



The sociodemographic characteristics and risk factors for tuberculosis morbidity between two decades at the beginning of the 21st century at the north of Kosovo, Serbia

Sociodemografske karakteristike i faktori rizika od oboljevanja od tuberkuloze između dve dekade na početku 21. veka na severu Kosova, Srbija

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Abstract

Background/Aim. Tuberculosis (TB) is a major cause of mortality and morbidity worldwide, affecting different countries disproportionately. Effective diagnosis and treatment of TB saved an estimated 43 million lives between 2000 and 2014. The aim of our study was to show socio-demographic influences, risk factors for the morbidity and clinical characteristics of tuberculosis among residents of northern Kosovo, Serbia, between two decades at the beginning of the 21st century. **Methods.** A prospective study was conducted at the Department for Pulmonology of the Clinical-health Centre, Kosovska Mitrovica, included all tuberculosis patients treated during two three-year periods, between 2000–2002 and 2012–2014. In total, 134 patients with tuberculosis were treated, 91 in the first observed period and 43 in the second period. **Results.** In both observed periods, male patients suffered from tuberculosis more frequently. In the first observed period, younger and middle age (18–49) persons suffered from tuberculosis more

frequently ($p = 0.014$). In relation to the place of residence, in the first reporting period there were more patients from urban areas, while in the second, there were significantly more patients from rural areas ($p = 0.008$). In the second observed period, TB was significantly more associated with chronic obstructive pulmonary disease ($p = 0.001$) and comorbidities with TB were significantly more frequent ($p = 0.006$). During the 2000–2002 period, there were more severe clinical forms, with severe radiological changes, bilateral parenchymal and cavernous forms ($p = 0.08$). Mild unilateral parenchymal lesions were more common in the last 3 years ($p = 0.02$). **Conclusion.** Social determinants, older age and comorbidities are the most important risk factors for the persistent number of patients, and therefore this target group needs attention during active approach in TB screening.

Key words:

tuberculosis; sociological factors; demography; risk factors; morbidity.

Apstrakt

Uvod/Cilj. Tuberkuloza (TB) je vodeći uzrok mortaliteta i morbiditeta širom sveta zahvatajući nesrazmerno razne zemlje. Tačna i proverena dijagnoza i adekvatno lečenje prema procenama sačuvali su 43 miliona života na početku 21. veka. Cilj studije bio je da se ukaže na sociodemografski uticaj, faktore rizika za oboljevanje i kliničke karakteristike tuberkuloze kod stanovnika severnog Kosova, Srbija, između dve dekade na početku 21. veka. **Metode.** Prospektivnom studijom obuhvaćene su obolele osobe od tuberku-

loze lečene na Grudnom odeljenju Kliničko-bolničkog centra u Kosovskoj Mitrovici, tokom dva trogodišnja perioda, između 2000–2002. i 2012–2014. godine. Lečena su ukupno 134 bolesnika obolela od tuberkuloze, 91 u prvom periodu i 43 u drugom posmatranom periodu. **Rezultati.** U oba perioda bilo je više obolelih muškaraca. U prvom posmatranom periodu, osobe mlađe i srednje životne dobi (18–49) značajno češće su oboljevale od tuberkuloze ($p = 0.014$). U odnosu na mesto stanovanja, u prvom posmatranom periodu bilo je više obolelih koji žive u gradu, dok je u drugom periodu, značajno više bolesnika bilo sa

sela ($p = 0.008$). U drugom posmatranom periodu, TB je bila značajno povezana sa hroničnom obstruktivnom bolešću pluća ($p = 0.001$) i komorbiditeti su bili značajno češći ($p = 0.006$). Tokom perioda 2000–2002. godina, bile su zastupljenije teže kliničke forme, sa ozbiljnim radiološkim promenama, bilateralne parenhimatozne i kavernoze forme ($p = 0.08$). Umerene unilateralne parenhimatozne lezije su bile češće u drugom trogodišnjem periodu ($p = 0.02$).

Introduction

Tuberculosis (TB) is a major cause of mortality and morbidity worldwide, affecting different countries disproportionately. Effective diagnosis and treatment of TB saved an estimated 43 million lives between 2000 and 2014¹.

According to the World Health Organization (WHO) and the European Centre for Disease Prevention and Control, a decrease in the frequency of tuberculosis has been registered². The Republic of Serbia registered less than 20 cases per 100,000 inhabitants which represents a low incidence rate of tuberculosis³. At the same time, it is reported that Kosovo has a higher incidence of tuberculosis diseases compared to other areas of the Balkans. Compared with the other neighbouring areas, such as Albania or Macedonia, the incidence of tuberculosis in Kosovo is twice as high^{4,5}.

