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PATIENT, HEALTHCARE SYSTEM AND TOTAL DELAY IN TUBERCULOSIS DIAGNOSIS AND TREATMENT AMONG SERBIAN POPULATION

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SUMMARY – Currently, topical are studies that examine different reasons for delay of tuberculosis (TB) diagnosis and its impact on disease prognosis. The aim was to examine three time periods associated with treatment delay: patient related, health system related and total delay. This retrospective-prospective study included 100 consecutive patients hospitalized at Department of Pulmonology, Clinical Center of Serbia, in the period from March to December 2015. Study results showed median patient delay to be 92.5 days. Total delay was affected by patient related delay. Median healthcare delay was 18.5 days. Patients that reported excessive alcohol consumption were more likely to have prolonged time to seek medical help. Years of alcohol consumption yielded moderate positive correlation with patient related delay ($r=0.362$, $p<0.001$). Correlation between the number of cigarettes and patient delay was moderate, positive and statistically significant ($r=0.314$, $p=0.001$). Delay in seeking medical help was more likely in patients with negative family history of TB. There was no difference in the effect of the presence of symptoms on patient related delay ($p>0.05$). Clinical characteristics such as patient TB category and chest radiograph abnormalities were not associated with prolonged patient related delay ($p>0.05$). Study results point to the importance of health education and/or health intervention in the population group at a high risk of TB.

Key words: *Tuberculosis; Prognosis; Retrospective Studies; Prospective Studies; Serbia; Alcohol Drinking; Health Education*

Introduction

Tuberculosis bacillus was discovered 120 years ago, but despite various treatments and medical efforts, this disease remains a global and undefeated health problem[1]. Due to the tuberculosis (TB) infectious nature, multiresistant form and possible transmission, timely diagnosis and treatment are the most important strategies for eradication. Dramatic increase of newly developed cases of TB worldwide that are caused by HIV co-infection and resistance to antituberculotic drugs have led the World Health Organization (WHO) declare TB a global threat. Other causes of the increasing TB incidence are poverty, insufficient education on diagnosis and treatment, and collapse of healthcare structure, which is common in developing countries[2].

Serbian population in 2014 was 8,900,000 inhabitants. The TB Control in Serbia project funded by Global Fund for Fighting AIDS, Tuberculosis and

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Malaria (GFATM), through directly observed treatment strategy (DOTS), started in Serbia in 2004, with the main aim of reducing TB incidence in a five-year period from 37 to 25 patients *per* 100,000 inhabitants (until 2009), and to 21/100,000 until 2015. This project reported TB incidence of 24, 23 and 18/100,000 people in 2008, 2009 and 2011, respectively[3]. The 2014 WHO report showed TB incidence of 24/100,000 people for Serbia[4,5].

Currently, topical are studies that examine different reasons for delay of TB diagnosis and its impact on disease prognosis. Delay of TB treatment can have several consequences, i.e. extensive disease, more complications, higher costs, and increased mortality[6]. Delayed time from first symptoms to diagnosis and treatment initiation can be divided into three main categories: patient related delay, healthcare system delay and total delay. Various factors can contribute to delayed diagnosis of tuberculosis but one factor stands out in poor and middle-income countries; it is patient education, which has been demonstrated to delay tuberculosis diagnosis and treatment[7].

The aim of this study was to examine three periods associated with delay, i.e. patient related delay, healthcare system delay and total delay, and their association with patient characteristics and socioeconomic status, positive/negative family history of TB, symptoms and chest radiograph abnormalities.

Subjects and Methods

This retrospective-prospective study included 100 consecutive patients hospitalized at Department of Pulmonology, Clinical Center Serbia, from March 2015 to December 2015. Physicians filled out the questionnaire for this study during interview with their patients. Patients were asked about their socioeconomic status (gender, age, smoking habit and alcohol consumption, occupation, and social status) and the time of appearance and presence of different symptoms (cough, chest pain, hemoptysis, breathlessness, weight loss, weakness and night sweats). Relevant medical information was extracted from medical history, i.e. the exact date of first visit to general practitioner (GP) office, first pulmonary radiology examination (chest x-ray, computed tomography (CT) scan) and first visit to the specialist and time of diagnosis.

Inclusion criteria were adults (age ≥18 years) with direct microscopic sputum or culture confirmed pulmonary TB. Patients who had no symptoms before the diagnosis were excluded from the study.

