotic events, HIV infection, sepsis, CNS involvement, and miliary TB. Africans showed lower mortality than did other populations (OR=0.4, 95% CI: 0.28–0.64; p < 0.001). Pleural involvement and lymph node TB were associated with low mortality risk. Subdivision into pulmonary (only lung involvement),

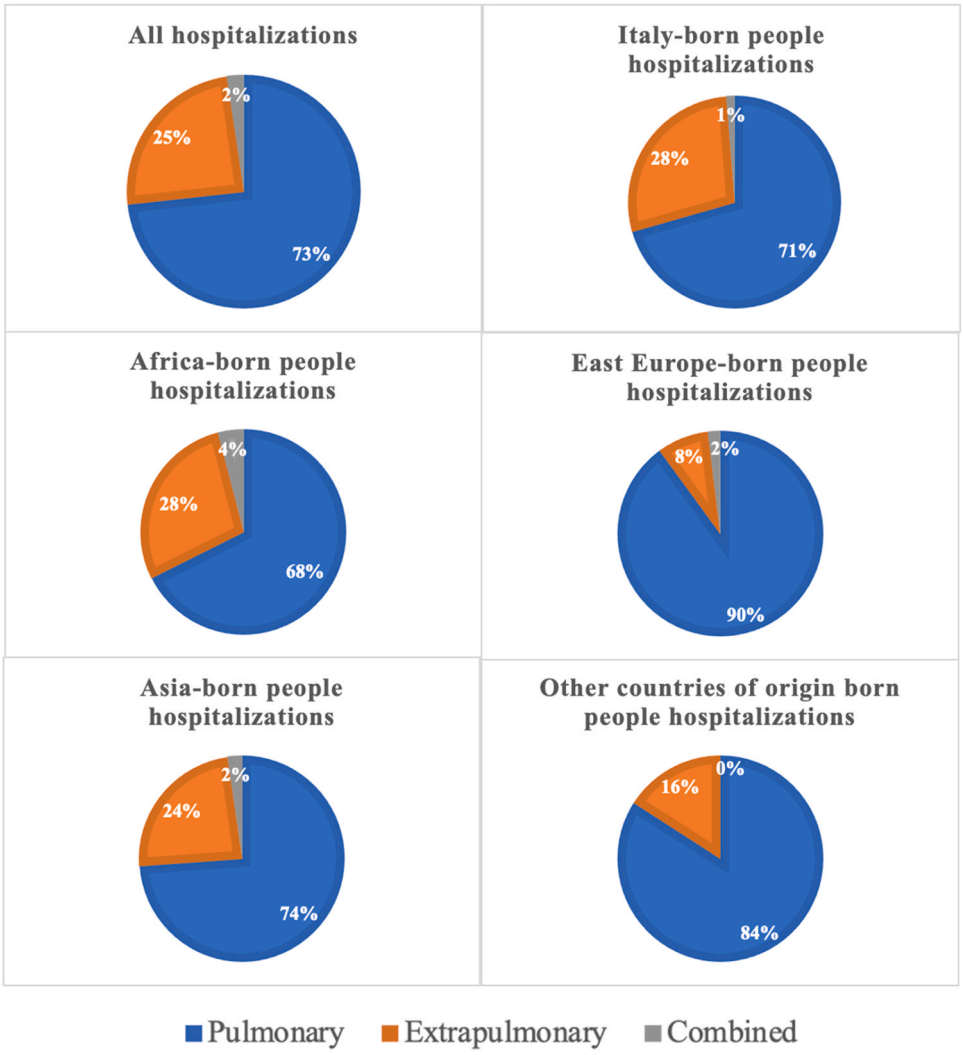

Fig. 3. Pulmonary, extrapulmonary or combined (pulmonary with other localizations except for the pleura and lymph nodes) TB according to country of origin.

extrapulmonary (non-lung involvement), and combined TB (lung and other localizations, except lymph nodes and pleura), according to the country of origin, is shown in Fig. 3. Combined TB was related to Africans' hospitalizations (OR=2.84; 95% CI:1.97–4.1, p < 0.001).