The decreasing trend in number of new cases of tuberculosis is accompanied by the change of sociodemographic and clinical characteristics of the disease. In the middle of the last century, the number of younger TB patients was significantly higher while the contact with the infected persons was a common reason for the occurrence of the disease^{6,7}. Fibrocavicular and cavernous phthisis were manifested as more severe clinical manifestations, which required long-term treatment and were often accompanied by the disease relapse with approximately 30%^{8–10}. At the end of the 1990's, pulmonary tuberculosis kept characteristics of a social disease with a morbidity peak in the fourth decade of life and clinical features dominated by the parenchymatous form with cavities and rare, but persistent, miliary pulmonary tuberculosis (1.9% to 2.4%)¹¹. These characteristics of the tuberculosis has remained as such up to date, but only in regions with a high incidence of disease, mainly in Africa and Asia^{11,12}.

In the last decade in areas with a lower incidence of TB, it often affects elderly, over 40%^{13–15}, while in countries with a high rate of disease the most vulnerable are people in their middle age^{12,16}. The clinical TB features are often disguised by symptoms of comorbidities such as diabetes mellitus (DM) and chronic obstructive pulmonary disease (COPD) thus making the diagnosis identification more difficult¹⁷. Characteristic of the old age is that the tuberculous changes may occur in the lower lung fields, which is atypical for pulmonary tuberculosis (PTB)^{9,13,18}.

In the last two decades, social determinants and risk factors changed. Social and economic reasons (place of residence, occupation) as well as habits (smoking, alcohol consumption and drug use) remained equally important¹⁹. In contemporary society, the improvement of living standard

Zaključak. Socijalne determinante, starija životna dob i komorbiditeti su najvažniji faktori rizika za održavanje perzistentnog broja obolelih i zato je to ciljna grupa na koju treba obratiti posebnu pažnju u skriningu tuberkuloze.

Ključne reči: tuberkuloza; socijalni faktori; demografija; faktori rizika; morbiditet.

increased the number of patients suffering from cardiovascular diseases, diabetes or obstructive lung disease. The comorbidity with diabetes mellitus is invariable. DM is documented in all groups of patients with TB, but the association of the DM and TB is significantly higher in the elderly and in the obese – ones with greater waist circumference. Comorbidities are risk factors that contribute to the incidence of diseases such as TB that is now more common in the elderly^{9,17}. Tuberculosis is a major health problem and it is a difficult task for doctors to suspect tuberculosis and recognize the typical symptoms of the disease without proper consideration of social determinants and risk factors. One of the reasons for continual maintenance of new cases of tuberculosis in most areas of the world is the increasing number of human immunodeficiency virus (HIV) – positive patients^{1,2}.

There is insufficient published data on the number of newly discovered cases of tuberculosis as well as risk factors for the maintenance of the number of patients in population in the northern Kosovo, Serbia. The aim of our study was to examine sociodemographic influences, risk factors for the morbidity and clinical characteristics of tuberculosis among residents of the northern Kosovo by analysis and comparison of the two three-year periods, 2000–2002 and 2012–2014.

Methods

The survey was conducted in full respect of the ethical principles and was approved by the Ethics Committee of the Faculty of Medicine, University of Priština with temporary seat in Kosovska Mitrovica.

A prospective study was conducted at the Department of Pulmonology of the Clinical-health Centre in Kosovska Mitrovica, the reference institution for the tuberculosis treatment. The study included patients with tuberculosis who had been treated in the period between 2000 and 2002 and in the period between 2012 and 2014. All hospitalized patients were divided into 2 groups, depending on the observed period of time and compared afterwards.

On admission, the patients' data regarding demography, age, gender, body weight as well as the initial symptoms of the disease were processed. Patients were considered to have positive symptoms of cough, expectoration, weight loss, night sweats and fatigue if these symptoms had been present for two or more weeks. Haemoptysis were positive if it occurred only once.

The following social determinants have been processed: place of residence, family status, education and occupation. Also, we processed risk factors of getting infected with tu-

berculosis, including previous tuberculosis and anti-tuberculosis treatment, the possibility of contact with persons suffering from tuberculosis, alcohol consumption, smoking, drug use, prolonged use of corticosteroids, the use of immunosuppressive therapy and comorbidities such as diabetes mellitus, chronic renal failure, cancer, chronic obstructive pulmonary disease, liver cirrhosis, congestive heart failure and HIV infection.

