A CASE CONTROL STUDY OF RISK FACTORS ASSOCIATED WITH PULMONARY TUBERCULOSIS IN ROMANIA: EXPERIENCE AT A CLINICAL HOSPITAL OF PNEUMOLOGY

PACIFIQUE NDISHIMYE¹, ², ³, BIANCA DOMOKOS³, ⁴, JONATHAN STILLO⁵, FOUAD SEGHROUCHNI⁶, OULAYA MRABET⁶, DANIELA HOMORODEAN⁴, ⁷, CARMEN MONICA POP³, ⁴, ABDERRAHIM SADAK²

¹National Institute of Hygiene, Rabat, Morocco
²Faculty of Sciences, Mohammed V University, Rabat, Morocco
³Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania
⁴Leon Daniello Pneumology Hospital, Cluj-Napoca, Romania
⁵The City University of New York Graduate Center, New York, USA
⁶Ibn Tofail University, Kénitra, Morocco
⁷National Tuberculosis Reference Laboratory, Cluj-Napoca, Romania

Abstract

Background and aim. Tuberculosis (TB) remains a major public health issue in Romania. The aim of the present study was to evaluate the potential demographic, socioeconomic and behavioral risk factors for TB among hospitalized patients in Romania.

Methods. This is a case-control study conducted between March 1st 2014 and March 30th 2015 at Leon Daniello Clinical Hospital of Pneumology, Cluj Napoca. A total of 150 TB patients defined as “cases” were matched for age, sex and county of residence to 150 controls selected from patients attending the same hospital with respiratory diseases other than TB. Data collection was obtained through patient interviews using a structured questionnaire. Factors potentially associated with TB infection were analyzed using univariate and multivariate logistic regression.

Results. Factors independently associated with TB were illiteracy (OR=2.42, 95% CI 1.09-5.37), unemployment (OR=2.08, 95% CI 1.23-3.53), low household income (OR=4.12, 95% CI 2.53-6.71), smoking (more than 20 cigarettes per day) (OR=2.12, 95% CI 1.20-3.74), poor knowledge of TB (OR=3.46, 95% CI 1.97-6.07), presence of TB patient in household (OR=4.35, 95% CI 1.42-13.36), prior TB treatment (OR=2.2, 95% CI 1.93-2.5) and diabetes (OR=3.32, 95% CI 1.36-8.08).

Conclusion. This study provided useful information that might help to develop and adapt effective policies for TB control in Romania.

Keywords: tuberculosis, risk factors, prevention, odds ratio, Romania

Introduction

Tuberculosis (TB) remains a public health concern worldwide. Efforts to control this disease have been largely focused on improving treatment and diagnosis of patients with active disease. However, in spite of those intensive efforts, high per capita rates of TB are still common, particularly in developing countries in Asia, Africa, Eastern Europe and the former Soviet Union [1].

With an estimated annual TB incidence of 94 new
cases and a prevalence of 144 per 100,000 population, Romania has the highest incidence and prevalence in the European Union [2]. It accounts for 27% of the EU’s total cases [3]. WHO has identified Romania as one of the eighteen high-priority countries in the European region [2]. However, few studies have been performed in Romania to clarify how different factors interact in the development of active TB. Studies that address risk groups help to prioritize TB research and intervention among the most vulnerable in the community, enabling effective and efficient TB control.

The aim of the present study was to evaluate the potential demographic, socioeconomic and behavioral risk factors for tuberculosis among hospitalized patients in Romania.

Methods

Study setting and Data collection

We conducted a case-control study at Leon Daniello center, a clinical hospital of pneumology serving predominantly patients from Cluj County and its surroundings. Cases were patients aged >15 years with confirmed pulmonary TB according to the World Health Organization (WHO) and Romania’s National Tuberculosis Control Program guidelines. Controls were patients matched for sex, age and county of residence attending the same hospital with respiratory diseases other than TB.

A structured questionnaire prepared in local language was administered to both cases and controls through face-to-face interviews. Studied factors included demographic, socioeconomic, behavioral and biological indicators. Exclusion criteria were refusal to participate, serious illness (Human Immuno-Deficiency Virus and mental disorders), death and respondents with missing major data.

