Pulmonary Versus Extrapulmonary Tuberculosis Associated Factors: A Case-Case Study

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ABSTRACT

BACKGROUND: Tuberculosis (TB) incidence remains low in health departments of Castellon and La Plana-Vila-real, but TB elimination is challenging. The objective of this study was to estimate associated factors of pulmonary tuberculosis (PTB) compared with extrapulmonary tuberculosis (ETB) and investigate epidemiological characteristics of these pathologies to orient control and prevention actions.

MATERIALS AND METHODS: A prospective case-case study was implemented by comparing PTB and ETB incidences during 2013-2016 from notification reports, epidemiological surveillance, and microbiological results of hospitals' laboratories Hospital General Castellon and La Plana-Vila-Real in the province of Castellon of Valencia region in Spain. In this design, cases were patients with PTB and controls were patients with ETB. Directed acyclic graph approach was used for selection of potential risk and confounding factors. Adjusted odds ratios (AORs) were estimated by logistic regression models.

RESULTS: The study included 136 patients with PTB and 57 patients with ETB, with microbiological confirmation of 93.4% and 52.6%, and the annual median of incidence rates were 7.5 and 3.1 per 100 000 inhabitants, respectively. In general, patients with PTB were younger with higher male proportion than patients with ETB. Risk factors of PTB were smoking tobacco (AOR = 3.98; 95% confidence interval [CI] = 1.66-9.56), social problems (social marginalization, homeless, residence in shelters for the poor, or stay in prison) (AOR = 3.39; 95% CI = 1.05-10.94), and contact with patients with TB (AOR = 2.51; 95% CI = 1.06-5.95). No-smoking tobacco and no-drug abuse interaction decrease PTB risk (AOR = 0.27; 95% CI = 0.12-0.64). From these results, specific measures of health promotion and prevention can be addressed.

CONCLUSIONS: The estimated associated factors of PTB may be prevented, and it was demonstrated that the case-case design is useful in the study of TB.

KEYWORDS: tuberculosis, pulmonary, extrapulmonary, smoking, social class, social problems

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Introduction

Tuberculosis (TB) incidence is maintained in low levels in health departments of Castellon (DSC) and La Plana-Vila-Real (DSLP) with a median incidence rate of 10.2 per 100 000 inhabitants during 2013-2016 and similar to median incidence rate of Spain in the same period, 10.7 per 100 000 inhabitants.[1] However, TB elimination is challenging. It is frequent to find patients with TB, whose disease is very difficult to control because these patients are often marginalized and homeless. In addition, an increase in extrapulmonary tuberculosis (ETB) has occurred in past years, and its cause is not well known.[2]

In Spain, crucial changes in the epidemiology of TB have taken place, including a decrease in TB associated with HIV and an increase in immigrant people from countries with high TB endemicity.[3] There is an interest to study risk factors of pulmonary tuberculosis (PTB) and ETB,[2,4] and there are a few studies on the comparison of these pathologies in recent years in Spain and occidental countries.[5–7] Our study may improve the knowledge of TB epidemiology to detect new aspects, principally of ETB, and may serve to develop specific measures of TB control and prevention.

In this context, the aims of this study were to find associated factors with PTB incidence by comparison with ETB incidence, to describe epidemiological characteristics of these pathologies with the identification of high-risk groups, and to evaluate the case-case design.

Material and Methods

An incident prospective case-case design was carried out with TB reported cases in DSC and DSLP during the period 2013-2016. Tuberculosis cases were diagnosed and reported by physicians, in private and public sectors, and by epidemiological

surveillance, which contains all microbiological results of laboratories of public hospitals in the 2 health departments (General Hospital of Castellon and Hospital of La Plana-Vila-Real) in the province of Castellon in Valencia region (Spain) with 473 000 inhabitants.

The case definition of TB case was based on the following criteria[8]:

- TB clinical case was a patient who presents signs, symptoms, or radiological features compatible with active TB in any location, plus a medical decision of administration of a completed cycle of anti-tuberculosis medication, or patient death with pathological results of necropsy compatible with active TB, and who would have required anti-tuberculosis treatment.
- TB confirmed case was based on the isolation of *Mycobacterium tuberculosis* (*M tuberculosis*) complex in a culture of clinical samples or detection of nucleic acid of *M tuberculosis* complex in a clinical sample jointed smear-positive acid-fast bacilli (AFB) by optical or fluorescent microscopy. Tuberculosis probable case had one of the following criteria: positive smear-positive AFB by optical or fluorescent microscopy, detection of nucleic acid *M tuberculosis* complex in a clinical sample or granulomas in pathological studies.
- The International Classification of Diseases 10th Revision[9] was used to define PTB, excluding pleural TB and miliary TB. Extrapulmonary tuberculosis can affect any localization, except pulmonary, including pleural, and lymphatic when there are no intra-thorax lesion of pulmonary parenchyma.
- With regard to TB report, it was considered TB confirmed if the patient meets the criteria of laboratory confirmed case, and TB probable if the patient meets clinical criteria and/or laboratory criteria of probable cases. When a patient with TB suffers pulmonary and extrapulmonary affectation at the same time, PTB was reported.