The results of the lung affection on chest radiography were categorized according to the extent of changes, their localization and approximately to their morphological structure. Presence or absence of cavity was the basis of TB division to initial and advanced forms confirmed by radiologist. Sputum samples were taken from all the patients for direct microscopy of the preparations coloured according to Ziehl-Neelsen method. Also, a cultivation of bacillus on Lowenstein-Jansen medium was performed for all samples. Sputum was collected in the morning, before eating, after a spontaneous expectoration. Each sputum positive for direct microscopy was verified by the culture on Lowenstein-Jansen medium. Pulmonary tuberculosis was bacteriologically confirmed if the two sputum findings confirmed bacillus and/or in the case of positive sputum cultivation. Chest radiographies have been also performed. Each abnormality in the lungs was confirmed by the radiologists.

Descriptive statistics were calculated for the sociodemographic characteristics, risk factors, and clinical characteristics of patients with tuberculosis who had been treated in two observed periods. Differences between groups were analyzed by using Pearson's χ^2 test for categorical variables.

All tests were two-tailed. $p < 0.05$ was considered statistically significant. The IBM SPSS 21(Chicago, IL, 2012) package was used for these analyses.

Results

The study included all tuberculosis patients treated during two three-year periods, between 2000 and 2002 and between 2012 and 2014. In total, 134 patients with tuberculosis were treated, 91 in the first observed period and 43 in the second one. The differences in sociodemographic characteristics in two periods, from the very beginning of the 21st century and 10 years after, were examined. In both observed periods, male patients suffered from tuberculosis more frequently (Table 1).

In the first observed period, younger and middle aged (18–49) people suffered from tuberculosis more frequently. Among the patients, treated between 2012 and 2014, there were significantly more persons older than 50 years of age ($p = 0.014$). In relation to the place of residence, in the first reporting period there were more patients from urban areas, while in the second, significantly more patients were from rural areas ($p = 0.008$). Social determinants, such as family and employment status as well as education level did not differ between the observed periods and represent a variable that has remained unchanged in the observed period as well as important factor determining morbidity of tuberculosis (Table 1).

Table 1
Sociodemographic characteristics of patients with tuberculosis (TB) (n= 134)

Variables	2000–2002 n (%)	2012–2014 n (%)	<i>p</i> value
Numbers of patients	91	43	
Sex			
male	60 (65.9)	29 (67.4)	0.512
female	31 (32.1)	14 (32.6)	
Age group, years			
18–29	15 (16.5)	7 (16.3)	< 0.014*
30–39	18 (19.8)	5 (11.6)	
40–49	23 (25.3)	5 (11.6)	
50–59	12 (13.2)	14 (32.6)	
≥ 60	23 (25.3)	12 (27.9)	
Residence			
urban	49 (46.2)	10 (76.7)	< 0.001
rural	42 (53.8)	33 (23.3)	
Marital status			
married	49 (53.8)	19 (45.2)	0.195
single	42 (46.2)	24 (55.8)	
Employment status			
employed	55 (60.4)	31 (72)	0.098
unemployed	33 (39.6)	12 (28)	
Education			
no education	5 (5.5)	3 (7)	0.289
primary	22 (22.2)	5 (11.6)	
secondary	61 (67)	32 (74.4)	
More than secondary	3 (3.3)	3 (7)	

Table 2

Comparison of the risk factors in patients with active tuberculosis (TB) between 2000–2002 and 2012–2014 (n = 134)

Variables	2000–2002	2012–2014	p value
	n (%)	n (%)	
Social determinant	33 (36.3)	12 (26.6)	0.225
TB contact	16 (17.6)	6 (14)	0.398
History of anti-TB treatment	15 (16.5)	4 (9.3)	0.201
Smoking status	41 (45.1)	22 (51.2)	0.317
Alcohol status	22 (24.2)	14 (32.6)	0.207
Daibetes mellitus	3 (3.3)	5 (11.6)	0.070
COPD*	3 (3.3)	10 (23.3)	0.001
Comorbidity	28 (30.8)	21 (49)	0.006

*COPD – chronic obstructive pulmonary disease.

