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Determinants of patient and health system delay among Italian and foreign-born patients with pulmonary tuberculosis: a multicentre cross-sectional study

Annalisa Quattrocchi,[1] Martina Barchitta,[1,2] Carmelo G A Nobile,[3] Rosa Prato,[4] Giovanni Sotgiu,[5] Alessandra Casuccio,[6] Francesco Vitale,[6] Antonella Agodi,[1,2] on behalf of the CCM 2013 TB network

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For numbered affiliations see end of article.

Correspondence to
Prof. Antonella Agodi; agodia@unict.it

ABSTRACT

Objectives The aim of this cross-sectional study was to identify key factors associated with patient delay (PD), health system delay (HSD) and total delay (TOTD) in patients with tuberculosis (TB) to inform control programmes.

Setting The study was conducted in four Italian regions in 2014–2016. Data were obtained using a questionnaire including: sociodemographic and lifestyle data, TB comorbidities, patient knowledge and attitudes towards TB, stigma, access to TB care and health-seeking behaviours.

Participants Patients' inclusion criteria were being diagnosed as a new smear positive pulmonary TB case and living in one of the participating Italian regions. Overall, 344 patients from 30 healthcare centres were invited to participate and 253 patients were included in the analysis (26.5% non-response rate); 63.6% were males and 55.7% were non-Italian born.

Outcome measures Risk factors for PD, HSD and TOTD in patients with TB were assessed by multivariable analysis. Adjusted ORs (aOR) and 95% CIs were calculated.

Results Median PD, HSD and TOTD were 30, 11 and 45 days, respectively. Factors associated with longer PD were: stigma (aOR 2.30; 95% CI 1.06 to 4.98), chest pain (aOR 2.67; 95% CI 1.24 to 6.49), weight loss (aOR 4.66; 95% CI 2.16 to 10.05), paying for transportation (aOR 2.66; 95% CI 1.24 to 5.74) and distance to the health centre (aOR 2.46; 95% CI 1.05 to 5.74) (the latter three were also associated with TOTD). Shorter HSD was associated with foreign-born and female status (aOR 0.50; 95% CI 0.27 to 0.91; aOR 0.28; 95% CI 0.15 to 0.53, respectively), dizziness (aOR 0.18, 95% CI 0.04 to 0.78) and seeking care at hospital (aOR 0.35; 95% CI 0.18 to 0.66). Prior unspecific treatment was associated with longer HSD (aOR 2.25; 95% CI 1.19 to 4.25) and TOTD (aOR 2.55; 95% CI 1.18 to 5.82). Haemoptysis (aOR 0.12; 95% CI 0.03 to 0.43) and repeated visits with the same provider (aOR 0.29; 95% CI 0.11 to 0.76) showed shorter TOTD.

Conclusions This study identifies several determinants of delays associated with patient's behaviours and healthcare qualities. Tackling TB effectively requires addressing key risk factors that make individuals more vulnerable by the means of public health policy, cooperation and advocacy to ensure that all patients have easy access to care and receive high-quality healthcare.

Strengths and limitations of this study

- ► This is the first multiregional cross-sectional study, in Italy, investigating the association of key factors with patient delay, health system delay and total delay in patients with pulmonary tuberculosis.
- ► Data were collected by healthcare providers and cultural mediators, using a multilingual standardised questionnaire.
- ► The prospective collection of data and the adjustment for confounding factors with logistic regression analysis are among the strengths of the present study.
- ► A selection bias should be considered, especially for foreign-born patients who may have experienced difficulties during the interview, resulting in refusal or in missing data.
- ► Self-reported dates for onset of symptoms and healthcare seeking may have been affected by recall bias.

INTRODUCTION

Early diagnosis and prompt treatment of tuberculosis (TB) disease represent key components of any effective national TB control programme.[1 2] If adequately implemented and scaled-up, they can contribute to the reduction of *Mycobacterium tuberculosis* transmission and TB elimination by 2050.[3]

However, delays in diagnosis and treatment of TB frequently occur.[4] Long delays lead to a more advanced disease that may result in poor response to therapies, undesirable clinical *sequelae* and higher mortality risk.[5]

In addition, delay contributes to *M. tuberculosis* transmission within the community.[6 7] It has been shown that an untreated smear-positive patient can infect, on average, 10 healthy contacts annually.[8] Finally, TB diagnosis delay is associated with higher direct and indirect costs.[9]

Delay may occur at patient or at health system level. Factors contributing to patient delay (PD) can be: sociodemographic, physical, financial, health literacy, religious-cultural and stigma.[10] Health system delay (HSD)-related factors can be: poor TB knowledge among healthcare providers, lack of effective diagnostic tools, number and types of providers encountered before TB diagnosis, patient satisfaction with TB services and waiting time.[10 11] Thus, understanding and identifying the causes of delay in diagnosis and treatment initiation are critical to strengthen TB control programmes. Particularly, the importance of social variables as drivers of epidemics and disease risk has been long recognised. Incorporating the perspectives and methods of social epidemiology into studies of infectious disease arises many opportunities to control the disease.[12]

However, in Europe, and especially in Italy, few studies have focused on social determinants and TB delays.