The criteria for TB diagnosis were positive sputum in direct microscopy or in culture, in combination with clinical findings and chest radiograph abnormalities. Smoking status was classified as non-smoker, ex-smoker (previously smoking at any time in life), and current smoker. Subjects were classified as non-consumer (no alcohol consumption in the last 12 months), rare consumer (occasionally up to two drinks), moderate consumer (up to 7 drinks *per* week), and excessive consumer (more than 4 drinks *per* day). Patient related delay was defined as the number of days elapsed from the first symptoms of TB to the first GP consultation. Healthcare system delay was defined as the number of days elapsed from the first consultation to the initiation of treatment. Total delay was calculated as the sum of patient delay and healthcare delay.

Ethics

Ethics Committee of the Clinical Centre of Serbia approved this study to be published in a medical journal. A written informed consent was obtained from patients participating in this study.

Statistics

Data were analyzed using the methods of descriptive and analytical statistics. The methods of descriptive statistics were measures of central tendency (mean and median), measures of variability (standard deviation and interquartile range), and relative numbers. The methods of analytical statistics were identification methods of empirical distributions, methods to assess the significance of differences, i.e. χ^2-test and Fisher test for categorical variables, and Pearson or Spearman correlation for numerical variables. Patient delay was treated as a dichotomous variable; cut-offs were chosen based on median of patient delay of 92.5 days in this sample; logistic regression was performed. The level of $p<0.05$ was considered statistically significant.

Results

This study included 100 consecutive patients, 67 (67%) male and 33 (33%) female. Marital status was as

follows: 53 (53%) married, 26 (26%) single and 21 (21%) widowed/divorced. Seventy-five (75%) patients were from urban area and 25 (25%) from rural area. Employment was reported in 48 (48%), unemployment in 32 (32%), retirement in 16 (16%) and student status in 4 (4%) cases. Low income was reported by 17 (17%) and middle income by 83 (83%) subjects, while none of the patients reported high income. Smoking habits were reported in 61 (61%) and alcohol consumption in 42 (42%) cases. Positive family history of TB was reported in 20 (20%) cases.

The most common symptoms present among TB patients were cough in 95 (95%), weakness in 84 (84%), weight loss in 70 (70%) and elevated body temperature in 61 (61%) patients. Other TB symptoms of lower frequency reported by our patients were night sweats in 54 (54%), chest pain in 26 (26%), hemoptysis in 19 (19%) and breathlessness in 10 (10%) patients. Clinical characteristics of the patients are presented in Table 1.

Table 1. Clinical characteristics of tuberculosis patients

		n	%
Patient category	Newly diagnosed	87	87.0
	Recurrence	7	7.0
	Treatment failure	2	2.0
	Treatment after discontinuation	4	4.0
TB classification	Pulmonary	98	98.0
	Extra pulmonary	2	2.0
Chest radiograph abnormalities	Initial	7	7.0
	Moderately expanded	61	61.0
	Extensive	32	32.0
Cavern	Yes	83	83.0
	No	17	17.0
Sputum	Smear positive for TB	88	88.0
	Culture positive	8	8.0
	Histologically confirmed	4	4.0

TB = tuberculosis

Most of the patients were newly diagnosed with the pulmonary form of TB and moderately expanded chest radiographic abnormalities and presence of cavern. The mean and median time of patient related, healthcare system related and total delay are shown in Table 2.

Patient delay accounted for a substantial part (78.4%) of total delay of 118.0 days. Patient characteristics and socioeconomic factors were examined as the possible predictors of delayed time to seek for medical help (Table 3).

Patients having reported excessive alcohol consumption were more likely to prolong the time to seek for medical help. Study results also showed positive and moderate correlation between the years of alcohol consumption and patient delay ($r=0.362$, $p<0.001$). Correlation between the number of cigarettes and patient delay was moderate, positive and statistically significant ($r=0.314$, $p=0.001$). Patients with a negative family history of TB were more likely to have delay in seeking for medical help.

There were no differences in the effect of the presence or absence of symptoms on patient delay from the first symptoms of TB to the first consultation with GP ($p>0.05$). Clinical characteristics such as patient TB category, TB classification, chest radiograph abnormalities, and presence of cavern were not associated with prolonged patient delay ($p>0.05$).