Data analysis

Data were recorded in Excel worksheet and the analysis was conducted using cases and controls. Odds ratios (OR) and their 95% confidence intervals (CI) were estimated using conditional logistic regression, with TB as an outcome. The likelihood ratio test used to assess the association between the explanatory variables and the risk of TB, and to test for interaction and trend. Univariate analyses were performed to examine the effect of each variable on the risk of TB. Multivariable models were then constructed, including variables that showed an effect in the prediction of TB in the univariable analyses at the p=0.05 level of significance. The analyses were performed using SPSS version 20 (Chicago, IL, USA).

Ethical consideration

The study was approved by the Ethics Committee of the Iuliu Hatieganu University of Medicine and Pharmacy. The objective of the study was explained in detail to study participants and an informed consent form was signed by each individual before conducting the interview.

Results

Baseline characteristics of the study participants

A total of 300 participants were enrolled in the study between 01st March 2014 and 30th March 2015. Of the 300 participants, 150 were diagnosed positive for M. tuberculosis and 150 were negative for M. tuberculosis. The average age was 42.92 years with a range of 17 to 84 years. Clinical symptoms mainly included weight loss (68.6%), cough (55.4%), fever (45.3%), expectoration (43.3%) and hemoptysis in 12% cases. Seventy-six (25.3%) and 94 (31.3%) participants had cavities and nodular lesions respectively on their chest X-ray (Table I).

| Variable                                      | Cases (n)=150 | Controls (n)=150 |
|-----------------------------------------------|---------------|------------------|
| Age (mean, SD)                                | 43.9 (7.8)    | 42.5 (9.3)       |
| Gender (n, %)                                 |               |                  |
| Male                                          | 118 (78.6)    | 118 (78.6)       |
| Female                                        | 32 (21.3)     | 32 (21.3)        |
| White Blood Cells (*10³/µl), Mean (range)     | 8.24 (2.4-15.9)| 8.36 (4.1-15.8) |
| Lymphocytes (*10³/µl), Mean (range)           | 1.78 (0.05-3.1)| 1.91 (0.05-3.2) |
| % Lymphocytes, Mean (range)                   | 21.09 (6.4-41.9)| 22.52 (6.4-39)  |
| Erythrocyte Sedimentation Rate (mm), Mean (range) | 64.29 (7-132) | 52.56 (2-125)   |
| Weight loss (n)                               | 114           | 92               |
| Persistent cough (n)                          | 116           | 49               |
| Cavitation on chest X-ray (n)                 | 64            | 12               |
| Nodular lesion on chest X-ray (n)             | 95            | 9                |

Table I. Baseline characteristics of the study participants.
Factors associated with pulmonary tuberculosis

The relationship between studied risk factors and TB infection as evaluated by univariate analysis is presented in Tables II and III. The final multivariate model identified several risk factors independently associated with TB (Table IV).

Table II. Univariate analysis of demographic, socioeconomic and behavioral factors associated with pulmonary tuberculosis in a case-control study, Cluj-Napoca, Romania.

