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Original Article

Extrapulmonary tuberculosis among immigrants in a low-TB burden and high immigrant receiving city of northern Italy

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Abstract

Introduction: The constantly increasing immigration flows are influencing tuberculosis (TB) epidemiology in several European countries as well as in Italy. Extrapulmonary tuberculosis (EPTB) incidence rate is not decreasing and, among immigrants, it occurs in a remarkable number of cases. This study aimed to provide further insights regarding EPTB among natives and immigrants in a low TB burden and high immigrant receiving setting.

Methodology: A total of 217 TB cases admitted to the University-Hospital of Ferrara from 2009 through 2015 were enrolled in the study. Clinical and demographical data including age, gender, origin, single comorbidities such as HIV status, chronic viral disease, chronic lung disease, diabetes, neoplasm, and multimorbidity were analyzed.

Results: Of the 217 cases enrolled, 60.0% were immigrants and 40.0% natives, 68.7% presented pulmonary TB and 31.3% EPTB. By binary logistic regression, we observed that female gender (O.R. (95% C.I.): 1.95 (1.08-3.50), $p < 0.05$), Asian origin (5.70 (2.00-16.24), $p < 0.001$) and multimorbidity (6.42 (2.37-17.41), $p < 0.001$) were significantly associated to the development of EPTB compared to PTB. Nodal TB was the most common site of reactivation (56.5% among immigrants and 27.3% among natives).

Conclusions: The data we found could be useful in increasing EPTB medical suspicion and decreasing EPTB diagnostic delay in low TB burden and high immigrant receiving settings.

Key words: extrapulmonary tuberculosis; immigrant; gender; ethnicity; comorbidity.

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Introduction

Tuberculosis (TB) is one of the most important communicable disease worldwide; most of TB cases are reported in Asia and sub-Saharan Africa [1]. Europe is a low burden region and its TB incidence rate is decreasing [1], although the proportion of immigrant TB cases is increasing [1]. Italy and Emilia-Romagna (ER), a region of Northern Italy, recorded the same pattern of data [2,3]. Worldwide, most of TB cases are pulmonary (PTB), while extrapulmonary (EPTB) accounts for a minor part [1]. However, in Europe the proportion of EPTB cases increased from 16.4% in 2002 to 22.4% in 2011 and most of these were immigrants [4]. EPTB is reported to occur more often among women [4-7], HIV positive subjects [8] and immigrants [4,5,9]. Moreover, the site of EPTB reactivation seems to associate with the country or geographical area of origin, as shown by immigrants from Pakistan who were more susceptible to develop nodal TB [5].

EPTB is not responsible for TB transmission, but it contributes to its burden. However, it does not receive specific attention in international control strategies.

Diagnosis of EPTB is often delayed or even missed due to insidious clinical presentation that hinders differential diagnosis, and poor performance of diagnostic tests, including culture, which suffers from increased technical and logistical restrictions especially for EPTB cases.

This study aimed to analyze the EPTB characteristics among natives and immigrants in a city of Northern Italy, Ferrara, between the years 2009 and 2015 with special regard to age, gender, subjects' origin and concomitant comorbidities.

Methodology

Patients Recruitment and Definitions

The present study is an epidemiological retrospective analysis, where we evaluated 217 adult TB patients, aged 18 or more, 130 immigrants and 87 natives, admitted to the University-Hospital of Ferrara, a city of Northern Italy settled in ER region, from January 1, 2009 through December 31, 2015.

ER and Ferrara are a low TB burden and high immigrant receiving settings; in this period, 8.37% of Ferrara's population was represented by immigrants, who mainly come from Romania, Morocco, Ukraine and Pakistan [10] and TB incidence rate in Ferrara was considerably higher (10 cases per 100.000 inhabitants) when compared to the national one (5.6 cases per 100.000) [2].

Demographic data on immigrant population in Ferrara's province were acquired from the local report on immigration [10]. Data on TB cases were collected from chart reviews and the hospital discharge forms.