Case-case design is a variant of a case-control study, which is used in transmissible and non-transmissible diseases.[10] In this design, controls are patients with the same disease that case patients have, but they present differences in some aspects, such as clinical and molecular variations of an infectious agent, potential risk factors, or tuberculosis multidrug resistance.[11] This study followed a methodology comparable with a case-control design, where patients with PTB were cases and patients with ETB were controls.

A medical staff of the Epidemiology Division of Public Health Center of Castellon conducted an interview of each patient with PTB or ETB. With the same questionnaire, the following items were collected:

- Demographic data: birthplace, age, gender, residence, origin, occupation, and time living in Spain for foreign people.
- Clinical and epidemiological data: symptoms, TB type, laboratory results, Mantoux test or interferon-gamma release assays (IGRAs), smear studies, *Mycobacteria* cultures, radiographic and pathology studies, treatments, strain resistances, and patient evolution.
- Associated diseases, including alcoholism, tobacco abuse, HIV co-infection, drug abuse, cancer, diabetes mellitus, and other diseases.
- Risk factors of TB: social marginalization, homeless, residence in shelters for the poor, immigrants from TB endemic zone, stay in prison, life in a nursing home and other closed collectives, and health staff. Social problems included patients with a positive answer for any of the following variables: social marginalization, homeless, residence in a shelter for the poor, and/or stay in prison.

Statistical Methods

Characteristics of patients with PTB and ETB were studied by frequency and distribution measures. In a univariate analysis, patients with PTB and ETB were compared with non-parametric statistical tests, including chi-square and Fisher exact tests for qualitative variables, and Kruskal-Wallis test for quantitative variables. In the case-case study, logistic regression was used to estimate the effect of potential risk factors on TBP by odds ratio (OR) with 95% confidence interval (CI). After a review of TB epidemiology, a selection of potential risk and confounding factors was carried out following directed acyclic graph (DAG) approach.[12–14] Logistic regression models were used and adjusted odds ratio (AOR) of each factor was presented. Characteristics of risk factors were considered in interaction study, and it was implemented by stratification. Only one interaction was found smoking tobacco and drug abuse, and to avoid zeros in denominators, no-smoking tobacco with no-drug abuse interaction was studied. All models presented an acceptable goodness of fit following Hosmer-Lemeshow test with 10 groups. Stata version14[15] was used in the statistical analysis and DAGitty version 3.0[16] in DAG implementation (Figures 1 to 6).

Data of this investigation come from the epidemiological surveillance of transmissible diseases, because TB is a disease with obligatory report in Spain. The study was approved by the health authority of the DSC and DSLP, and all information was collected from the archives of Epidemiology Division at the Public Heal Center of Castellon.

Results

During 2013-2016, in the departments of DSC and DSP, 194 TB cases were reported, 136 cases were PTB, and 58 cases were ETB. The annual medians of incidence rates per 100 000 inhabitants were 7.5 for PTB and 3.1 for ETB. The study included 136 PTB cases and 57 ETB cases, because a reported ETB case in 2014 suffered a reactivation in 2016. The follow-up rate was 98.5% for PTB, and 100% for ETB, with loss of 2 patients in the PTB group.

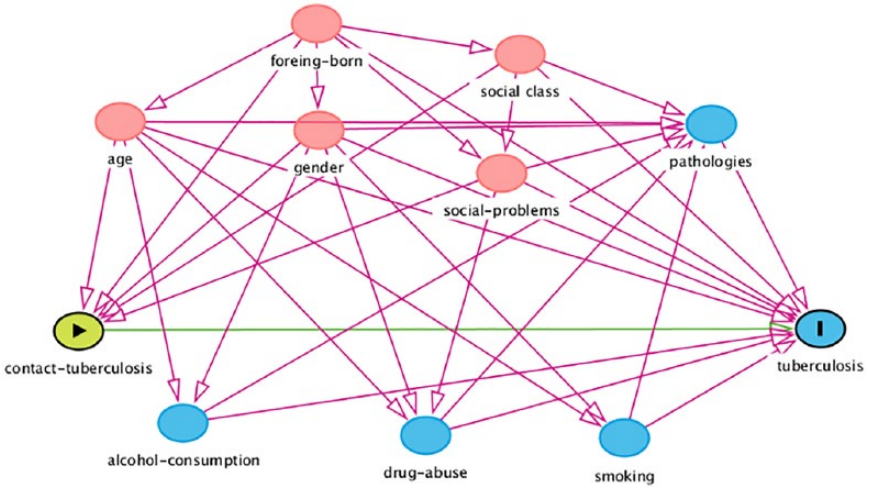

Figure 1. Directed acyclic graph for the association between contact with patients with TB (exposure) and tuberculosis (outcome). Red color variables indicate ancestors of the exposure and blue ancestors of exposure and outcome. DAGitty version 3.0.