| Variable                        | Cases n (%) (N=150) | Controls n (%) (N=150) | OR (95% CI)          | P-value |
|---------------------------------|----------------------|------------------------|----------------------|---------|
| Marital status                  |                      |                        |                      |         |
| Single                          | 67 (44.6)            | 62 (41.3)              | 1.17 (0.86-1.60)     | 0.324   |
| Married                         | 63 (42)              | 62 (41.3)              | -                    |         |
| Other (widowed, divorced)       | 20 (13.3)            | 26 (17.3)              | 0.83 (0.57-1.21)     |         |
| Education (Schooling)           |                      |                        |                      |         |
| No                              | 25 (16.6)            | 11 (7.3)               | 1.43 (1.08-1.91)     | 0.026   |
| 1-5 years                       | 58 (38.6)            | 62 (41.3)              | 0.59 (0.35-0.99)     |         |
| >5 years                        | 67 (44.6)            | 77 (51.3)              | -                    |         |
| Household monthly income        |                      |                        |                      |         |
| ≥ 800 lei/month                 | 60 (40)              | 110 (73.3)             | -                    |         |
| < 800 lei/month                 | 90 (60)              | 40 (26.6)              | 1.96 (1.55-2.47)     | 0.001   |
| Occupation                      |                      |                        |                      |         |
| Employed                        | 29 (19.3)            | 50 (33.3)              | -                    |         |
| Unemployed                      | 121 (80.6)           | 100 (66.6)             | 1.49 (1.09-2.04)     | 0.006   |
| Residential area                |                      |                        |                      |         |
| Large city / urban              | 73 (48.6)            | 82 (54.6)              | -                    |         |
| Small city / rural              | 77 (51.3)            | 68 (45.3)              | 1.27 (0.80-2.00)     | 0.298   |
| Persons per room                |                      |                        |                      |         |
| 1-2                             | 125 (83.3)           | 20 (13.3)              | -                    |         |
| >2                              | 25 (16.6)            | 130 (86.6)             | 1.30 (0.68-2.45)     | 0.419   |
| Smoking history                 |                      |                        |                      |         |
| Never                           | 53 (35.3)            | 105 (70)               | -                    |         |
| Past/Current                    | 97 (64.6)            | 45 (30)                | 0.78 (0.48-1.27)     | 0.325   |
| Frequency of smoking            |                      |                        |                      |         |
| < 1 pack/day                    | 46 (30.6)            | 69 (46)                | -                    |         |
| > 1 pack/day                    | 51 (34)              | 36 (24)                | 1.46 (1.10-1.94)     | 0.009   |
| Alcohol history                 |                      |                        |                      |         |
| Never                           | 66 (44)              | 59 (39.3)              | -                    |         |
| Past/Current                    | 84 (56)              | 91 (60.6)              | 0.82 (0.52-1.30)     | 0.412   |
| Frequency of drinking           |                      |                        |                      |         |
| Less than once a week           | 30 (20)              | 43 (28.6)              | -                    |         |
| Several times a week            | 54 (36)              | 48 (32)                | 1.61 (0.87-2.95)     | 0.122   |
| Drug user                       |                      |                        |                      |         |
| No                              | 143 (95.3)           | 140 (93.3)             | -                    |         |
| Yes                             | 7 (4.6)              | 10 (6.6)               | 0.81 (0.45-1.4)      | 0.45    |

OR = odds ratio; CI = confidence interval.
* P ≤ 0.05 (significance level).
Table III. Univariate analysis of clinical and disease-related factors associated with pulmonary tuberculosis in a case–control study, Cluj-Napoca, Romania.

| Variable                                | Cases n (%) (N=150) | Controls n (%) (N=150) | OR (95% CI)          | P-value |
|-----------------------------------------|---------------------|------------------------|----------------------|---------|
| Diabetes                                |                     |                        |                      |         |
| Yes                                     | 21 (14)             | 7 (4.6)                | 1.58 (1.23-2.02)     | 0.005   |
| No                                      | 129 (86)            | 143 (95.3)             | -                    |         |
| BCG vaccination status                  |                     |                        |                      |         |
| Un-vaccinated                           | 9 (6)               | 12 (8)                 | 0.84 (0.3-1.79)      | 0.49    |
| Vaccinated                              | 141 (94)            | 138 (92)               | -                    |         |
| Knowledge of TB                         |                     |                        |                      |         |
| Poor                                    | 56 (37.3)           | 22 (14.6)              | 1.69 (1.37-2.08)     | 0.001   |
| Well                                    | 94 (62.6)           | 128 (85.3)             | -                    |         |
| Presence of TB patient in household     |                     |                        |                      |         |
| Yes                                     | 16 (10.6)           | 4 (2.6)                | 1.67 (1.30-2.14)     | 0.005   |
| No                                      | 134 (89.3)          | 146 (97.3)             | -                    |         |
| History of prior TB treatment           |                     |                        |                      |         |
| Yes                                     | 25 (16.6)           | 0                      | -                    |         |
| No                                      | 125 (83.3)          | 150 (100)              | -                    |         |
| Satisfaction with health services       |                     |                        |                      |         |
| Yes                                     | 137 (91.3)          | 129 (86)               | -                    |         |
| No                                      | 13 (8.6)            | 21 (14)                | 0.58 (0.28-1.21)     | 0.145   |

OR = odds ratio; CI = confidence interval.
* P ≤ 0.05 (significance level).