As shown in Table 2, multivariate analysis adjusted for age and significant comorbidities in the univariate analysis showed that age, development of acute kidney failure, alcohol consumption, malignant tumors, HIV infection, sepsis, CNS, and miliary TB were independent predictors of mortality in our population.

Table 2
Multivariable analysis and independent predictors of mortality in TB hospitalizations.

Variables	B	P value	aOR	95%CI for aOR	
				Lower	Upper
Age (years)		**< 0.001**	1.039	1.031	1.048
Acute kidney failure		**< 0.001**	7.222	3.033	17.196
Alcohol consumption		**0.001**	8.936	2.537	31.471
Hematologic malignancies		0.149	2.060	0.772	5.496
Malign tumours		**0.022**	2.105	1.113	3.984
Thrombosis		0.221	1.908	0.678	5.368
HIV infection		**< 0.001**	3.434	1.765	6.680
Sepsis		**< 0.001**	15.208	8.464	27.327
CNS		**< 0.001**	9.907	5.605	17.512
Miliary		**0.004**	2.504	1.351	4.640
Constant	-5.837	< 0.001			

Italy and Africa were the most prevalent countries of origin. The differences between African and non-African patient hospitalizations are shown in Table 3. Africans were younger, had fewer comorbidities, and had more frequent HBV and HIV coinfections. As compared with patients from other countries, people from Africa presented more frequently with osteoarticular TB (mainly spondylodiscitis, 80/92 vs. 110/144; OR=1.5; 95%. CI: 1.13–2.03; p = 0.005) and TB of the digestive system, lymph nodes, pleura, and miliary form. Non-African patients predominantly came from highly developed countries, and their hospitalizations were significantly associated with lung, kidney, and urinary tract TB localization compared with African hospitalizations.

Sub-analysis of age, sex, and HIV status (see Table 4) showed significant differences in TB localization between patients aged ≤ 16 and > 16 years, males and females, and HIV-positive and HIV-negative TB localizations. The percentage of miliary form and pleural, CNS, lymph node, and skin involvement was significantly higher in the pediatric population (≤16 years old), whereas patients aged > 16 years were more likely to have cavitary pulmonary form and renal localization. Cavitary forms and pleural involvement were more common in males, whereas females showed more frequent upper respiratory tract, CNS, lymph nodes, and renal TB localization. Females (average age, 40 ± 20 years) were younger than males (43 ± 22 years), with a p-value of < 0.001. The male/female ratio favored male hospitalization among all nationalities (all, 2.4;

Table 3
Difference between African and non-African patient hospitalizations for TB.