Table 3
Comparison of clinical characteristics of patients with tuberculosis (TB) between two periods, 2000–2002 and 2012–2014 (n = 134)

Variables	2000–2002	2012–2014	p value
	n (%)	n (%)	
Site of TB			
pulmonary	83 (91.2)	37 (86)	0.292
extrapulmonary	8 (8.8)	6 (14)	
Treatment category			
new	82 (90)	39 (90.7)	0.484
retreatment	9 (10)	4 (9.3)	
Clinicals characteristics			
Parenchymal involvement			
unilateral	6 (21.4)	11 (61.1)	0.008
bilateral	22 (78.6)	7 (38.9)	
cavities	55 (60.4)	18 (41.9)	
Radiological severity			
initial	6 (7.2)	11 (30.6)	0.002
advanced TB	77 (92.8)	25 (69.4)	
Mycobacteriology characteristics of total TB /sputum or smear			
negative	36 (39.6)	15 (34.9)	0.373
positive	55 (60.4)	28 (65.1)	

Socioeconomic factors, smoking and alcohol consumption are the risk factors for developing TB, but there was no distinction between the observed periods. In the second observed period, with a greater number of respondents older than 50 years, TB was significantly more associated with chronic obstructive pulmonary disease ($p = 0.001$) and comorbidities which were significantly more frequent ($p = 0.006$) (Table 2). One of the most important risk factors, HIV infection, could not be listed, since there were not HIV positive among the patients.

The occurrence of pulmonary tuberculosis was more frequent than extrapulmonary (Table 3). Similarly, the number of newly found cases was higher than relapse ones and there was no significant difference between groups. There was significant difference in clinical manifestations of the disease 15 years ago and now. At the very beginning of the century, there were more severe clinical forms, with severe radiological changes, bilateral parenchymal and cavernous forms ($p = 0.08$). Mild unilateral parenchymal lesions were more common over the last 3 years ($p = 0.02$). There were no significant differences Mycobacterial characteristics and

confirmation of the disease, did not differ significantly in the examined period (Table 3).

Discussion

This is the first study on social determinants and risk factors for developing tuberculosis at the north of Kosovo. At the same time, it delivers clinical and radiographic features in patients with tuberculosis in two observed periods. The study provides original descriptive data on the profile of the TB patients, social determiners and risk factors of morbidity in northern Kosovo during the two 3-years periods with the time distance of 10 years. The trend of tuberculosis morbidity rate in the Republic of Serbia declined in last 10 years. In 2012, the rate of incidence in Serbia was 23/100,000, while in Kosovo, it was 47/100,000¹. The high rate of incidence in Kosovo could be the result of numerous factors including the low level of health protection of the local population, poverty and low level of education^{4,5}.

As a result of good organization and effective operation of anti-tuberculosis dispensaries in Serbia, a low incidence of AIDS and rare resistant strains of *Mycobacterium tuberculo-*

sis, the incidence and mortality are significantly reduced, despite the worsening of socioeconomic conditions during the 1990's¹⁴. According to the data of the World Health Organization, the largest number of tuberculosis patients in Serbia in 2014 were older than 65 years and predominantly males. Age and sex were observed elsewhere as strong determinants of TB disease with a higher risk of TB disease observed among older individuals and men. The distribution of patients, according to urban/rural place of residence varied between the groups. According to 15 years old data, patients from the urban area were predominant, but in the last 3 years patients from rural areas prevail. The migrations of population after 2000 in Kosovo and Metohija changed the structure of the population at the north of Kosovo between the two observed periods. The data in the literature differ; some state that there are more patients in urban areas²⁰, and some show that patients from rural areas prevail^{16,21}.

Family status, as a social determinant, was not different in the observed periods. Employment status is an important social determinant. There is no significant difference between the compared groups, but in the period 2000–2002, there were more patients without employment. During that period, among TB patients, there were more displaced persons with the undefined employment status. Although there were significantly more patients with TB among those with primary and secondary education¹⁶, there was no significant difference in the observed period.

In addition to socioeconomic status as a factor for tuberculosis morbidity, contacts with patients and previous history of tuberculosis treatment represent important risk factors. Increased duration of exposure is associated with the risk of tuberculosis infection²².

Tobacco smoking is associated with significantly increased risks of latent tuberculous infection, active tuberculosis, TB recurrence and mortality²³. These results are consistent with other studies in which tobacco smoke was found to alter mucociliary function and the clearance of inhaled substances, promote the adherence of bacteria to the epithelial cells of the airways, increase alveolar permeability and reduce humoral and cell-mediated immunity. This would facilitate *Mycobacterium tuberculosis* infection, while also subsequently favouring the onset of disease and its increased severity²⁴. Approximately half of our respondents, in both observed periods, were smokers, with a long-time habit of smoking. The link between smoking and tuberculosis was described in many studies^{12, 20, 25, 26}. The habit of tobacco smoking is, even nowadays, still represented in the population of northern Kosovo, and therefore aggressive campaigns about the harmfulness of tobacco might lead to the reduction in the number of tuberculosis patients²⁷.