Table IV. Multivariable logistic regression model showing risk factors associated with pulmonary tuberculosis in a case–control study, Cluj-Napoca, Romania.

| Variable                                | OR (95% CI)          | P-value |
|-----------------------------------------|----------------------|---------|
| Education (Schooling)                   |                      |         |
| No                                      | 2.42 (1.09-5.37)     | 0.026   |
| 1-5 years                               | -                    |         |
| Household monthly income                |                      |         |
| < 800 (lei/month)                       | 4.12 (2.53-6.71)     | 0.001   |
| ≥ 800 (lei/month)                       | -                    |         |
| Occupation                              |                      |         |
| Unemployed                              | 2.08 (1.23-3.53)     | 0.006   |
| Employed                                | -                    |         |
| Frequency of smoking                    |                      |         |
| > 1 pack/day                            | 2.12 (1.20-3.74)     | 0.009   |
| < 1 pack/day                            | -                    |         |
| Diabetes                                |                      |         |
| Yes                                     | 3.32 (1.36-8.08)     | 0.005   |
| No                                      | -                    |         |
| Knowledge of TB                         |                      |         |
| Poor                                    | 3.46 (1.97-6.07)     | 0.001   |
| Well                                    | -                    |         |
| Presence of TB patient in household     |                      |         |
| Yes                                     | 4.35 (1.42-13.36)    | 0.005   |
| No                                      | -                    |         |
| History of prior TB treatment           |                      |         |
| Yes                                     | 2.2 (1.93-2.5)       | 0.001   |
| No                                      | -                    |         |
Discussion

This study aimed at reassessing the main risk factors that influence the development of TB in Romania in order to collect information which might help adjust and adapt effective policies for TB control in this country.

The results showed that smoking more than a pack (20 cigarettes) per day was associated with TB infection. Previous studies both in developed and developing countries have shown an increased vulnerability of smokers to the infection and development of TB, most probably owing to patho-physiological changes in the lungs induced by chronic smoking [4, 5, 6]. Bronchoalveolar macrophages among smokers contain high levels of iron implicated in promoting the growth of M. tuberculosis [7, 8]. Smoking 1 pack of cigarettes is equivalent to inhaling 1.1 μg of iron [9]. In this study, patients smoking more than one pack per day were twice as likely to have TB as those who smoke less than one pack per day. Smoking is great public health issue in Romania, even in hospitalized patients. Our results might reinforce the need to devise effective strategies for counseling TB patients and their relatives about quitting smoking. Anti-smoking campaigns also need to be strengthened to have considerable effects on the health of all population, following the recommendations contained in the WHO Framework Convention on Tobacco Control [10]. This is an especially important finding for Romania, where free smoking cessation services are unavailable to most Romanian TB patients.

The present study found no association between alcohol consumption and TB, which differs from other studies which concluded that alcohol had a stronger association with tuberculosis [11]. Ruffino-Neto, several decades ago, investigated the role of alcohol consumption and smoking in the risk of developing tuberculosis and found that smoking was associated with tuberculosis only in the group of drinkers [12, 13]. However, alcoholics should also be counseled effectively to wean them away from these unhealthy behaviors and minimize the risk of developing the disease.

The low household income (<800 lei per month, approximately 230 US Dollars) appears to be a risk factor for developing TB in our study. Measures of poor living conditions like low family income, poor household equipment and malnutrition have been found to be associated with an increased risk of developing tuberculosis [14, 15]. Poverty undoubtedly contributes to the incidence of tuberculosis through increased progression from infection to disease due to poor diet or stress, and greater difficulties in using health services [16]. In Romania, Stillo has also observed that poverty is not only a risk factor for TB, but also the single greatest barrier that prevents people under treatment from becoming cured. This is especially true when one’s household responsibilities do not allow them to submit to the long hospitalization periods that are standard in Romanian TB treatment, particularly for drug-resistant TB [2, 17, 18]. Lower level of education and poor knowledge about TB appeared to favor the development of the disease. TB more strongly affects disadvantaged population groups [18, 19]. However, illiterate individuals need to be focused on a priority basis for educational interventions regarding the disease. WHO also recognizes the importance of tuberculosis-related knowledge, attitude and practice surveys in advocacy, communication and social mobilization strategy planning [20]. Romania’s most recent KAP survey took place in 2012 and, like previous ones, revealed serious deficits in knowledge about TB in the population [21].