Variables	Hospitalizations		P value
	Africans	Non-Africans	
	n: 1719	n: 3520	
Demographics			
Age (average ± SD)	26.9 ± 11.4	48.3 ± 21.5	**< 0.001**
Gender			
Male	1476 (85.9%)	2247 (63.8%)	**< 0.001**
Female	243 (14.1%)	1273 (36.2%)	
Comorbidities (%)			
Acute kidney failure	8 (0.5%)	24 (0.7%)	0.345
Alcohol consumption	5 (0.3%)	17 (0.5%)	0.313
Asma	3 (0.2%)	9 (0.2%)	0.564
Cirrhosis	3 (0.2%)	66 (1.9%)	**< 0.001**
Chronic obstructive pulmonary disease	53 (3.1%)	263 (7.5%)	**< 0.001**
Chronic kidney disease	12 (9.7%)	56 (1.6%)	**0.007**
Diabetes	26 (1.5%)	300 (8.5%)	**< 0.001**
Dialysis	2 (0.1%)	6 (0.2%)	0.638
Erythema nodosum	0 (0.0%)	7 (0.2%)	0.064
Hematologic malignancies	9 (0.5%)	46 (1.3%)	**0.009**
Intestinal bowel diseases	3 (0.2%)	29 (0.8%)	**0.005**
Malign tumours	9 (0.5%)	124 (3.5%)	**< 0.001**
Obesity	0 (0.0%)	8 (0.2%)	**0.048**
Rheumatologic diseases	19 (1.1%)	89 (2.5%)	**< 0.001**
Thrombosis	14 (0.8%)	42 (1.2%)	0.211
Infections (%)			
HBV	55 (3.2%)	22 (0.6%)	**< 0.001**
HCV	19 (1.1%)	69 (1.9%)	**0.023**
HIV	88 (5.1%)	62 (1.8%)	**< 0.001**
Sepsis	26 (1.5%)	45 (1.3%)	0.491
Localizations TB (%)			
Bones and Joints	92 (5.3%)	144 (4.1%)	**0.039**
CNS	40 (2.3%)	83 (2.3%)	0.944
Digestive system	103 (6.0%)	60 (1.7%)	**< 0.001**
Endocrine glands	1 (< 0.1%)	3 (0.1%)	0.739
Eye	1 (< 0.1%)	2 (< 0.1%)	0.984
Genitals	9 (0.5%)	12 (0.3%)	0.325
Kidney	8 (0.5%)	60 (1.7%)	**< 0.001**
Lungs	1231 (71.6%)	2695 (76.6%)	**< 0.001**
Lymph nodes	226 (13.1%)	200 (5.7%)	**< 0.001**
Miliary form	94 (5.5%)	115 (3.3%)	**< 0.001**
Pleura	221 (12.8%)	228 (6.5%)	**< 0.001**
Respiratory tract	28 (1.6%)	84 (2.4%)	0.075
Skin	10 (0.6%)	20 (0.6%)	0.951
Urinary tract	1(< 0.1%)	34 (1.0%)	**< 0.001**

Italians, 1.8; Africans, 6.1; Eastern Europeans, 1.3; Asians, 3.7), except for Americans (0.4).

HIV-TB coinfection is associated with miliary form and CNS and lymph node involvement.

Laboratory TB diagnosis was reported in 52.2% of hospital discharge forms: a positive Ziehl Nielsen was reported 1619 times (31.0%), positive sample culture was reported 258 times (5.0%), positive histology was reported 309 times (6.0%), and another laboratory confirmed 587 cases (11.2%).

The Spearman coefficient showed a significant ($p < 0.001$) correlation between Eastern Europa-born-people hospitalizations with positive microscopic sputum (rho=0.14) and cavitary form (rho=0.14).

Discussion

Here, we describe the features of the admissions of patients with TB in Sicily. Most hospitalizations were for Italians and Africans, with male cases being more frequent. Older age, sepsis, HIV infection, alcohol consumption, malignant tumors, and acute kidney failure were independent predictors of mortality in our population. A few studies have explored trends in TB hospitalization in Italy and other developed countries, including those for characteristics and relative burden. According to our data, the TB hospitalization trend among NIBP increased over the years in Sicily. A previous epidemiological evaluation in Emilia Romagna (Italy) showed a more pronounced increase in TB hospitalizations among NIBP from 1996 to 2006 [4]. An Irish study showed 3158 cases of active TB between 2011 and 2020. Of these, 46.3% involved migrants [7], with a percentage similar to our results that showed approximately 54% of TB hospitalizations in Sicily for NIBP. A higher rate of migrants (69.3%) was found in an Italian study based on disease notification conducted in a large province in Northern Italy during 2004–2020, where Asian cases were the most reported [8]. However, the cited studies showed an overall reduction in TB cases, which conformed to the decline in admissions observed in our investigation in recent years.

The impact of COVID-19 on TB services resulted in a reduction in hospitalizations, as evidenced by the hospitalization trend, with a lower number of hospitalizations for TB in Sicily in 2020. Another study supported this finding and highlighted that deaths due to TB were higher in 2020 than in 2019 in most countries [3,8]. However, in Sicily, TB-related mortality was approximately stationary in the

Table 4
Significant statistical result ($p < 0.005$) of a sub-analysis of TB localization according to age, sex, and HIV status.