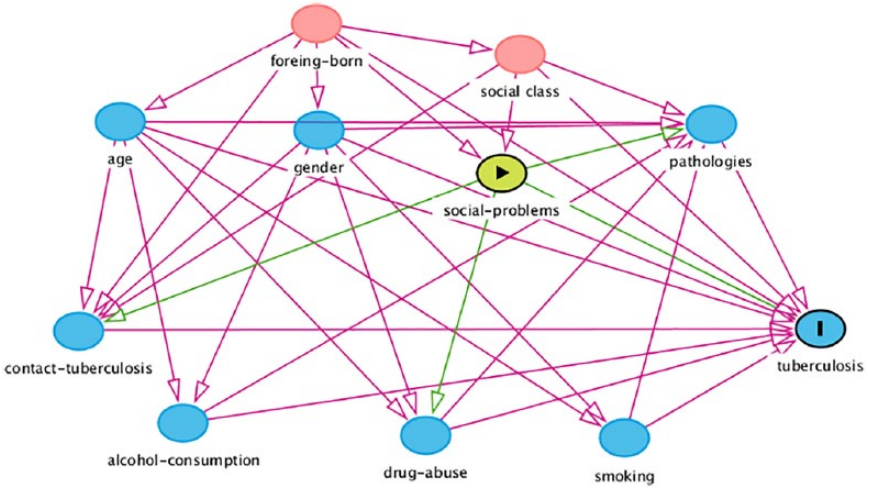

Figure 2. Directed acyclic graph for the association between social problems (exposure) and tuberculosis (outcome). Red color variables indicate ancestors of the exposure and blue ancestors of exposure and outcome. DAGitty version 3.0.

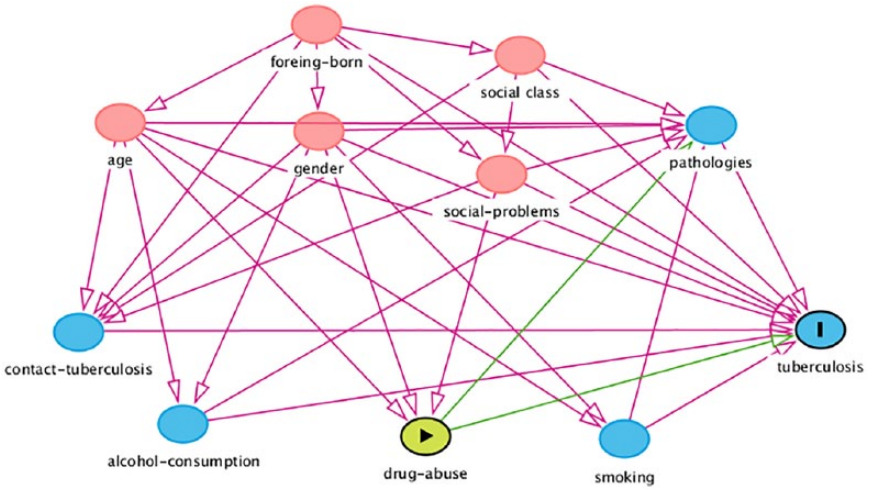

Figure 3. Directed acyclic graph for the association between drugs abuse (exposure) and tuberculosis (outcome). Red color variables indicate ancestors of the exposure and blue ancestors of exposure and outcome. DAGitty version 3.0.

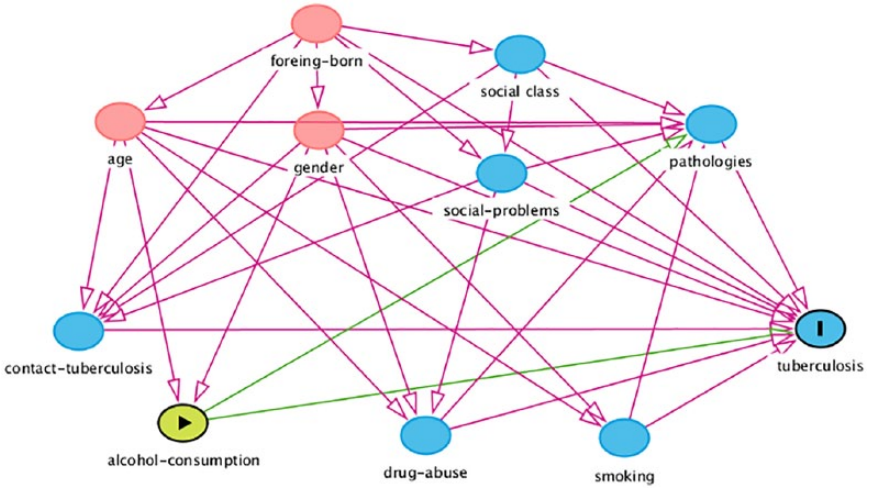

Figure 4. Directed acyclic graph for the association between alcohol consumption (exposure) and tuberculosis (outcome). Red color variables indicate ancestors of the exposure and blue ancestors of exposure and outcome. DAGitty version 3.0.