We used the definitions and categories provided in the ECDC/WHO report TB surveillance and monitoring in Europe 2015.

Pulmonary TB (PTB) was defined as TB affecting the lung; EPTB has been used to describe the isolated occurrence of TB at body sites other than the lung, including pleura, intra-thoracic lymphatic, extrathoracic lymphatic, spine, bone/joint other than spine, meninges, central nervous system other than meninges, genitourinary (GU) tract, gastrointestinal (GI) system, disseminated and other TB. TB affecting the lung and concurrent EPTB was considered a PTB case [2]. All TB cases, confirmed, probable or possible, were included in the study. According to these criteria, 149 subjects were affected by PTB whereas 68 subjects presented EPTB.

Of the 217 studied subjects, we recorded age, gender, comorbidities, and the site of disease. We reported as comorbidity every chronic disease that affected the patient. In particular, we recorded the presence of diabetes, neoplasm, chronic lung disease (CLD), chronic viral hepatitis (CVH), and HIV infection.

Multimorbidity was intended as the presence of two or more comorbidities. Patients were classified as natives or immigrants according to place of birth. All immigrant TB cases, regular and irregular, were included in the study.

Immigrants were divided into 6 different groups according to the place of birth: Europe (Ukraine, Moldova, Romania, Bulgaria, Turkey, Albania and the countries of the former Yugoslavia), Asia (Pakistan, Thailand, China), North Africa (Morocco, Libya, Algeria), Sub-Saharan Africa (Cameroon, Ghana, Senegal, Nigeria), America (Dominican Republic), Oceania (Philippines, Indonesia).

Each patient was included once. If a patient was admitted with TB more than once from January 1, 2009, through December 31, 2015, only information from the first registration was included.

Statistics

Pearson's Chi-square test was used to analyze differences in proportions between groups. Mann-Whitney U-test was performed to compare mean age of different groups. To examine the association between EPTB development and the possible risk factors such as gender, native or immigrant status, subjects' origin, presence or absence of one or more than one comorbidity (multimorbidity), different single comorbidities, univariate and multivariate logistic regression analyses were performed, by including age as covariate. As a further measure of association, the excess risk fraction (ERF) was calculated. Since Relative Risk and Odds Ratio showed a large difference, excess risk fraction (ERF) was calculated from RR by using the formula: $[(RR-1)/RR] \cdot 100$ as previously stated [11]. The ERF has been suggested as an alternative to attributable risk when the causality has not firmly established. Percent population attributable risk was calculated from the formula: $[Pe \cdot (RR-1)/Pe \cdot (RR-1) + 1] \cdot 100$, where Pe represented the prevalence of exposure, as previously reported [11].

For each analysis, a p value of $p < 0.05$ was considered statistically significant.

Ethical standards

Written informed consent was given by all patients before inclusion. All registries with patient identification information were handled in a confidential manner and in accordance with the Italian law 196/2003 on the protection of personal character data.

Results

Patients characteristics

The characteristics of the patients enrolled in the study are summarized in Table 1.

Among the patients affected by TB (68.7% PTB and 31.3% EPTB cases), 60% (n = 130) were immigrants and 40% (n = 87) were natives. Immigrants were mainly from Europe (44 subjects, 30 of which from Romania), Asia (37 subjects, 31 of which from Pakistan), North Africa (26 subjects, 22 of which from Morocco), and

Sub-Saharan Africa (n = 20), whereas only few patients were from America (n = 2) and Oceania (n = 1). According to WHO definition, 45/130 (34.6%) TB immigrant cases came from high TB burden countries [1], whereas 120/130 (92.3%) were from high TB incidence rate countries (TB incidence rate > 40/100000). Immigrants (mean age 36.4 years, range: 18-86) were younger than natives (mean age 62.5 years, range: 22-94; $p < 0.001$).