The aim of the present study was to identify the duration and the key factors related to PD, HSD and total delay (TOTD) in pulmonary patients with TB, in four Italian Southern regions, with a focus on social determinants.

METHODS

Study design

The present cross-sectional study was conducted in four Italian regions (Calabria, Apulia, Sardinia and Sicily) from October 2014 to July 2016, and was approved and financed by the Italian Ministry of Health.

Patients' inclusion criteria were being diagnosed as a new smear-positive pulmonary TB case (with or without extrapulmonary TB) and living in one of the above-mentioned Italian regions. Foreign-born patients were enrolled regardless of their legal migrant status (eg, refugees, asylum seekers and illegal migrants). Negative smear, relapse, retreatment cases and those with only extrapulmonary TB were excluded.

The participants were fully informed of the purpose of the study and signed a written informed consent. All data collected were treated confidentially and analysed in aggregated and anonymous form.

Patient and public involvement

The present study was conducted without patient and public involvement. Results of the research will be available on request to any study participant to disseminate key study findings providing feedback on the research outcome towards which they have contributed.

Sample size calculation and sampling procedure

A sample size of 261 was estimated by using single population proportion estimation formula with an assumption of 95% CI, 6% margin of error and 50.4% proportion of PD (>30 days).[13]

Furthermore, considering 20% of non-response rate, the final sample size was 321. All patients meeting the inclusion criteria, attending the healthcare facility during the study period, were prospectively invited to participate in the study.

Data collection and definitions

Data were collected by healthcare workers of each participating centre, during a face-to-face interview at the time when patients were diagnosed and/or initiated treatment. A standardised questionnaire available in Italian, English and French was used, and if possible, a cultural and linguistic mediator assisted the interview with the task to facilitate communication and understanding, both on linguistic and cultural level. Operators with adequate background of the health topic, within the specific cultures/languages, supported and assisted patients and healthcare professionals during clinical examinations.

The questionnaire contained several domains: i) sociodemographic and lifestyle data; ii) integration index (II) in Italy (only for foreign-born patients), computed as described in a previous study[14]; iii) TB comorbidities; iv) patient knowledge of TB-associated symptoms and attitudes towards TB; v) TB-related stigma, measured according to the WHO questionnaire[15]; vi) access to TB diagnosis and treatment and health-seeking behaviours; vii) dates of: onset of symptoms, first contact with healthcare service, TB diagnosis confirmation and treatment initiation; viii) satisfaction with care, assessed by adopting and modifying the United States Agency for International Development (USAID) questionnaire.[16]

PD was defined as the time interval between the onset of symptoms and patient's first contact with any type of healthcare service (including hospital and primary healthcare).[15 16] HSD was defined as the time interval between the first consultation with a healthcare provider and the initiation of treatment.[15 16] This can be subdivided into: diagnostic delay (DD) as the time interval between the presentation to a healthcare provider and the date of diagnosis and treatment delay (TD) as the time interval between TB diagnosis and initiation of anti-TB treatment. Thus, TOTD was defined as the time interval from onset of symptoms until treatment initiation.[16 17]

Statistical analysis

Statistical analyses were performed using the SPSS software (IBM SPSS Statistics for Windows, V.22.0).

The response rate and descriptive statistics were used to characterise the sample using frequencies, means, medians and IQRs. Valid percentage was reported when data were missing (pairwise deletion method). Furthermore, the magnitude (proportion) of missing data was quantified and is reported in online supplementary table S1.

Poverty was defined in relation to housing circumstances as living in community centres, first aid centres or prisons. Education level was dichotomised into two categories (high and low), using a cut-off of 8 school years.

Variables related to stigma and satisfaction with care were recorded on a 5-point Likert scale.[15 16] Scores were converted as mean percentage score, calculated as follows: (sum of score obtained/maximum score that could be obtained)×100.

For TB cases born abroad, the II was calculated based on the score sum of 11 selected variables from the study questionnaire and then standardised to range from 0 to 10.[14]

Longer delays (outcome) were defined according to previous Italian studies. Particularly, long PD was defined as >30 days, while long HSD and TOTD were defined as >the median value observed in the study population, for HSD and TOTD, respectively.[13 18]

Prevalence estimates of longer delay, using cut-off values reported from other studies, are reported in online supplementary table S2.

Median values were also used as cut-off points to dichotomise quantitative variables (eg, age and stigma). The two-tailed X^2 test was used for the statistical comparison of categorical variables, whereas quantitative variables were compared using Student's t-test, as the sample was big enough. The Levene's test was performed to verify the homogeneity of variance across groups.