Low to moderate alcohol intake is not associated with the tuberculosis morbidity. On the other hand, persons who drink more than 40 g/day or have alcohol use disorders are at significant risk. Persons who regularly consume alcohol suffer more frequently from severe clinical forms and have poorer treatment outcomes^{12, 26, 28}.

Alcohol can have direct toxic effects on the immune system. Chronic alcohol consumption directly reduces macrophage activity and cellular immunity and inhibits activity

of the tumor necrosis factor²⁹. Increased risk for developing tuberculosis among alcohol users can be explained by the pattern of behaviour- staying in bars, shelters, prisons and social institutions^{30,31}.

WHO reports indicate that DM is associated with a significantly increased risk of TB morbidity, treatment failure and disease relapse or fatal outcome³². The comorbidity of diabetes mellitus and tuberculosis has been confirmed in several studies, regardless of the study design or geographical area in which they are conducted^{26, 33, 34}. High incidence of DM and pre-DM in adults suffering from TB was noted, which results in more severe clinical features and poorer tuberculosis treatment outcomes. Diabetes is associated with multi-drug resistant tuberculosis (MDR-TB) in patients without a previous history of tuberculosis. In patients with diabetes, cellular immunity is suppressed, which is a key defence mechanism against *Mycobacterium tuberculosis*. Macrophages and T-lymphocytes have the most important role in the protection of the organism against tuberculosis. Therefore, attention should be paid to the treatment of latent tuberculosis in diabetics.

The global burden of diabetes mellitus (DM) is immense, with numbers expected to rise to over 550 million by 2030. TB is an infectious disease of equally great antiquity as DM, with evidence of spinal involvement being found in Egyptian mummies dating back to several thousand years BC. There is now strong evidence that there is an important association between DM and TB and that this association results in poor TB treatment outcomes. Heightened clinical suspicion for TB is needed for people with DM, especially among those who live in TB-endemic areas, and systematic screening should be considered³⁵. The results of our study indicate a necessity of expansion of public health programs that connect TB and DM, diagnostic and therapeutic measures.

Comorbidities, especially chronic obstructive pulmonary disease, represent a significant risk factor for developing tuberculosis and poorer treatment outcome. In the period between 2012 and 2014, in which the majority of respondents were older than 50 years of age, there were significantly more comorbidities. WHO ranked COPD as a significant risk factor for tuberculosis¹⁹. An increasing number of people are suffering from COPD, and it may be due to habit of tobacco smoking and life in urban areas with serious air pollution. The significance of comorbidities for developing tuberculosis is described in numerous studies^{12, 26, 34}.

In northern Kosovo, there are significantly more patients with pulmonary tuberculosis. The number of patients suffering from extrapulmonary tuberculosis (EPTB) is lower than in some underdeveloped countries with high incidence of TB, or in countries with more HIV-infected persons^{18, 36}. The diagnosis in our respondents was made based on mycobacterial confirmation of the disease, with direct microscopy sputum for bacillus cultivation, which was positive in a significant number of patients, but with no differences for both observed periods^{32, 36}. Clinical features and radiographic characteristics differed in the two observed periods. Tuberculosis that affects both lungs ($p = 0.008$) and cavernous form ($p = 0.005$) were significantly more frequent in

the period between 2000 and 2002. In the last 3 years, unilateral parenchymal form was more frequent. Lung radiographic findings indicated that milder changes were recorded in the second study group, while 15 years ago, moderate and extensive radiological changes were observed ($p = 0.002$). In the second observed period, there were more persons aged 50 and older with less extensive radiographic changes, similar to data from the other studies³⁴.

Unemployment, alcohol consumption and smoking are important social determinants and comorbidities in the elderly are the most significant risk factors for developing TB.

Conclusion

Sociodemographic factors relating to unemployment, lower level of education and poorer housing conditions were not significantly different between the reporting periods.

Among treated TB patients in the period between 2000 and 2002 there were more unemployed, working-age young man from urban areas who suffered from severe clinical form of TB with extensive radiographic changes. Comorbidities were rare. The link between smoking and alcohol consumption and the morbidity of tuberculosis is confirmed.

In the period between 2012 and 2014, there were significantly more patients from rural areas older than 50 years. Comorbidities were more frequent, especially DM and COPD.

Immunodeficiency diseases, especially HIV, are not predictors for developing TB in the northern Kosovo nowadays. Social determinants, older age and comorbidities are the most important risk factors for the persistent number of patients, and therefore this target group needs attention during the TB screening.

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