Of the 68 EPTB cases, the most frequent sites of EPTB were lymph node, followed by GI tract, bone, pleura, GU tract and meninges. The different EPTB sites are summarized in Table 2.

Comparing the frequencies of EPTB localization between natives and immigrants, we did not find any statistical significant difference ($\chi^2(6) = 11.544$, $p = 0.073$). The same was observed when immigrants were divided in groups (origin) according to the place of birth (Europe, Asia, North Africa, Sub-Saharan Africa, America, Oceania) $\chi^2(36) = 31.248$, $p = 0.694$).

Gender data

Of the 217 TB cases enrolled, 116 were males (73 immigrant and 43 native males), 101 females (57 immigrant and 44 native females). No significant difference between men and women mean age was found when stratified by PTB or EPTB (PTB: 46.5 ± 17.9 and 49.2 ± 19.8 years for males and females, respectively; EPTB: 41.6 ± 20.5 and 48.2 ± 19.9 years for males and females, respectively). When we compared the percentages of women and men within the EPTB and PTB groups, we found statistically significant differences ($\chi^2(1) = 4.651$, $p < 0.05$) among women, in whom EPTB was more frequent than in men (57.4% vs. 42.6%, $p < 0.05$) whereas PTB was more frequent in men than women (58.4% vs. 41.6%, $p < 0.05$). No difference was found between male and female in the distribution of EPTB sites ($\chi^2(6) = 11.521$, $p = 0.074$). Gender data are reported in Table 1, 2 and 3.

Prevalence of comorbidities among natives, immigrants, PTB and EPTB cases

Analyzing the absence or presence of single comorbidities or multimorbidity between natives and immigrants, we found a significant difference in the frequencies ($\chi^2(2) = 69.003$, $p < 0.001$) with natives who were characterized by higher presence of single comoribidy and multimorbidity than immigrants ($p < 0.05$ for both comparisons), whereas the last were mainly without comorbidities (Table 1, 66.2% vs. 10.3%, $p < 0.05$).

Within the single comorbidities, there were no statistically significant differences between natives and immigrants regarding diabetes, CLD and neoplasm, whereas CVH and HIV seropositive status were more frequently associated with immigrant population ($p < 0.05$). On the contrary, other minor comorbidities were more frequent among natives than immigrants ($p < 0.05$).

When patients affected by EPTB or PTB were compared for the presence of one comorbidity,

Table 1. Comorbidity and multimorbidity among natives and immigrants, EPTB and PTB cases.

	All patients n. (%)			All patients n. (%)			Natives n. (%)			Immigrants n. (%)		
	Natives n. (%)	Immigrants n. (%)	p Value	PTB	EPTB	p value	PTB	EPTB	p Value	PTB	EPTB	p Value
Total	87(40.0)	130 (60.0)	-	149 (68.7)	68 (31.3)	-	65(74.7)	22(25.3)	-	84 (64.6)	46 (35.4)	-
Gender (Female; Male)	44; 43 (50.6; 49.4)	57; 73 (43.8; 56.2)	-	62; 87 (41.6; 58.4)	39; 29 (57.4; 42.6)	p < 0.05	30; 35 (46.2; 53.8)	14; 8 (63.6; 36.4)	-	32; 52 (38.1; 61.9)	25; 21 (54.3: 45.7)	-
Single comorbidities	50 (57.5)	35 (26.9)	p < 0.01	67 (45.0)	18 (26.5)	p < 0.01	45 (69.2)	5 (22.7)	p < 0.01	22 (26.2)	13 (28.3)	-
Diabetes	5 (10.0)	1 (2.9)	-	5 (7.5)	1 (5.6)	-	4 (8.9)	1 (20.0)	-	1 (4.5)	0 (0.0)	-
CVH	4 (8.0)	10 (28.6)	p < 0.05	11 (16.4)	3 (16.7)	-	4 (8.9)	0 (0.0)	-	7 (31.8)	3 (23.1)	-
CLD	4 (8.0)	5 (14.3)	-	8 (11.9)	1 (5.6)	-	4 (8.9)	0 (0.0)	-	4 (18.2)	1 (7.7)	-
Neoplasm	4 (8.0)	2 (5.7)	-	8 (61.5)	5 (38.4)	-	4 (8.9)	0 (0.0)	-	2 (9.1)	0 (0.0)	-
HIV status	1 (2.0)	6 (17.1)	p < 0.05	4 (6)	3 (16.7)	-	1 (2.2)	0 (0.0)	-	3 (13.3)	3 (23.1)	-
Other	32 (64.0)	11 (31.4)	p < 0.05	33 (49.3)	10 (55.6)	-	28 (62.2)	4 (80.0)	-	5 (22.7)	6 (46.2)	-
Multimorbidity	28 (32.2)	9 (6.9)	p < 0.01	15 (10.1)	22 (32.4)	p < 0.01	11 (16.9)	17 (77.3)	p < 0.01	4 (4.8)	5 (10.9)	-
N. comorbidies	9 (10.3)	86 (66.2)	p < 0.01	67 (45.0)	28 (41.2)	-	9 (13.8)	0 (0.0)	-	58 (69.0)	28 (60.9)	-