The characteristics of patients with longer delays (all forms) were compared with those of patients without (comparators) and the crude ORs and the corresponding 95% CIs were computed.

All variables with p<0.1 on univariate analysis were included in the multivariable logistic regression analysis, using a backward-stepwise selection procedure. The analysis was only run on cases which have a complete set of data. The breakpoint for variable removal was set at p=0.10. The adjusted ORs (aOR) with the respective 95% CIs were reported. A p value <0.05 was considered to be statistically significant.

RESULTS

A total of 344 patients from 30 healthcare centres were invited to participate. Overall, 91 (26.5%) refused the interview, and 253 patients were included in the analysis. Patients who refused the interview were older than patients who agreed (mean age: 46.0 and. 40.7 years, respectively; p=0.023). However, no statistical differences resulted for country of birth and gender. Completion rate for all questions included in the analysis was ≥80%. Missing data ranged from 0.4% to 21.7% (online supplementary table S1).

Overall, 55.3% of patients were temporary or permanently living in Sicily, 22.1% in Calabria, 17.4% in Apulia and 5.2% in Sardinia.

Table 1 shows the main characteristics of the study population and comparisons by origin and gender. Mean age was 40.7 years (median 38; IQR 27–53) and 63.6% were males. One hundred forty-one (55.7%) patients were born abroad and they were younger than Italians (mean age 34.3 and 48.7 years, respectively; p<0.001).

Stratifying by country of origin, 47.9% of patients came from European countries, and mostly from Romania (82.1%), 28.6% from the African countries, 11.4% from Eastern Mediterranean countries, 9.3% from South-East Asia, 2.1% from Western Pacific countries and 0.7% from American countries. Foreign-born patients reported higher degree of poverty and literacy: they lived in nursing homes or did not have permanent residency (47.8%), 64.7% were unemployed or occasional workers and 79.4% were illiterate or had <8 years of educational activities (p<0.05).

About one-third suffered of chronic diseases (ie, HIV/AIDS, diabetes, chronic obstructive pulmonary disease, disability, renal failure and cardiovascular disease), particularly those born in Italy (39.1%). Current smokers and alcohol users were 27.2% and 6.9%, respectively. Higher percentages of smokers and alcohol users were found among male patients (32.5% and 10.1%). However, no significant differences were observed between Italian and foreign-born patients (table 1).

Patient knowledge and symptoms recognition

Foreign-born patients reported lack of knowledge on the disease more often compared with Italian-born (see online supplementary table S3). Foreign-born patients were less aware that TB is an infectious disease and is transmitted by airborne bacteria. They did not know the symptoms most frequently associated with the disease, how TB is diagnosed and cured and that multidrug-resistant TB may require a longer treatment time to achieve a cure (p<0.05).

Only 3.6% of patients with TB reported no symptoms, while 49% of patients reported three or more symptoms. Overall, 65.6% had cough for >3 weeks. Sputum with blood was reported by only 13.4% of patients. The main reason for not seeking care was that they perceived the TB symptoms to be mild (58.9%).

Foreign-born patients reported more frequently the following symptoms: cough, sputum with blood, weakness, weight loss and chest pain, compared with Italian-born patients. Furthermore, women reported tiredness/weakness, weight loss, chest pain and night sweating less frequently compared with men. Being irregular migrant was the only reason for delayed seeking care in women, while in men other motivations were reported (see online supplementary table S3).

Attitude towards TB and stigma

A higher percentage of men (38.6%) and foreign-born patients (44.9%) did not inform their families and friends on the disease, compared with women (12.2%) and Italian-borns (9.1%) (p<0.001). Detailed results are reported in online supplementary table S4.

A moderate level of stigma was found (mean: 59.5%; median and IQR: 58.7%, 22.7%–94.7%) in all patients. Overall, 53.9% of foreign-born patients reported