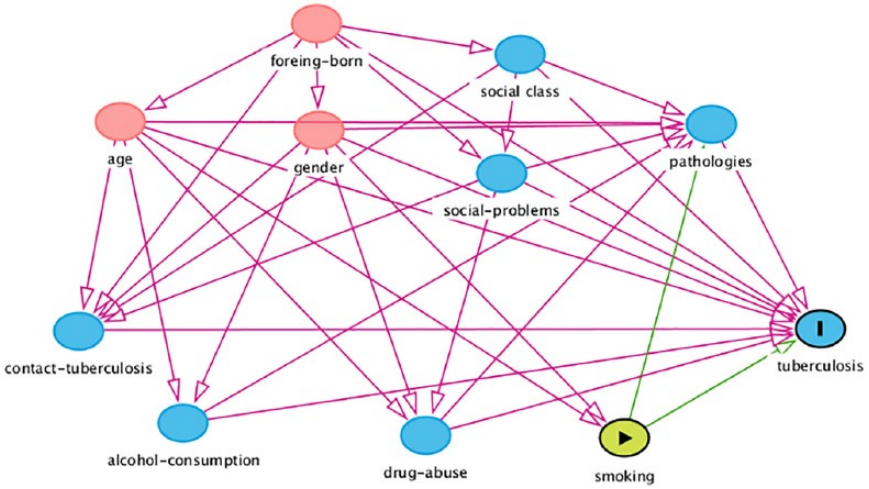

Figure 5. Directed acyclic graph for the association between smoking tobacco (exposure) and tuberculosis (outcome). Red color variables indicate ancestors of the exposure and blue ancestors of exposure and outcome. DAGitty version 3.0.

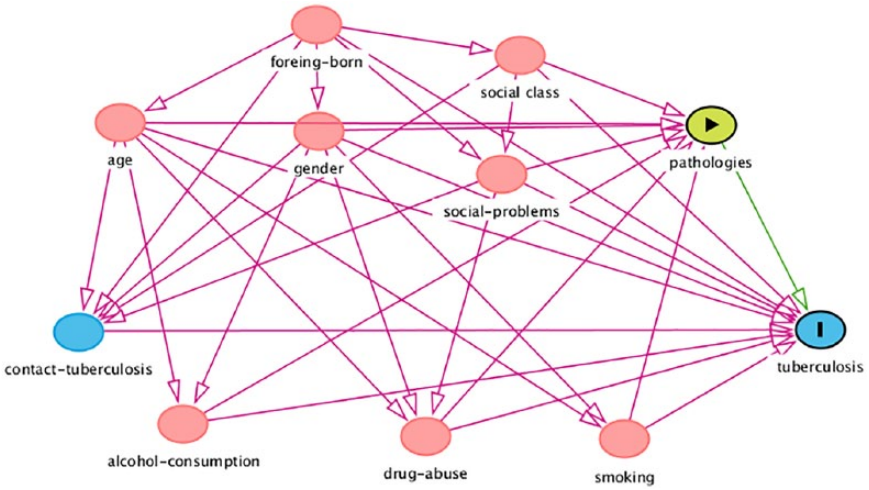

Figure 6. Directed acyclic graph for the association between pathologies (exposure) and tuberculosis (outcome). Red color variables indicate ancestors of the exposure and blue ancestors of exposure and outcome. DAGitty version 3.0.

Table 1. Characteristic of pulmonary tuberculosis (PTB) compared with extrapulmonary tuberculosis (ETB) in the health departments of Castellon and La Plana-Vila-real during 2013-2016.