Variables	Age ≤ **16**years (n = 393)	Age > 16 years (n = 4846)	OR (95%CI)	p
Male	255 (64.9%)	3468 (71.6%)	0.734 (0.591, 0.912)	0.005
Dead	2 (0.50%)	164 (3.4%)	0.146 (0.036, 0.591)	0.002
Miliary form	24 (6.1%)	185 (3.8%)	1.639 (1.057, 2.540)	0.026
Cavitary form	34 (8.6%)	1459 (30.1%)	0.220 (0.154, 0.314)	< 0.001
Lung	274 (69.7%)	3652 (75.4%)	0.753 (0.601, 0.943)	0.013
Pleura	49 (12.5%)	400 (8.2%)	1.583 (1.154, 2.172)	0.004
CNS	18 (4.6%)	105 (2.2%)	2.167 (1.300, 3.613)	0.002
Lymph nodes	43 (11.0%)	383 (8.0%)	1.432 (1.026, 1.998)	0.034
Kidney	0 (0%)	68 (1.4%)	NA	0.018
Skin	6 (1.5%)	24 (0.5%)	3.115 (1.266, 7.666)	0.009
	Male (n = 3723)	**Female (n = 1516)**	**OR (95%CI)**	**p**
Lung	2858 (76.8%)	1068 (70.4%)	1.386 (1.212, 1.585)	< 0.001
Cavitary form	1117 (30.0%)	376 (24.8%)	1.300 (1.134, 1.489)	< 0.001
Respiratory tract	70 (1.9%)	42 (2.8%)	0.673 (0.457, 0.991)	0.043
Pleura	357 (9.6%)	92 (6.1%)	1.642 (1.295, 2.081)	< 0.001
CNS	73 (2.0%)	50 (3.3%)	0.586 (0.407, 0.845)	0.004
Lymph nodes	282 (7.6%)	144 (9.5%)	0.781 (0.633, 0.964)	0.021
Kidney	37 (1.0%)	31 (2.0%)	0.481 (0.297, 0.778)	0.002
	Non-HIV patient admissions (5089)	**HIV patient admissions (n = 150)**	**OR (95%CI)**	**p**
Miliary form	187 (3.7%)	22 (14.7%)	4.506 (2.801, 7.247)	< 0.001
CNS	114 (2.24%)	9 (6.0%)	2.786 (1.385, 5.604)	0.003
Lymph nodes	404 (7.9%)	22 (14.7%)	1.993 (1.254, 3.169)	0.003

same biennium. Despite a reduction in hospitalizations, TB is expensive for the healthcare system. In our analysis, the median LOS was 16 days (IQR, 8–30), which is slightly lower than the results of a review that showed an LOS of newly diagnosed TB cases of 20–60 days in Europe [9].

The hospitalization rate per 100,000 inhabitants in Sicily was higher than the TB notification rate in Italy (Fig. 2). Considering that our data did not report information on outpatients with TB, we can conclude that the actual Sicilian TB burden is greater than that of Italy. This can be explained by migratory flows from Africa, which peaked in 2016 [10].

No data on TB-related rehospitalization have been reported in the literature. Italian data published by the European Center for Disease Control do not distinguish between new TB cases and relapses [2]. Our data on rehospitalization do not fully reflect any TB recurrence, as this is not specified in the ICD-9 diagnoses of H-SDF. However, we found that 21% of hospital admissions were rehospitalizations, suggesting that TB is a disease with high complexity and an elevated likelihood of relapse, probably due to low compliance with a long course of therapy, toxicities, or drug interactions.

A previous cross-sectional study based on discharge data from the United States showed an increase in the average charges from 1998 to 2014, although there was a steady decrease in the number of pulmonary and extrapulmonary TB hospitalizations. Similar to our study, miliary TB and TB of the meninges have been associated with increased mortality and higher costs [11]. In addition to the costs, TB patient management requires isolation in negative-pressure rooms and lengthier hospital stays, as derived from the time necessary to obtain negative sputum, permitting the patient to be readmitted to the community. Furthermore, directly observing therapy is often required due to the low compliance of some patients; blood examinations are needed for the early recognition of adverse hepatic or renal events, especially in elderly patients, and for the evaluation of drug-drug interactions.