Discussion

Our study showed the median patient delay to be 92.5 days and total delay to treatment of TB was affected by patient delay. Previous studies that analyzed delayed time to diagnosis and treatment of TB showed very variable results. Median time elapsed between the onset of symptoms and first visit to a health facility has been reported in several studies, e.g., in Tanzania 120 days[8], Argentina 59 days[9], and Australia 11 days[10]. A recent systematic review concludes that the mean patient delay was 31.7 days[11].

Table 2. Patient delay, healthcare system delay and total delay

	Mean	Standard deviation	Median	25th Percentile	75th Percentile
Patient delay	106.80	71.96	92.50	60.00	127.50
Healthcare delay	24.95	24.80	18.50	10.00	31.00
Total delay	131.75	74.02	118.00	82.50	158.50

Table 3. Patient characteristics and socioeconomic parameters as factors for prolonged patient delay

		Patient delay					
		<92.5		>92.5			
		n	%	n	%	OR (95% CI)	p*
Age (years)	≤50	30	49.2	31	50.8	1	
	>50	20	51.3	19	48.7	0.919 (0.411-2.054	0.838
Gender	Male	29	43.3	38	56.7	1	
	Female	21	63.6	12	36.4	0.436 (0.185-1.029)	0.058
Marital status	Married	30	56.6	23	43.4	1	
	Single	12	46.2	14	53.8	1.522(0.593-3.908)	0.383
	Widowed/Divorced	8	38.1	13	61.9	2.120 (0.753-5.965)	0.155
Place of residence	Urban	38	50.7	37	49.3	1	
	Rural	12	48.0	13	52.0	1.113 (0.450-2.753)	
Education	None	5	71.4	2	28.6	1	
	Elementary school	10	45.5	12	54.5	3.000 (0.475-18.929)	0.242
	High school	27	47.4	30	52.6	2.778 (0.497-15.517)	0.244
	Higher education	8	57.1	6	42.9	1.875 (0.266-13.202)	0.528
Employment	Employed	25	52.1	23	47.9	1	
	Unemployed	17	53.1	15	46.9	0.959 (0.392-2.345)	0.927
	Retired	6	37.5	10	62.5	1.812 (0.568-5.778)	0.315
	Student	2	50.0	2	50.0	1.087 (0.141-8.360)	0.936
Socioeconomic status	Moderate	41	49.4	42	50.6	1	
	Low	9	52.9	8	47.1	0.868 (0.305-2.467)	
Smoking	Yes	29	47.5	32	52.5	1	
	No	16	59.3	11	40.7	0.623 (0.249-1.560)	0.312
	Ex-smoker	5	41.7	7	58.3	1.269 (0.362-4.441)	0.710
Alcohol consumption	None and rare consumption	37	63.8	21	36.2	1	
	Moderate	9	52.9	8	47.1	1.566 (0.525-4.670)	0.421
	Excessive	4	16.0	21	84.0	9.250 (2.789-30.584)	<0.001
Family history	Positive for TB	16	80.0	4	20.0	1	
	Negative	34	42.5	46	57.5	5.412 (1.660-17.646)	0.005

*Logistic regression; OR (95% CI) = odds ratio (95% confidence interval)

In our study, median healthcare delay was 18.5 days. A recent meta-analysis showed that healthcare procedure took 7 to 79 days[12]. Although our median healthcare delay was shorter than that reported in most studies[13], this time could be even shorter provided better healthcare organization and diagnostic tools available.

Total delay to TB treatment also varied among low- and middle-income countries, e.g., Iran 88 days[14], Ethiopia 80 days[15], China 71 days[16], and Columbia 120 days[17]. In most of developed countries with high income, total delay to TB treatment was shorter, e.g., Norway 63 days[14], Italy 65 days[18], and Australia 66 days[10]. As presented, our study results were in agreement with total delay reported in middle- and low-income countries.

We further examined factors that could contribute to patient delay to TB diagnosis and treatment. We found that among patient characteristics and socioeconomic factors, alcohol consumption was associated with prolonged time to diagnosis of TB. Alcohol consumption is associated with increased rates of TB[19]. Most of excessive alcoholics may neglect symptoms of the disease, which can prolong the time to diagnosis

and treatment. Besides that, other studies found that alcohol consumption can be a risk factor for TB delay[20,21]. Recent studies in the population at an increased risk of TB infection suggest that TB knowledge among high-risk population is suboptimal in low-income countries[22], as well as in developed countries[23]. TB education of population groups at a high risk of TB through health education and intervention is important.