VARIABLES	PTB N = 136 N (%)	ETB N = 57 N (%)	*P*-VALUE
Health department of Castellon	103 (75.7)	44 (77.2)	
Health department La Plana-Vila-real	33 (24.3)	13 (22.8)	1.000
Gender male	89 (65.4)	31 (54.4)	
Gender female	47 (34.6)	26 (45.6)	.193
Age groups, y			
0-4	5 (3.7)	3 (5.3)	
5-14	4 (2.9)	1 (1.8)	
15-24	14 (10.3)	7 (12.3)	
25-44	55 (40.4)	13 (22.8)	
45-64	38 (27.9)	14 (24.6)	
⩾65	20 (14.7)	19 (33.3)	.041
Mean age (y) ± standard deviation	43.2 ± 20.1	48.5 ± 23.8	.138
Birthplace			
Spain	76 (55.9)	36 (63.2)	
Eastern Europe[a]	34 (25.0)	8 (14.0)	
Maghreb countries[b]	16 (11.8)	11 (19.3)	
Other countries	10 (7.4)	2 (3.5)	.170
Residence city >50 000 inhabitants	76 (55.9)	30 (52.6)	
Residence town 5000-49 000 inhabitants	51 (37.5)	20 (35.7)	
Residence village <5000 inhabitants	9 (6.6)	7 (12.2)	.442
Residence in nursing homes	9 (6.6)	2 (3.4)	.522
Residence in shelters for the poor	10 (7.3)	2 (3.4)	.515
Social class			
I Professional occupations	1 (0.7)	4 (7.0)	
II Managerial and technical occupations	6 (4.4)	4 (7.0)	
III Skilled non-manual occupations	10 (7.4)	8 (14.0)	
IV Skilled manual occupations	15 (11.0)	2 (3.4)	
V Partly skilled occupations	27 (19.9)	12 (21.1)	
VI Unskilled occupations	77 (56.6)	27 (47.4)	.061

[a]Eastern Europe (Romania and Bulgaria).
[b]Maghreb (Morocco and Algeria).

Demographic characteristics of patients with TB are shown in Table 1. No differences by health departments were found, but PTB presented higher incidence in cities with more than 50 000 inhabitants. In contrast, ETB had higher incidence in villages with less than 5000 inhabitants. In PTB, male/female proportion was higher than in ETB. With respect to age distribution, differences were found ($P = 0.041$). The 25- to 44-year-old group presented high incidence of PTB and 65 years and more group high incidence of ETB. Mean age was higher in patients with ETB. Pulmonary tuberculosis or ETB was not associated with birthplace; however, PTB incidence was predominant among Eastern Europe patients and ETB

Table 2. Results of confirmatory tests, *Mycobacterium tuberculosis* antibiotic resistances, and outcome of pulmonary tuberculosis (PTB) and extrapulmonary tuberculosis (ETB) in health departments of Castellon and La Plana-Vila-real during 2013-2016.

VARIABLES	PTB N = 136 POSITIVE N (%)	ETB N = 57 POSITIVE N (%)
Radiology (Thorax, abdomen, bone, etc)	135 (99.3)	27 (47.4)[a]
Laboratory tests		
AFB+[b]	96 (70.6)[c]	6 (10.5)
M tuberculosis culture+	117 (86.0)[d]	27 (47.4)[e]
AFB+ *M tuberculosis* culture+	86 (63.2)	5 (8.8)
AFB+ *M tuberculosis*–	9 (6.6)	0
AFB–[a] *M tuberculosis* culture+	31 (22.8)	22 (38.6)
AFB–[a] *M tuberculosis* culture–	8 (5.9)	22 (38.6)
AFB+ *M tuberculosis* (did not)	1 (0.7)	1 (1.8)
AFB– *M tuberculosis* (did not)	0	7 (12.3)
AFB and *M tuberculosis* (both did not)	1 (0.7)	0
PCR[f] of *M tuberculosis*+ N = 65 samples: 46 samples+	30 (22.1%)	16 (28.1)
Pleural fluid ADA[g] > 50 UI/L n = 17 samples+	2 (1.5)	15 (26.3)
Pathology + N = 25 samples+	9 (6.6)	16 (28.1)
PCR of *M tuberculosis*+ only	0	2 (3.5)
Pleural fluid ADA > 50 UI/L alone	0	8 (14.0)
Pathology + only	1 (0.7)	6 (10.5)
PCR[b] of *M tuberculosis*+ and Pathology + alone	0	1 (1.8)
Pleural fluid ADA[c] > 50 UI/L and Pathology + alone	0	1 (1.8)
M tuberculosis antibiotic resistances		
Isoniazid	9 (6.6)	2 (3.6)
Rifampicin	0	0
Multidrug-resistance (MR)	1 (0.7)	0
Outcome		
Loss of follow-up	2 (1.5)	0
Cure	122 (89.7)	50 (87.7)
Death by tuberculosis	0	3 (5.3)
Death by other causes	12 (8.8)	4 (7.0)

[a]One case not done.
[b]Acid-fast bacilli.
[c]One case not done.
[d]Two cases not done.
[e]Eight cases not done.
[f]Polymerase chain reaction.
[g]Adenosine deaminase.

among Maghreb patients. Unskilled occupations were the social class more affected ($P = .061$); it comprises 56.2% of PTB and 48.2% of ETB cases, respectively.