Table 1 Patients' characteristics by origin and gender

	All % (N)	Italian-born % (N)	Foreign-born % (N)	P-value*	Male % (N)	Female % (N)	P-value*
Age (mean)	40.7 (246)	48.7 (109)	34.3 (137)	**<0.001**	41.0 (157)	40.1 (89)	0.941
Country of birth (n=253)							
Italy	44.3 (112)	–	–	–	42.2 (68)	47.8 (44)	0.389
Abroad	55.7 (141)	–	–		57.8 (93)	52.2 (48)	
Gender (n=253)							
Males	63.6 (161)	60.7 (68)	66.0 (93)	0.389	–	–	–
Females	36.4 (92)	39.3 (44)	34.0 (48)		–	–	
Education level (n=251)							
Low	72.5 (182)	63.6 (70)	79.4 (112)	**0.005**	70.8 (114)	75.6 (68)	0.419
High	27.5 (69)	36.4 (40)	20.6 (29)		29.2 (47)	24.4 (22)	
Living condition (n=240)							
Homeless/prison/ nursing homes	20.8 (50)	3.7 (4)	34.8 (46)	**<0.001**	26.6 (41)	10.5 (9)	**0.003**
Apartment (own or rented)	79.2 (190)	96.3 (104)	65.2 (86)		73.4 (113)	89.5 (77)	
Employment (n=241)							
Unemployed or occasional work	42.7 (103)	14.3 (15)	64.7 (88)	**<0.001**	47.1 (73)	34.9 (30)	**0.019**
Permanent job	26.6 (64)	33.3 (35)	21.3 (29)		28.4 (44)	23.3 (20)	
Housewife/retired/ student	30.7 (74)	52.4 (55)	14.0 (19)		24.5 (38)	41.9 (36)	
Smoking habits (n=236)							
Current	27.2 (67)	29.9 (32)	25.2 (35)	0.409	32.5 (51)	18.0 (16)	**0.014**
Never/former	72.8 (179)	70.1 (75)	74.8 (104)		67.5 (106)	82.0 (73)	
Alcohol abuse† (n=248)							
Yes	6.9 (17)	6.3 (7)	7.3 (10)	0.758	10.1 (16)	1.1 (1)	**0.007**
No	93.1 (231)	93.7 (104)	92.7 (127)		89.9 (142)	98.9 (89)	
Chronic diseases‡ (n=251)							
Yes	28.3 (71)	39.1 (43)	19.9 (28)	**0.001**	31.2 (50)	23.1 (21)	0.167
No	71.7 (180)	60.9 (67)	80.1 (113)		68.8 (110)	76.9 (70)	
Stigma (n=252)							
>Median	48.4 (122)	41.4 (46)	53.9 (76)	**0.049**	51.6 (83)	42.9 (39)	0.185
≤Median	51.6 (130)	58.6 (65)	46.1 (65)		48.4 (78)	57.1 (52)	
Integration index (mean)§	4.4 (141)	–	–	–	4.1 (93)	5.1 (48)	**0.008**
Years in Italy (mean)§	7.1 (127)	–	–	–	6.6 (85)	8.2 (42)	0.242
Patient delay (n=231)							
Median (IQR)	30 (8–60)	15 (7–60)	30 (14–60)	**–**	30 (10–60)	28 (7–60)	–
(>30 days)	64.5 (149)	29.1 (30)	40.6 (52)	0.069	37.2 (55)	32.5 (27)	0.480
Health system delay (n=225)							
Median (IQR)	11 (5–33)	21 (7.25–61)	8 (4–22)	–	14.5 (6–37)	8 (4–31)	–
(>11 days)	48.1 (111)	61.5 (64)	37.0 (47)	**<0.001**	55.4 (82)	34.9 (29)	**0.008**
Diagnostic delay (n=225)							
Median (IQR)	7 (3–30)	15 (4.75–60)	7 (3–15)	–	14 (4–30)	6 (3–28)	–
(>7 days)	49.3 (111)	64.7 (66)	36.6 (45)	**<0.001**	55.9 (81)	37.5 (30)	**0.008**
Treatment delay (n=219)							

Continued

Table 1 Continued

	All % (N)	Italian-born % (N)	Foreign-born % (N)	P-value*	Male % (N)	Female % (N)	P-value*
Median (IQR)	2 (1–4)	2 (1–4)	2 (1–4)	–	2 (1–5)	2 (1–4)	–
(>2 days)	38.4 (84)	38.4 (38)	38.3 (46)	0.994	40.9 (56)	34.1 (28)	0.322
Total delay (n=208)							
Median (IQR)	45 (25–121)	53 (25–123)	40 (25–97)	–	47 (26–99)	41 (16–120)	–
(>45 days)	49.5 (97)	56.0 (50)	44.0 (47)	0.091	66.0 (64)	34.0 (33)	0.525

*P<0.05 are indicated in bold.
†≥4 times a week.
‡HIV/AIDS, diabetes, chronic obstructive pulmonary disease, disability, renal failure, cardiovascular disease.
§Only in foreign-born patients.

TB-related stigma above the median value, compared with 41.4% of Italian borns (p=0.049) (table 1).

Healthcare-seeking behaviour and access to TB care centres

General practitioners (GP) were consulted, as first choice, by 30% of patients, mostly Italians (46.8%). On the contrary, foreign-born cases were shown to seek more frequently the hospital care (70.3%). Around 41% of cases were visited by more than one healthcare provider, and this was mainly reported by the Italian group (53.2% vs 31.7%; p=0.001). Overall, 59% of the cases received unspecific treatment (mainly antibiotics) before TB diagnosis; this occurred more frequently among cases born in Italy (75.7% vs 51.6%; p=0.005).