EPTB: extrapulmonary tuberculosis; PTB: pulmonary tuberculosis; CVH: chronic viral hepatitis; CLD: chronic lung disease n.: number; -: not statistically significant.

Table 2. Sites of EPTB in all patients,and among natives and immigrants according to place of birth.

Site of EPTB	All patients n. (%) Male (%), Female (%)	Natives n. (%) Male (%), Female (%)	Immigrants n. (%) Male (%), Female (%)
Node	32 (47.1) 12 (37.5), 20 (62.5)	6 (27.3) 2 (33.3), 4 (66.7)	26 (56.5) 10 (38.5), 16 (61.5)
GI	10 (14.7) 2 (20.0), 8 (80.0)	3 (13.6) 0 (0.0), 3 (100.0)	7 (15.2) 2 (28.6), 5 (71.4)
GU	3 (4.4) 2 (66.7), 1 (33.3)	1 (4.5) 1 (100.0), 0 (0.0)	2 (4.3) 1 (50.0), 1 (50.0)
Bone	8 (11.8) 6 (75.0), 2 (25.0)	6 (27.3) 4 (66.7), 2 (33.3)	2 (4.3) 2 (100.0), 0 (0.0.)
Pleura	7 (10.3) 4 (57.1), 3 (42.9)	3 (13.6) 1 (33.3), 2 (66.7)	4 (8.7) 3 (75.0), 1 (25.0)
Meninges	2 (2.9) 2 (100.0), 0 (0.0)	0 (0)	2 (4.3) 2 (100.0), 0 (0.0)
Other	6 (8.8) 1 (16.7), 5 (83.3)	3 (13.6) 0 (0.0), 3 (100.0)	3 (6.5) 1 (33.3), 2 (66.7)
Total	**68 (100)**	**22 (100)**	**46 (100)**

EPTB: extrapulmonary tuberculosis; GI: gastro-intestinal; GU genito-urinary; n.: number.

multimorbidity or its absence, we observed that patients with PTB were more frequently affected by single comorbidities than EPTB cases (Table 1, All patients, PTB/EPTB stratification, $p < 0.01$). However, there were no differences considering the various single comorbidities between the two groups ($\chi^2(5) = 4.314$, $p = 0.505$). Conversely, multimorbidity was more frequent in EPTB than PTB cases (Table 1; $p < 0.01$).

Finally, analyzing the patients who developed PTB or EPTB by subjects' origin, we found that Asians developed more frequently EPTB (Table 1; 59.6% vs. 40.5, $p < 0.01$) whereas Europeans, PTB (88.6% vs. 7.4%, $p < 0.01$). The other groups did not show any difference in the frequencies of PTB or EPTB cases.