Clinical presentations of ETB were the following: pleural 18 cases (31.5%), lymphatic 17 cases (29.8%), genitourinary 5 cases (8.8%), miliary 5 cases (8.8%), bone and joints 3 cases

(5.3%) meningeal-brain 3 cases (5.3%), digestive 3 cases (3.3%), disseminated 1 case (1.8%), lupus erythematosus 1 case (1.8%), and pericardial 1 case (1.8%).

The PTB and ETB are compared with respect to diagnostic tests, antibiotic resistances, and patients' outcome (Table 2). Radiology was positive in 99.3% of PTB and 47.5% of ETB. Pulmonary tuberculosis was confirmed by microbiology in 93.4% of patients, and ETB in only 52.6%. Pathology was positive in 28.1% of patients with ETB, *M tuberculosis* polymerase chain reaction (PCR) was positive in 28.1% of patients with ETB, and ADA test in 26.3%. Considering all laboratory tests, patients with PTB were positive in 94.9%, and patients with ETB in 78.9%. Isoniazid resistances occurred in 6.6% of patients with PTB and 3.6% of patients with ETB and multiple resistances (isoniazid and rifampicin) in 0.7% of patients with PTB. Two PTB cases were lost to follow-up (1.5%); both patients were immigrants. Cure rate was achieved in 89.7% of patients with PTB and 87.7% of patients with ETB, and deaths by TB were 5.3% in patients with ETB and 0% in patients with PTB. Deaths by other causes were 8.8% in PTB and 7.0% in ETB.

Univariate logistic regression of PTB associated factors compared with ETB is shown in Table 3. Male, lower age, and East Europe birthplace were predominant in PTB, and birthplace in Maghreb countries in ETB. Elevated risks were found of PTB for V-VI social class occupations (OR = 2.82; 95% CI = 1.03-7.70), social problems (OR = 5.86; 95% CI = 2.19-15.64), social marginalization (OR = 4.18; 95% CI = 1.55-11.25), stay in prison (OR = 5.02; 95% CI = 1.14-22.18), and unemployment (OR = 2.82; 95% CI = 1.03-7.70). Higher risk factors of PTB were smoking tobacco (OR = 5.93; 95% CI = 2.82-12.47), alcohol consumption (OR = 9.63; 95% CI = 2.23-41.55), and drug abuse (OR = 10.33; 95% CI = 1.34-77.97). Contact with patients with TB raised the risk of TBP (OR = 2.64; 95% CI = 1.15-6.08). Coexisting pathologies were a risk factor of PTB (OR = 2.49; 95% CI = 1.15-5.35), and alcoholism presented a higher risk with PTB (OR = 13.37; 95% CI = 1.77-101.08). Birthplace in Maghreb countries (OR = 0.56; 95% CI = 0.24-1.29) and positive HIV (OR = 0.55; 95% CI = 0.13-2.52) were inverse factors of PTB but with unstable effect.

Adjusted OR (AOR) of associated factors of PTB is shown in Table 4 and Figures 1 to 6. Higher risk factors of PTB were contact with patients with TB (AOR = 2.51; 95% CI = 1.06-5.95), social problems (AOR = 3.39; 95% CI = 1.05-10.94), and smoking tobacco (AOR = 3.89; 95% CI = 1.66-9.56). Pathologies were a risk factor but with high dispersion (AOR = 2.06; 95% CI = 0.74-5.74). Drug abuse and alcohol consumption were risk factors with lower effect in the adjusted models. An interaction between no-smoking and no-drug abuse was found with AOR = 0.27 (95% CI = 0.12-0.64), and this interaction decreased PTB risk.

Discussion

Results of this study suggest that there are important differences between PTB and ETB incidences. Risk factors of TBP were social problems, smoking tobacco, and contact with patients with TB. Interaction of no-smoking and no-drugs abuse reduces PTB risk. Birthplace in Maghreb countries and HIV were associated factors with ETB with unstable effect. Other PTB factors such as alcohol consumption, drugs abuse, and pathologies had lower and unstable risk due to small statistical power; however, they represent common aspects of poverty and social vulnerability.

The comparison with other studies on the same pathologies, PTB percent (70%) with respect to ETB (30%), is consistent with their results,[2,17] and with respect to PTB associated factors, similar results are found: smoking tobacco and alcohol consumption, contact with patients with TB, and social problems.[5,18–22] Some of these factors, such as smoking tobacco, perform a direct action on the immune system,[23] or indirect action, such as social problems, and the mixture of different factors could decrease resistance and undermine defensive mechanisms of patients.[24] In addition, smoking tobacco is associated with the stress that lower social class suffers.[25] Contact with patients with TB indicates their transmissibility because it is an exogenous source of infection, such as the stay in prison or in closed institutions that allow TB transmission.