HIV coinfection and comorbidities may complicate patient management and worsen outcomes; people living with HIV have significantly higher mortality and healthcare costs.

Our study highlights the role of alcohol consumption, malignant tumors, and HIV infection in determining poor outcomes in patients with TB. Similar findings were reported in another study, in which malnutrition, socioeconomic deprivation, diabetes, silicosis, tobacco abuse, alcohol consumption, HIV infection, and other chronic illnesses or immunosuppressive therapies increased susceptibility to disease and mortality, making patient management more challenging [6,11–14].

Italians were older and had more comorbidities than Africans were. In an aging population, it is essential to evaluate the relationship between noncommunicable diseases and TB. Therefore, a holistic approach is necessary. Among non-communicable illnesses, diabetes mellitus has been studied as a determinant of complications and treatment failure during TB. Diabetic patients have a greater risk of developing new TB infections or reactivation due to poor glycemic control, resulting in immunodeficiency due to altered macrophage and lymphocyte activity [6,14,15]. In our study, 6.2% of patients were diabetic (6.1% alive vs. 9% dead), though diabetes was not significantly associated with mortality.

However, a limitation of our study is that up to six diagnoses may be included in the H-SDF, and some secondary comorbidities such as alcohol consumption and tobacco abuse could not be reported.

Tao et al., in a Chinese retrospective cohort study of patients with pulmonary TB, by univariate and multivariable analysis, demonstrated that comorbidity was significantly associated with drug-resistant TB, especially diabetes and chronic obstructive pulmonary disease [16]. Our investigation lacked antibiogram data, and we did not hypothesize the risk of drug-resistant TB and comorbidities. Notably, a significant proportion of our population comprised patients from Eastern Europe, which is associated with a high burden of multidrug-resistant TB [17]. Our study found a correlation between Western European and cavitary pulmonary bacilli populations. Elevated attention is necessary in these cases, considering the risk of diffusion of drug-resistant mycobacteria.

Our findings revealed differences in TB organ involvement, second only to the country of origin. Significant statistical differences were observed for the osteoarticular and digestive systems, lymph nodes, pleural involvement, and miliary forms, which were associated with African admissions. Instead, renal and urinary tract involvement was associated with non-African patients. Africans present a greater burden of HIV and HBV coinfection, emphasizing the importance of screening in this population.

A sub-analysis of the pediatric population (≤16 years), sex, and HIV status was also conducted. In our study population, miliary forms and CNS involvement were more common in children and people with HIV. This association is probably related to lower immune system efficiency in these subgroups. Females also presented a significant association with renal and CNS TB, the former likely due to their older age compared to males. To the best of our knowledge, very few data have been published in the literature, and our study adds information on the topics addressed.

In conclusion, TB is a major health concern in Sicily. The TB hospitalization burden is linked to both migratory flow and autochthonous cases. The lengthening of life expectancy and development of immunosuppressive therapy have led to TB case management in patients with numerous comorbidities. Non-African patients had the highest prevalence of comorbid conditions, consistent with an increase in age, which may impair defense against TB. This places the clinician in front of the interactions between noncommunicable diseases and tuberculosis, making patient management more complex. We believe that integration of TB care with management strategies for non-communicable diseases is necessary, and further studies are needed to investigate the interactions between comorbidities and TB and develop predictive models for mortality risk in this population.

Limits of the study

This study is subject to limitations related to the use of TB and comorbidity ICD-9 code administrative data. Consequently, TB types and comorbidities may be underreported. H-SDF was compiled by clinicians after the discharge or death of a patient, and up to six diagnoses were included. Thus, some comorbidities or TB localization may not have been reported. Furthermore, the result of the sample culture needs 1–2 months, and the data may be incomplete because the results could be unavailable at the time of discharge.

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Declaration of Competing Interest

We have no conflict of interest to declare.

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