Risk analysis of delay

Median PD, HSD and TOTD were 30, 11 and 45 days, respectively (table 1). On univariate analysis, factors associated with long PD (>30 days) were: TB-related stigma, paying for transportation, distance to the healthcare centre, presence of unintentional weight loss, fatigue, chest pain and suffering of chronic diseases. In the final model of the multivariable analysis, stigma (aOR 2.30, 95% CI 1.06 to 4.98), paying for transportation (aOR 2.66, 95% CI 1.24 to 5.74), distance to the healthcare centre (aOR 2.30, 95% CI 1.06 to 4.98), weight loss (aOR 4.66, 95% CI 2.16 to 10.05) and chest pain (aOR 2.67, 95% CI 1.24 to 6.49) remained associated with PD (table 2).

Prior unspecific treatment, patients referring to a GP at the first visit, and those visited by multiple providers in different facilities were more likely to report long HSD (>11 days), while female gender, non-Italian origin, seeking care at hospital level, presence of cough for >3 weeks and dizziness were associated with shorter HSD. On multivariable analysis, being foreign-born (aOR 0.50, 95% CI 0.27 to 0.91), female gender (aOR 0.28, 95% CI 0.15 to 0.53), seeking care at hospital (aOR 0.35, 95% CI 0.18 to 0.66) and presence of dizziness (aOR 0.18, 95% CI 0.04 to 0.78) remained associated with shorter HSD. Prior unspecific treatment was associated with longer HSD (aOR 2.25, 95% CI 1.19 to 4.25) (table 3).

Factors associated with long DD (>7 days) were the same as those associated with HSD, and in addition, having cough for >3 weeks was significantly associated with shorter DD (online supplementary table S5). No variables were associated with long TD (>2 days).

Finally, good knowledge of TB, paying for transportation, distance to reach the health centre, prior unspecific treatment and weight loss were associated with long TOTD (>45 days), while patients reporting cough and hemophthisis and those who had repeated visits with the same provider showed shorter TOTD. In the logistic regression analysis, paying for transportation (aOR 2.10, 95% CI 1.01 to 4.35), distance to the healthcare centre (aOR 3.09, 95% CI 1.38 to 6.90), prior unspecific treatment (aOR 2.55, 95% CI 1.18 to 5.82), weight loss (aOR 3.55, 95% CI 1.56 to 8.09), repeated visits with the same provider (aOR 0.29, 95% CI 0.11 to 0.76) and haemoptysis (aOR 0.12, 95% CI 0.03 to 0.43) were independently associated with TOTD (table 4).

DISCUSSION

Reducing the time interval between symptoms recognition and TB treatment can decrease mycobacterial transmission, morbidity and mortality. Although there is no general consensus on what may constitute an acceptable interval between onset of symptoms and initiation of TB treatment,[19] it has been suggested that overall TB delay could be used as a key indicator of programme performance.[4]

The TB notification rate in the general Italian population has been stable in the last years.[20] However, most of the cases occur in vulnerable groups, who do not recognise the symptoms or have poor access to healthcare services. The two most affected groups are the elderly and foreign-borns. The latter group accounts for about 50% of all TB cases in Italy (data until 2008).[21]

In our study, 55.7% patients were foreign-born, and they were younger than Italians. Younger age among foreign-born patients has also been reported in other studies.[13 22] Although the TB notification rate is decreasing in Europe, the reduction in individuals of foreign origin is still slower than in native residents. This represents one of the main challenges for TB elimination, especially in

Table 2 Risk analysis for patient delay (univariate and logistic regression analysis)

	PD >30 days %	OR (95% CI)	P-value*	aOR (95% CI)	P-value*
Foreign-born					
Not†	29.1	1.00	0.069	–	–
Yes	40.6	1.67 (0.96 to 2.89)			
Knowledge of TB as infectious disease			0.091	–	–
Not†	27.8	1.00			
Yes	39.1	1.66 (0.92 to 3.00)			
Knowledge of how TB is diagnosed			0.051	–	–
Not†	28.7	1.00			
Yes	41.3	1.75 (0.99 to 3.07)			
Stigma			**0.001**		**0.034**
<Median†	24.8	**1.00**		**1.00**	
>Median	46.5	**2.64 (1.51 to 4.61)**		**2.30 (1.06 to 4.98)**	
Pay for transportation to reach the health centre			**<0.001**		**0.012**
Not†	23.5	**1.00**		**1.00**	
Yes	49.4	**3.18 (1.77 to 5.73)**		**2.66 (1.24 to 5.74)**	
Did you think you had TB?			0.09	–	–
Not†	33.8	1.00			
Yes	52.4	2.15 (0.87 to 5.31)			
Close distance to the first visit place			**0.018**		**0.037**
Yes†	21.9	**1.00**		**1.00**	
No	39.2	**2.30 (1.15 to 4.62)**		**2.46 (1.05 to 5.74)**	
Weight loss			**<0.001**		**<0.001**
Not†	22.5	**1.00**		**1.00**	
Yes	56.2	**4.41 (2.48 to 7.83)**		**4.66 (2.16 to 10.05)**	
Tiredness/weakness			**0.001**	–	–
Not†	25.8	**1.00**			
Yes	45.9	**2.44 (1.40 to 4.25)**			
Chest pain			**0.026**		**0.031**
Not†	31.4	**1.00**		**1.00**	
Yes	47.5	**1.97 (1.08 to 3.61)**		**2.67 (1.24 to 6.49)**	
Chronic diseases			**0.009**	–	–
Not†	29.6	**1.00**			
Yes	47.8	**2.17 (1.21 to 3.90)**			