Two factors (Maghreb countries birthplace and positive HIV) were related to ETB incidence. This group is heterogeneous and encompasses different presentations, including pleural ETB. This type is regarded as recent TB infection against the other ETB types that could be TB reactivation. In addition, some ETB without laboratory confirmation may be caused by agents such as atypical *Mycobacteria*.[26] In general, the genesis of ETB is associated with immunity deficiencies, genetic susceptibility, and unknown factors.[27,28] Risk factors of ETB are considered immunosuppression, long-term diseases such as HIV, children younger than 5 years old, people with 60 years or more, women, race, and ethnic factors.[4,6,28–31] However, high differences in ETB among countries suggest that there may be several associated factors, like an increase in immigrant population from regions such as Africa with a frequent delay in medical treatment, under-reporting, and genetic variations of population and TB bacteria.[2,3,32,33] ETB presents a high mortality, considering the severity of some forms, like miliary or disseminate, and HIV prevalence.[34] Anti-tuberculosis drug resistance was more elevated in patients with PTB, and a small increment with respect to a previous study in Castellon was observed[35]; multidrug-resistance was low, with only one PTB case.

During 2013-2016, the medians of PTB and ETB incidence rates of Castellon were in a similar range of Spain, with incidence rates of PTB and ETB of 8.5 and 2.9 per 100 000 inhabitants, respectively.[1] In Spain under-reporting of TB was high a few years ago,[36] but more recently this situation has improved, and 5% of TB under-reporting in Castellon province and 14.4% (range, 0%-45.2%) in some Spanish hospitals have been found.[37,38] Factors associated with under-reporting

Table 3. Associated factors of pulmonary tuberculosis (PTB) compared with extrapulmonary tuberculosis (TBE) in the health departments of Castellon and La Plana-Vila-real during 2013-2016.

VARIABLES	PTB N = 136 N (%)	ETB N = 57 N (%)	OR[A] (95% CI[B])	*P*-VALUE
Gender (Male)	89 (65.4)	31 (54.4)	1.59 (0.85–2.98)	.150
Mean age (y) ± standard deviation	43.2 ± 20.1	48.5 ± 23.8	0.99 (0.97–1.00)	.119
Birthplace				
Spain	76 (55.9)	36 (63.2)	0.74 (0.39–1.40)	.351
Eastern Europe[c]	34 (25.0)	8 (14.0)	2.04 (0.88–4.73)	.097
Maghreb countries[d]	16 (11.8)	11 (19.3)	0.56 (0.24–1.29)	.173
Foreign-born	60 (44.1)	21 (36.8)	1.35 (0.72–2.56)	.351
Social class I-II: Professional-managerial	7 (5.1)	8 (14.0)	1.0	
Social class III-IV: Skilled occupations	25 (18.4)	10 (17.5)	2.86 (0.81–9.94)	.100
Social class VI-VI: Partly skilled and unskilled occupations	104 (76.5)	39 (68.4)	3.04 (1.04–8.97)	.043
Unemployment	29 (21.3)	5 (8.8)	2.82 (1.03–7.70)	.043
Stay in prison	21 (15.4)	2 (3.5)	5.02 (1.14–22.18)	.033
Homeless	16 (11.8)	2 (3.5)	3.67 (0.81–16.50)	.090
Social marginalization	39 (28.7)	5 (8.8)	4.18 (1.55–11.25)	.005
Social problems[e]	49 (36.0)	5 (8.8)	5.86 (2.19–15.64)	.000
Smoking tobacco	78[f] (58.7)	11 (19.3)	5.93 (2.88–12.47)	.000
Alcohol consumption	35[g] (25.9)	2 (3.5)	9.63 (2.23–41.55)	.002
Drugs abuse	21 (15.4)	1 (1.8)	10.33 (1.34–77.97)	.025
Contact with patients with TB	41 (30.1)	8 (14.0)	2.64 (1.15–6.08)	.022
History of TB	10 (7.4)	1 (1.8)	4.44 (0.56–35.56)	.160
Alcoholism	27 (19.9)	1 (1.8)[h]	13.37 (1.77–101.58)	.012
Cancer	5 (3.7)	3 (5.3)	0.69 (0.16v8.98)	.616
Diabetes mellitus	17 (12.5)	4 (7.0)	1.89 (0.61–5.90)	.271
HIV	4 (2.9)	3 (5.3)	0.55 (0.12–2.57)	.437
Pathologies[i]	47 (34.6)	10 (17.5)	2.49 (1.15–5.35)	.020

[a]Odds ratio.
[b]Confidence interval.
[c]Eastern Europe (Romania and Bulgaria).
[d]Maghreb countries (Morocco and Algeria).
[e]Social problems (social marginalization, homeless, residence in shelters for the poor, or stay in prison).
[f]Unknown 3 cases.
[g]Unknown 1 case.
[h]Unknown 2 cases.
[i]Pathologies (alcoholism, cancer, diabetes mellitus, HIV).

were ETB, retirement, and smear-negative TB. In some Spanish studies,[31,39,40] TB risk factors such as smoking habit, alcohol abuse, and contact with patients with TB were associated with PTB, and female gender, age, Morocco origin, and HIV positivity with ETB in line with some results of this study.