Sixteen (80%) patients with a positive family history of TB patients had shorter delay of seeking medical help. We found that patients with positive TB in the family had right information about the disease and consequently had shorter delay to the first visit to a healthcare facility.

Male gender was found to be close to the conventional level of significance (p=0.056) for patient delay. Several studies report that gender has no effect on the prolonged time to diagnosis of TB[14,24,25.] In contrast, other studies found female gender to be associated with a prolonged time to TB diagnosis[26].

Smoking status was not associated with patient delay. The number of cigarettes *per* day showed moderate, positive correlation with patient delay.

In our study, age, marital status, socioeconomic status and employment had no influence on patient delay. Old age was found to be a risk factor for delayed TB diagnosis and treatment in two studies[25,27]. Enkhbat *et al*. found age ≤29 to be associated with extended delay[28]. Besides that, many studies found low income to be a risk factor for diagnostic delay[24,29-31]. Madebo and Lindtjorn found in their study that married patients, people with no formal education and people living in rural areas were likely to postpone seeking for professional help[32].

The symptoms that were most frequently reported by patients were cough, weakness and weight loss. Unexpectedly, the presence or absence of different symptoms was not significantly associated with prolonged delay. Primary healthcare practitioners should warn their patients with smoking habit and advise them to report any change in the quality or/and quantity of cough, so they can act with right treatment as early as possible.

Conclusion

Our study examined delay to TB diagnosis and treatment, i.e. patient related delay, healthcare related delay, and total delay. Median patient delay was 92.5 days and healthcare delay 18.5 days. Patient delay accounted for a substantial part (78.4%) of total delay of 118.0 days. We also identified factors affecting patient prolonged time to seek for medical help, i.e. excessive alcohol consumption, number of cigarettes *per* day and negative family history, pointing to the importance of better health education and necessity of more preventive health interventions in the population at a high risk of TB.

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Sažetak

KAŠNJENJE ZBOG BOLESNIKA, ZDRAVSTVENOG SUSTAVA I UKUPNO KAŠNJENJE U DIJAGNOSTICIRANJU I LIJEČENJU TUBERKULOZE U POPULACIJI SRBIJE

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Trenutno su veoma aktualne studije koje istražuju razloge za kašnjenje dijagnosticiranja tuberkuloze (TB) te njihov utjecaj na prognozu bolesti. Cilj je bio ispitati tri razdoblja povezana s kašnjenjem dijagnoze: bolesnikovo, zdravstvenog sustava i ukupno kašnjenje. Ovo retrospektivno-prospektivno istraživanje uključilo je 100 uzastopnih bolesnika s dijagnozom TB i hospitaliziranih u Klinici za pulmologiju Kliničkog centra Srbije između ožujka i prosinca 2015. Studija je pokazala medijan vremena kašnjenja bolesnika od 92,5 dana, što je utjecalo i na ukupno vrijeme kašnjenja. Medijan vremena kašnjenja zdravstvenog sustava bio 18,5 dana. Kod bolesnika koji su prekomjerno konzumirali alkohol bilo je vjerojatnije da će imati produženo vrijeme do traženja liječničke pomoći. Godine konzumiranja alkohola bile su u pozitivnoj i umjerenoj korelaciji s vremenom kašnjenja bolesnika ($r=0,362$, $p<0,001$). Odnos broja popušenih cigareta i vremena kašnjenja bolesnika bio je umjeren, pozitivan i statistički značajan ($r=0,314$, $p=0,001$). Bolesnici s negativnom obiteljskom anamnezom za TB imali su veću vjerojatnost kašnjenja dijagnoze. Nije bilo razlike u utjecaju prisutnosti simptoma na vrijeme kašnjenja bolesnika ($p>0,05$). Kategorija bolesnika s TB i nenormalnosti radiograma nisu bile povezane s vremenom kašnjenja bolesnika ($p>0,05$). Sve ovo ukazuje na važnost zdravstvenog odgoja i/ili zdravstvene intervencije kod stanovništva s visokim rizikom od TB.

Ključne riječi: *tuberkuloza; prognoza; retrospektivne studije; prospektivne studije; Srbija; alkohol, konzumacija; zdravstveni odgoj*