Identification of risk factors for the development of EPTB

To identify possible risk factors for the development of EPTB over PTB, gender (male/female), immigrant status (native/immigrant), place of birth (Italy/Asia/North-Africa/Sub-Saharan Africa/Europe), comorbidity status (no/one/multiple) and presence of one comorbidity (absence/hepatitis/diabetes/HIV status/CLD/Others) were employed in logistic regression models corrected for age as confounding factor. After adjustment for age, we observed that female gender was moderately associated with the development of EPTB (O.R. (95% C.I.): 1.95 (1.08-3.50), $p < 0.05$), whereas Asian origin (O.R.: 5.70 (2.00-16.24), $p < 0.001$) and the presence of multiple comorbidities (O.R.: 6.42 (2.37-17.41), $p < 0.001$) were strongly associated with the development of EPTB compared to PTB. The different degree of association between the development of EPTB and gender, Asian origin and multimorbidity also resulted evident from the calculation of the ERF (Table 3).

Indeed, we observed a high ERF (> 50%) for both multimorbidity and Asian origin, with the last being more strongly associated with the development of EPTB. On the other hand, the female gender was mildly associated with EPTB, as evidenced by the low ERF (Table 2, 35.3%). Finally, the Asian showed the highest population attributable risk (28.73%) followed by multimorbidity (22.19%) and female gender (20.22%) suggesting that, although to a low extent and not well

Table 3. Calculated Relative Risk and estimated excess risk fraction (ERF) for the development of EPTB over PTB.

	Calculated relative risk (95% CI)	Estimated ERF % (95% CI)	Population exposure (%)	Population attributable risk (%)
Gender: Female *(reference: Male)*	**1.54 (1.03-2.30)**	35.3 (3.2-67.3)	46.54	20.22
Nationality: Asian *(reference: Native)*	**2.35 (1.50-3.68)**	57.5 (26.5-88.4)	29.84	28.73
Comorbidities: Multimorbidity *(reference: No comorbidity)*	**2.01 (1.34-3.03)**	50.4 (19.4-81.4)	28.03	22.19

For the calculations or the relative risks, the control categories were considered as gender: male, nationality: native, comorbidities: No comorbidity. ERF: Excess Risk Fraction; CI: Confidence Interval.

defined, all these factors can concur to the increased susceptibility to develop EPTB.

Discussion

The present study is an epidemiological retrospective analysis of EPTB characteristics among immigrant and native cases in a city of Northern Italy. It includes approximately a complete sampling of all active TB cases hospitalized in Ferrara, over a period of six years.

The experience reported in this article showed that a relevant portion of TB cases in immigrants (35.4%) were EPTB. Since TB screening protocol of newly arrived immigrants is mainly performed with chest X Ray, a considerable part of immigrant TB cases, even if not communicable cases, might be missed by chest X ray-based TB screening.

The results obtained in our work suggest that three risk factors could concur to develop an EPTB phenotype: female gender, multimorbidity and Asian origin.

Of all the three analyzed factors, the one that showed the strongest association with EPTB was the Asian origin. A specific role of geographical origin in the occurrence of EPTB has already been suggested [3,5,6]. For example, Yang *et al.*, found that American Indians and Asians/Pacific Islanders presented an increased risk for EPTB compared with non-Hispanic white subjects [8]. Moreover, a recent study showed that ethnicity was a stronger determinant of TB phenotype rather than M. tuberculosis lineage; in this regard, Afro-Caribbeans and subjects from the Indian subcontinent presented a stronger association with EPTB [12].

Therefore, in our study, we found that a specific geographical origin (Asians) represented a strong and statistical significant risk factor for EPTB, more than the immigrant status itself ($p = 0.073$).