*P <0.05 are indicated in bold.
†Reference category
aOR, adjusted OR; PD, patient delay; TB, tuberculosis.

those European countries where individuals of foreign-born origin represent a large proportion of TB cases.[23]

In our study, the median values of PD (30 days) and HSD (11 days;7 days of DD and 2 days of TD, respectively) are similar to those reported by other studies conducted in Italy and in other European countries with a low TB incidence. Particularly, a recent Italian study reported median PD and HSD values of 31 and 15 days, respectively.[13] European studies reported median PDs of 14 days (France),[24] 28 days (Norway)[25] and 29 days (UK).[19] Considering HSD (and its two components), studies reported median values of 15 days (Croatia),[26] 25 days (for DD in France),[24] 30 days (UK)[19] and 33 days (Norway).[25] However, in our study, median TOTD (45 days) was lower than values reported elsewhere, which ranged between 62 days (UK)[19] and 63 days (Norway).[25]

Online supplementary table S2 shows median values reported by other studies,[13 19 24–26] and the prevalence of delay that would have been detected in our study, by using them.

Table 3 Risk analysis for health system delay (univariate and logistic regression analysis)

	HSD >11 days %	OR (95% CI)	P- value*	aOR (95% CI)	P-value*
Foreign-born			**<0.001**		**0.024**
Not†	61.5	**1.00**		**1.00**	
Yes	37	**0.37 (0.22 to 0.63)**		**0.50 (0.27 to 0.91)**	
Age			0.1	–	–
>Median	43.7	1.00			
≤Median	54.6	1.55 (0.92 to 2.62)			
Gender			**0.003**		**<0.001**
Male†	55.4	**1.00**		**1.00**	
Female	34.9	**0.43 (0.25 to 0.75)**		**0.28 (0.15 to 0.53)**	
First visit with GP			**<0.001**	–	
Not†	39.9	**1.00**			
Yes	68.7	**3.30 (1.80 to 6.06)**			
First visit at hospital			**<0.001**		**0.001**
Not†	64.6	**1.00**		**1.00**	
Yes	35.7	**0.30 (0.17 to 0. 53)**		**0.35 (0.18 to 0.66)**	
Seeking treatment somewhere else, after first visit			**<0.001**	–	–
Not†	35.1	**1.00**			
Yes	66.7	**3.70 (2.12 to 6.44)**			
Cough>3 weeks			**0.036**	–	–
Not†	57.7	**1.00**			
Yes	43.1	**0.56 (0.32 to 0.97)**			
Dizziness			**0.04**		**0.023**
Not†	49.8	**1.00**		**1.00**	
Yes	21.4	**0.28 (0.75 to 1.01)**		**0.18 (0.04 to 0.78)**	
Prior unspecific treatment			**<0.001**		**0.012**
Not†	34.1	**1.00**		**1.00**	
Yes	57.1	**2.58 (1.49 to 4.46)**		**2.25 (1.19 to 4.25)**	
Repeated visits with different providers in a different facility			**<0.001**	–	–
Not†	37.3	**1.00**			
Yes	62.8	**2.84 (1.61 to 5.01)**			

*P <0.05 are indicated in bold.
†Reference category.
aOR, adjusted OR; GP, general practitioner; HSD, health system delay.

It is worth noting that some studies evaluated both forms of TB (pulmonary and extrapulmonary), and tools for data collection and definitions of delays were widely heterogeneous among studies, thus comparisons should be made with caution.

Nevertheless, median values detected in our study are encouraging. Indeed, for PD a median value of 30 days has been considered an acceptable value by many authors,[18 27] although others have suggested values <3 weeks.[28]

Regarding HSD, our median value is below the accepted value, which is considered to be 15 days.[27] Low values of HSD and TOTD might probably due to a higher level of awareness of TB among involved healthcare professionals in Italy, in recent years. Similarly to our results, other studies have found that PD was longer than HSD,[13 29] while others have found the opposite,[24 25] or no differences.[19] It is likely that patients who contact the health system later could have more severe symptoms facilitating TB suspicion and prompt diagnosis,[13] thus the higher the PD, the lower the HSD, and vice versa.[4 25]

In our study, longer PD was associated with high degree of stigma, paying for transportation, distance to healthcare facility, presence of unintentional weight loss and chest pain. Aside from stigma and chest pain, all others were also detected as risk factors for TOTD. Our results are consistent with findings of the WHO Eastern Mediterranean Region study, where stigma, economic factors