Consistent with the previous studies, this study found a strong association between a reported presence of TB patient in the family and the development of TB [22]. This risk increases with the number of persons in the household having had TB in the past, due to a higher chance of getting the TB bacillus via their respiratory tract. This result supports the recommendation of the Tuberculosis Control Cluster, which recommends the special care of persons who have had close contact with a TB patient. Our results also suggest that prior TB history is the predominant risk factor for developing TB. We defined patients with prior TB history as those who had a history of anti-tuberculosis treatment for active TB infection based on medical record review. Those patients were more likely to develop the disease than patients without a history of TB.

We found a strong association of diabetes with pulmonary TB, which agree with the findings of other studies [15, 23, 24]. It is known that diabetes mellitus could affect chemotaxis, phagocytosis, and antigen presentation by macrophages in response to M. tuberculosis. Production of interferon γ, growth, function, and proliferation of T lymphocytes might be adversely affected by diabetes [25, 26].

Our study has some limitations. First, the study was conducted at a referral hospital, which usually manages patients with more severe and extensive disease. Some of our results, particularly concerning X-ray data, may not be representative of patients with less severe disease. Second, diabetes status collected by self-report and types I vs. II could not be differentiated.

Conclusion

This study confirmed the multifactorial aspect of TB and showed that interventions for this disease need to be appropriate for those most at risk. Our findings may help to plan and implement country-specific prevention strategies aiming at reducing the morbidity and transmission of this burden.

Acknowledgements

The authors are grateful to the staff of Leon Daniello Hospital of Pneumology and National TB Reference
Laboratory, Romania, for their help in conducting the study. Thanks also to Dr Alexandra Handa and Dr Vasilescu Alexandru for the significant assistance in recruiting patients. The study was financially supported by the Rwanda Education Board, Romanian Government and “Agence Universitaire de la Francophonie” through Eugen Ionescu Scholarship Program.