Multimorbidity has never been described as a risk factor for EPTB, although it is well known that EPTB cases occur more frequently among immunocompromised patients [5]. To explain our finding, we might assume that the sum of several underlying diseases could be the cause or the consequence of an impaired immune status, and this could contribute to an increased risk of EPTB.

When we analyzed each comorbidity individually (diabetes, neoplasm, CLD, CVH, HIV infection), we did not find any association with PTB or EPTB, although in European studies diabetes is reported to have a modest association with EPTB [13,14].

HIV infection and CVH did not associate with EPTB in our study, although in literature HIV seropositivity and liver cirrhosis are considered risk factors for EPTB [6,8,15]. This difference could be partly due to the lack of analysis on the severity of both diseases.

In our study, female gender was another risk factor associated with EPTB. A gender difference in the development of PTB or EPTB has already been reported [5,8, 16]. Certain studies showed that female gender was a risk factor for EPTB [8], whereas other studies conducted in different geographical regions (Nepal, Turkey and South America) reported a majority of EPTB cases among males [17-19].

Thus, besides gender, the geographical origin of TB cases may contribute to the differences in EPTB epidemiology and clinical presentation [5,12,20-22]. The fact that data suggested a role of subjects' origin in TB development could be linked to genetic factors related to the host, or to the bacteria (tubercular lineages), or both [12,23,24].

Furthermore, we did not find any association between age and TB phenotype, although certain studies showed an increased risk of EPTB among younger patients [3,15].

Finally, we did analyze the epidemiological characteristics of different EPTB sites. Node was found to be the most common extrapulmonary site involved. This is in line with some studies [15,25] and in contrast with others [6,9,16] that found bone/joint or GI system and skin the sites more frequently involved [7,16]. These studies were done in different geographic areas, suggesting again the role of particular subject origin in the site of EPTB reactivation. So far, nodal TB was reported as a typical EPTB site of reactivation among non-Caucasian subjects, especially those coming from Asia [5,8,20, 22].

The present study confirmed that Asian immigrants, which in our series came mainly from Pakistan, developed mostly nodal TB. Meninges were found to be the less involved EPTB sites, the two cases registered, occurred among Pakistani patients. Interestingly, a study from Pakistan reported meningeal TB as the third most common EPTB site after nodal and bone TB [20], whereas in other countries, meningeal TB was one of the less common EPTB sites [2,10], as we found.

We have tried to give insight into EPTB, a disease difficult to diagnose for the insidious clinical characteristics, but also for the epidemiological ones. Indeed, it frequently involves socially marginalized populations as women and immigrants.

In Ferrara's province, immigrants from Asia region, in particular from Pakistan, represent a significant and increasing subgroup of the immigrant population.

The present findings add new and important epidemiological features that should be considered in local TB epidemiology and in differential diagnosis with other diseases.

A limitation of our study is the lack of data regarding social and economic condition, M. tuberculosis lineages, drug resistance and treatment outcomes. However, owing to the retrospective design, these data could not be fully achieved from medical files.

Another limitation of our study was that data concerning the mode of diagnosis (patients diagnosed through an active TB screening protocol or passively), the diagnostic delay, the time of arrival in Italy for immigrants, the Tuberculin Skin test (TST) and Interferon-Gamma Release Assay (IGRA) results were incomplete or not available from chart reviews and hospital delivery forms.

Conclusion

To the best of our knowledge there are few studies describing EPTB characteristics among immigrants and natives in Northern Italy. In our study, Asian origin, female gender and multimorbidity were associated with EPTB, and nodal TB was the most common site of reactivation.

We have tried to give insight into EPTB, a disease difficult to diagnose for the insidious clinical characteristics, but also for the epidemiological ones. Indeed, it frequently involves socially marginalized populations as women and immigrants. In Ferrara's province, immigrants from Asia region, in particular from Pakistan, represent a significant and increasing subgroup of the immigrant population.

Therefore, the present findings add to the TB epidemiology and the differential diagnosis with other diseases.

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