Table 4 Risk analysis for total delay (univariate and logistic regression analysis)

	TOTD >45 days %	OR (95% CI)	P-value*	aOR (95% CI)	P-value*
Foreign-born			0.091	–	–
No†	56	1.00			
Yes	44	0.62 (0.35 to 1.08)			
Knowledge of TB as infectious disease			**0.012**	–	-–
No†	37.1	**1.00**			
Yes	55.8	**2.14 (1.18 to 3.88)**			
Pay for transportation			**0.004**		**0.047**
No†	40.5	**1.00**		**1.00**	
Yes	62.3	**2.43 (1.32 to 4.46)**		**2.10 (1.01 to 4.35)**	
Close distance to the first visit place			**0.003**		**0.006**
Yes†	32.8	**1.00**		**1.00**	
No	56.9	**2.71 (1.38 to 5.31)**		**3.09 (1.38 to 6.90)**	
Cough>3 weeks			**0.038**	–	–
No†	60.3	**1.00**			
Yes	44.5	**0.53 (0.29 to 0.97)**			
Sputum with blood			**0.005**		**0.001**
No†	53.5	**1.00**		**1.00**	
Yes	25	**0.29 (0.12 to 0.72)**		**0.12 (0.03 to 0.43)**	
Weight loss			**0.004**		**0.003**
No†	41.9	**1.00**		**1.00**	
Yes	63.4	**2.40 (1.32 to 4.36)**		**3.55 (1.56 to 8.09)**	
Prior unspecific treatment			**0.003**		**0.026**
No†	37.4	**1.00**		**1.00**	
Yes	57.4	**2.26 (1.32 to 3.89)**		**2.55 (1.18 to 5.82)**	
Repeated visits with the same provider			**0.029**		**0.012**
No†	53.6	**1.00**		**1.00**	
Yes	34.1	**0.45 (0.22 to 0.93)**		**0.29 (0.11 to 0.76)**	

*P<0.05 are indicated in bold.
†Reference category.
aOR, adjusted OR; TB, tuberculosis; TOTD, total delay.

and time to reach the health facility were among the main determinants for delayed access to healthcare system.[15]

TB-related stigma represents a cultural aspect which drives individuals to hide their condition from others, and refusing seeking care,[30] but evidence shows that stigma barriers may be avoided through interventions addressed improving TB-related health literacy.[10]

The reason why chest pain and weight loss were associated with long PD is not clear since these symptoms, together with persistent cough, are considered key TB signs. Other studies retrieved similar results. Chest pain was found positively associated with longer PD (>90 days) in a Brazilian study,[31] and with TOTD (>60 days) in Ethiopia.[27] Similarly, weight loss was associated with longer PD, both in Brazil (>30 days)[31] and in Italy (>15 days),[13] with PD (>27 days) and TOTD (>50 days) in Uzbekistan,[32] and with HSD (>18 days) in another Brazilian study.[33] These results could be explained by the assumption that patients consider these as transient symptoms from a general illness, hence, maybe, initiating self-treatment lasting until deterioration and manifestation of other specific symptoms. Furthermore, timely referral to healthcare facilities for disabling symptoms may be challenging due to financial constraints, poor health literacy and stigma. In addition, a long delay until diagnosis favours disease progression and therefore symptom appearance. Also, non-specific symptoms could lead to longer suspicion delays by the clinician.

Especially for foreign-born patients, language barriers, poor knowledge of symptoms, fear of immigration authorities and long wait for appointment have been associated with delay in seeking care,[34 35] raising concerns about the equity of access to care among patients with TB. Thus, understanding immigrants' views of TB and the obstacles that they face when accessing the health system, taking into consideration the social, economic and legislative context of the new country where they live, has an important role and should be considered in TB control programmes.

The association of HSD with birth place might be due to the low TB rate in Italy, thus TB would be less suspected and investigated in the Italian-born population, or by contrast, being a migrant may point physicians to a prompt TB diagnosis.[13] This finding is consistent with other studies.[13 19]

Female gender was associated with shorter HSD, in contrast with other studies.[4] In general, female patients are reported to encounter greater barriers (financial, physical and health literacy) for appropriate medical care and treatment. Further investigations on possible confounders should be considered.