References
1. World Health Organization, “Global tuberculosis report 2013,” 2013. Available from: http://apps.who.int/iris/bitstream/10665/19355/1/9789241564656_eng.pdf
2. “Review of the national tuberculosis programme in Romania” no. March, 2015. Available from: http://www.euro.who.int/__data/assets/pdf_file/0007/269269/Review-of-the-national-tuberculosis-programme-in-Romania.pdf
3. European Centre for Disease Prevention and Control and World Health Organization, Tuberculosis surveillance and monitoring in Europe 2013. 2013. Available from: http://ecdc.europa.eu/en/publications/Publications/Tuberculosis-surveillance-monitoring-2013.pdf
4. Aubry MC, Wright JL, Myers JL. The pathology of smoking-related lung diseases. Clin Chest Med. 2000;21(1):11-35.
5. Alcaide J, Altet MN, Plans P, Parron I, Folguera L, Salto E, et al. Cigarette smoking as a risk factor for tuberculosis in young adults: a case-control study. Tuber Lung Dis. 1996;77(2):112-116.
6. Kolappan C, Gopi PG. Tobacco smoking and pulmonary tuberculosis. Thorax. 2002;57(11):964-966.
7. Lounis N, Truffot-Pernot C, Grosset J, Gordeuk VR, Boelaert JR. Iron and Mycobacterium tuberculosis infection. J Clin Virol. 2001;20(3):123-126.
8. Thomas A, Gopi PG, Santha T, Chandrasekaran V, Subramani R, Selvakumar N, et al. Predictors of relapse among pulmonary tuberculosis patients treated in a DOTS programme in South India. Int J Tuberc Lung Dis. 2005;9(5):556-561.
9. Leung CC, Li T, Lam TH, Yew WW, Law WS, Tam CM, et al. Smoking and tuberculosis among the elderly in Hong Kong. Am J Respir Crit Care Med. 2004;170(9):1027-1033.
10. “WHO Framework Convention on Tobacco Control,” WHO, 2003. Available from: http://www.who.int/tobacco/framework/WHO_FCTC_english.pdf
11. Kolappan C, Gopi PG, Subramani R, Narayanan PR. Selected biological and behavioural risk factors associated with pulmonary tuberculosis, Int J Tuberc Lung Dis. 2007;11(9):999-1003.
12. Ruffino-Netto, Caron-Ruffino M. Interacao De Fatores Riscos Em Tuberculose. Rev Saude Publica. 1979;13(2):119-122.
13. d’Arc Lyra Batista J, de Fátima Pessoa Militão de Albuquerque M, de Alencar Ximenes RA, Rodrigues LC. Smoking increases the risk of relapse after successful tuberculosis treatment. Int J
14. Liu JJ, Yao HY, Liu. EY. Analysis of factors affecting the epidemiology of tuberculosis in China. Int J Tuberc Lung Dis. 2005;9(4):450-454.
15. Shetty N, Shemko M, Vaz M, Souza GD. An epidemiological evaluation of risk factors for tuberculosis in South India: a matched case control study. Int J Tuberc Lung Dis. 2006;10(1):80-86.
16. Lönroth K, Castro KG, Chakaya JM, Chauhan LS, Floyd K, Glaziou P, et al. Tuberculosis control and elimination 2010-50: cure, care, and social development. Lancet. 2010;375(9728):1814-1829.
17. Stillo, Jonathan. 2011. The Romanian Tuberculosis Epidemic as a Symbol of Public Health. In: Romania Under Basescu: Aspirations, Achievements, and Frustrations during his First Presidential Term, pp. 273-92. Ronald F. King and Paul E. Sum, eds. Lantham, MD: Lexington Books
18. Stillo JJ. All My Prolems Started With Tuberculosis :’ an Ethnographic Analysis of Treatment Failure in Romania,” Int. Res. Exch. Board, February, 2012. Available from: https://www.irex.org/sites/default/files/Stillo-%20Final%20Research%20Brief-%20Revised.pdf
19. Stillo J. Tuberculosis in Romania: an Anthropological Perspective.” Rev. Rom. Comun. si Relatii Publice, vol. 11, no. 3, pp. 37-42, 2009.
20. W.H.O. Advocacy, communication and social mobilization for TB control: a guide to developing knowledge, attitude and practice surveys. WHO/HTM/STB/2008.46, p. 68, 2008.
21. “CENTRUL PENTRU POLITICI ŞI SERVICII DE ŞANĂTATE (Bucureşti) Percepţia populaţiei României privind tuberculoza,” no. CPSS - Centrul pentru Politici şi Servicii de Sănătate. - Buzău : Alpha MDN, 2012.
22. Coker R, McKee M, Atun R, Dimitrova B, Dodonova E, Kuznetsov S, et al. Risk factors for pulmonary tuberculosis in Russia: case-control study. BMJ. 2006;332(7533):85-87.
23. Pérez-Guzmán C, Vargas MH, Torres-Cruz A, Pérez-Padilla JR, Furuya ME, Villarreal-Velarde H. Diabetes modifies the male:female ratio in pulmonary tuberculosis. Int J Tuberc Lung Dis. 2003;7(4):354-358.
24. Ezung T, Devi NT, Singh NT, Singh TB. Pulmonary tuberculosis and diabetes mellitus--a study. J Indian Med Assoc. 2002;100(6):376, 378-379.
25. Faureh-Jepsen D, Range N, PrayGod G, Jeremiah K, Faureh-Jepsen M, Aabye MG, et al. The role of diabetes on the clinical manifestations of pulmonary tuberculosis. Trop Med Int Health. 2012;17(7):877-883.
26. Delamare M, Maugendre D, Moreno M, Le Goff MC, Allamnic H, Geneteb B. Impaired leucocyte functions in diabetic patients. Diabet Med. 1997;14(1):29-34.