Strengths of this study include high participation rate, good follow-up of patients with TB, elevated laboratory confirmation of PTB and less in ETB. In addition, the case-case design found PTB-associated factors, which were consistent with PTB case-control studies with controls from the general population, such as poverty, homeless, tobacco consumption, drugs

Table 4. Odds ratios of pulmonary tuberculosis (PTB) versus extrapulmonary tuberculosis (ETB) of each associated factors adjusted for confounding by logistic regression.

FACTORS	ODDS RATIO	95% CONFIDENCE INTERVAL	*P*-VALUE	HOSMER-LEMESHOW *P*-VALUE
Contact with patients with TB	2.51[a]	1.06–5.95	.037	.311
Social problems	3.39[b]	1.05–10.94	.041	.970
Smoking tobacco	3.98[c]	1.66–9.56	.002	.265
Alcohol consumption	2.11[d]	0.38–11.85	.396	.265
Drugs abuse	1.91[e]	0.21–17.58	.568	.265
Pathologies[f]	2.06[g]	0.74–5.74	.168	.265
No-smoking tobacco with no-drugs abuse interaction[h]	0.27[i]	0.12–0.64	.003	.364

[a]Adjusted for age, gender, social class, social problems, and foreign-born.
[b]Adjusted for age, gender, social class, foreign-born, smoking tobacco, alcohol consumption, drugs abuse, pathologies, and contact with patients with TB.
[c]Adjusted for age, gender, social class, social problems, alcohol consumption, drugs abuse, and pathologies.
[d]Adjusted for age, gender, social class, social problems, smoking tobacco, drugs abuse, and pathologies,
[e]Adjusted for age, gender, social class, social problems, smoking tobacco, alcohol consumption, and pathologies.
[f]Pathologies (alcoholism, cancer, diabetes mellitus, HIV).
[g]Adjusted for age, gender, social class, social problems, smoking tobacco, alcohol consumption, and drugs abuse.
[h]No-smoking tobacco with no-drugs abuse: PTB 55 cases (55/133) and ETB 45 cases (45/57). OR = 0.19 (95% CI 0.08-0.37) *P* = .000.
[i]Adjusted for age, gender, alcohol consumption, social class, social problems, and pathologies.

abuse, stay in prison, and contact with patients with TB.[41–44] Case-case design may allow more efficient and rapid actions with low cost with respect to case-control design, and it may improve traditional measures.

This study has some limitations including the following: first, microbiological confirmation of ETB was low, 52.6%, but higher than ETB detection in Spain, 41%, during 2007-2012.[31] Second, the criteria for cases classification present some differences with the ones used by other authors[3]; nevertheless, pathology results and PCR *M tuberculosis* improve these aspects. Third, sometimes ETB has pulmonary alterations, and TB mixed types are considered in some studies,[2] it may be an indication of misclassification with a bias toward not significant associations.[45] Fourth, some potential interesting variables, such as BCG vaccination (Bacillus Calmette-Guérin), that could make protection against ETB,[5,19] serum vitamin D levels,[46] genetic variations,[47] or body mass index,[26] were not studied. Fifth, the study had a reduced power because of the low sample of patients with ETB. Finally, no revision of TB under-reporting was included in this study, but TB under-reporting was low, 11.1% (3/24), in the Hospital General of Castellon during 2011-2012 period.[38]

From PTB-associated factors, health promotion and preventive and control measures could be addressed. Several actions may be proposed, including the battle against poverty and housing shortage; promotion of full employment; health education against the consumption of tobacco, alcohol, and other drugs; and finally accurate control of TB patient and their contacts. With respect to ETB, to improve the microbiological confirmation of ETB cases, an increase in research of risk factors is recommended. In our region, specific actions include reduction of TB diagnostic delay, increase of social assistance of homeless and marginalized patients with TB, and implementation of whole genome sequencing of all isolated *M tuberculosis* to improve the control of TB transmission chains.[48]

In conclusion, the estimated associated factors of PTB found in this study may be prevented, and it was demonstrated that the case-case design is useful in the study of TB.

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Author Contributions

AA-P and MAR-G designed the study; MAR-G, NM-F, IV-F, AV-B, and LS-A collected data and did follow-up of participants; RM-M performed microbiological determinations; AA-P, JBB-B, and NM-F implement statistical analysis; AA-P, MAR-G, and RM-M contributed to writing the manuscript. All authors read and approved the final manuscript.

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