In line with others,[4 30 36 37] a first healthcare contact in hospital, was strongly associated with shorter HSD, while referring to GP was a risk factor for longer HSD. A combination of several factors may explain this result: lack of TB suspicion among primary care providers in low-endemic countries; seeking assistance in hospital for patients at higher risk of TB (eg, migrants from endemic countries) and/or with more severe TB disease who are thus investigated faster; availability and easier access to diagnostic tests and specialists within the hospital.[24]

Furthermore, repeated visits, especially with different healthcare workers in different health facilities, has been retrieved as predictor of HSD in other studies[15 17 38–40]; however, we did not find this association in the final model. It has been reported that generally, patients see different healthcare providers in case of poor clinical suspicions of signs and symptoms, failure to request for proper investigations, refer patients to specialised TB centre for further investigations[41] or when they receive inappropriate treatment that can modify the clinical picture of the disease.[40]

The association of HSD and TOTD with previous unspecific treatment is in agreement with other results.[13 24] This is of a particular concern in the current global epidemiological scenario where antimicrobial resistance is rapidly developing and spreading and a more prudent use of antimicrobials is urgently needed by, for instance, limiting the use of empirical antibiotics in patients with respiratory symptoms.[24] Training GP for the early identification of signs and symptoms and prompt referral of suspected cases to TB diagnosis and treatment health centres is essential.

Finally, other factors associated with shorter TOTD were presenting sputum with blood and having visits by the same provider. Sputum with blood is usually recognised as a late sign of TB, thus patients with severe symptoms are immediately suspected for TB. Intuitively, having visits with the same provider might reduce repetition of examinations and misdiagnosis.

Our study has some limitations, some of them specific to the cross-sectional study design. A selection bias should be considered. In fact, the cultural mediator was not often available in hospitals, thus, foreign-born patients recently arrived in Italy, may have experienced difficulties during the interview, resulting in refusal or in missing data. In any case, no difference has been detected for country of birth among responders and non-responders and the completion rate for the questions included in the analyses was at least 80%.

Missing data are a challenge which could affect the quality of the evidence, limit power and reduce generalisability, causing a distortion from the truth.[42 43] There is no general consensus from the literature regarding an acceptable percentage of missing data in a data set for valid statistical inferences, yet. Cut-off values have been proposed ranging from 5% to 20%.[44 45] In our study, we retrieved a certain amount of missing data, up to 21%, and observations with missing data have been excluded in the multivariable analysis, hence reducing the final sample size. In addition, the pattern of missingness was not explored. Thus, missing data may represent potential bias in our findings. The questionnaire used for data collection could have been a plausible cause for missing data in our study, because of the length of the survey, and the unavailability of translation in languages other than English and French. Thus, to prevent missing data in further studies, the data collection tool should be designed and adapted to the needs of the target population, piloted and monitored during the study.

Also, the low education level of the overall population may have contributed to an information bias. However, since a higher frequency of low educational level was shown in foreign-born patients than in those born in Italy, a differential misclassification could be supposed and thus the direction of the bias is unpredictable. Furthermore, as the onset date of symptoms was self-reported it may have been affected by recall bias that could have occurred heterogeneously in the whole sample. Another limitation is that data on HIV status and other risk factors (eg, alcohol and drug use and detention status) were not available for the majority of patients.

In the present study, several aspects have been investigating as key factors contributing to PD and HSD in patients with TB. However, further studies addressing other components of delays[6 30 46] may be necessary to understand all factors that are closely associated with delay in the diagnosis and treatment of TB. Furthermore, in our regression model we did not take into account for the potential collinearity of explanatory variables, which could explain complex relationship involving several risk factors at the same time, for example, the use of unspecific antibiotics and multiple visits with healthcare providers.

A possible approach to combine the relevant variables into summary scores or indexes and to assess the relationship of these with the outcome of interest should be explored.

Nevertheless, this is the first multiregional cross-sectional study, conducted in Italy, which investigated the association of several factors with PD, HSD and TOTD in patients with pulmonary TB. It provides new evidence which can be addressed through tailored actions, in order to reduce the burden of TB in Italy. Furthermore, the prospective collection of data in four Italian regions, using a multilingual standardised questionnaire and the adjustment for confounding factors with logistic regression analysis are among the strengths of the present study.

In conclusion, this study detected several modifiable factors associated with longer delay in patients with TB, both attributable to patients and health system service. Interventions designed to empower the general population and stakeholders, by increasing knowledge and awareness and screening of active TB in migrants on arrival are key actions to reduce PD and HSD and achieve TB control.[47] Strategies should mainly target alleviating stigma around TB, improving TB-related health literacy and access to care among the general population, education of GP, earlier referral of TB suspects to the hospital, where appropriate investigations for final diagnosis are readily available, and limiting the use of unspecific treatment in patients with respiratory symptoms.

Author affiliations
[1]Department of Medical and Surgical Sciences and Advanced Technologies 'GF Ingrassia', University of Catania, Catania, Italy
[2]LaPoSS, Laboratory of Policies and Social Services, University of Catania, Catania, Italy
[3]Department of Health Sciences, University of Catanzaro 'Magna Græcia', Catanzaro, Italy
[4]Department of Medical and Surgical Sciences, University of Foggia, Foggia, Italy
[5]Department of Biomedical Sciences, Clinical Epidemiology and Medical Statistics Unit, University of Sassari, Sassari, Italy
[6]Department of Sciences for Health Promotion and Mother-Child Care 'G. D'Alessandro', University of Palermo, Palermo, Italy

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