ORIGINAL ARTICLE

UDC: 616.24-002.5-079.4
https://doi.org/10.2298/VSP170301080S

Differences and similarities between the symptoms and clinical signs in patients with pulmonary tuberculosis and pneumonia

Razlike i sličnosti u simptomima i kliničkim znacima bolesti među bolesnicima lečenim od tuberkuloze pluća i pneumonije

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Abstract

Background/Aim. Tuberculosis in the second decade of the 21st century is an infectious disease with the highest mortality rate. In addition, in developed countries, pneumonia is the major couse of morbidity and mortality in adults. The aim of our study was to point out the differences and similarities between symptoms, laboratory parameters and clinical indicators in patients with pulmonary tuberculosis (PTB) and patients with pneumonia in the general population and in people belonging to the high risk groups for developing tuberculosis. **Methods.** This prospective study included patients with PTB (n = 70) and pneumonia (n = 75) treated at the Pulmonology Department of Clinical Hospital Center in Kosovska Mitrovica. **Results.** PTB was more frequent in men, 30–39 years of age (OR; 6:08), mainly from rural areas (p = 0.001), and with lower levels of education (p = 0.031). Pneumonia was more frequent in women older than 60 years of age (p = 0.0012). Night sweats (p = 0.001) and weight loss (p = 0.062) were significantly more frequent in patients with PTB, while chest pain (p = 0.001) and high temperature (p = 0.036) were more common in patients with pneumonia. X-ray changes in patients with PTB were located in the upper fields (p = 0.001), or appeared to be bilateral (p = 0.004). The strongest predictor associated with an increased risk of night sweats was diagnosed PTB (OR = 30.0). The chest pain was a predictor of pneumonia, unilateral changes (OR = 4.65) in the lower lung fields (OR = 0.08). **Conclusion.** Night sweats, weight loss and chest X-ray abnormalities in upper fields were significant indicators of PTB. Chest pain, fever and chest X-ray abnormalities in lower fields were significant indicators of pneumonia.

Key words:
tuberculosis, pulmonary; pneumonia; signs and symptoms; risk factors.

Apstrakt

Uvod/Cilj. Tuberkuloza je u drugoj dekadi 21. veka infektivna bolest sa najvišom stopom mortaliteta. Uz to, u razvijenim zemljama, pneumonija je glavni uzrok morbiditeta i mortaliteta odraslih osoba. Cilj našeg istraživanja bio je da se ukaže na razlike i sličnosti u simptomima, laboratorijskim parametrima i kliničkim pokazateljima u ranoj dijagnozi tuberkuloze u opštoj populaciji i kod osoba koje pripadaju rizičnim grupama za oboljevanje od tuberkuloze pluća. **Metode.** Prospektivnom studijom smo obuhvatili sve obolele od tuberkuloze pluća (n = 70) i pneumonije (n = 75) lečene na Odeljenju pulmologije Kliničkobolničkog centra u Kosovskoj Mitrovici. **Rezultati.** Od tuberkuloze pluća češće su obolevali muškarci, starosti 30–39 godina (OR 6.08, 95 CI% 1,16–31,84), uglavnom sa sela (p = 0,001), nižeg stepena obrazovanja (p = 0,031). Od pneumonije su češće obolevale ženske osobe starije od 60 godina (p = 0,012). Kod obolelih od tuberkuloze pluća bilo je značajno češće noćno znojenje (p = 0,001) i gubitak težine (p = 0,062), kod obolelih od pneumonije bol u grudima (p = 0,001) i visoka temperatura (p = 0,036). Radiografske promene kod obolelih od tuberkuloze pluća bile su uglavnom u gornjim poljima pluća (p = 0,001) i obostrano (p = 0,004). Najjači prediktor povezan sa dijagnozom tuberkuloze je noćno znojenje (OR = 30,0). Bol u grudima je bio prediktor pneumonije i bilateralnih promena (OR = 4,65) u donjim plućnim poljima (OR = 0,08). **Zaključak.** Noćno znojenje, gubitak težine i radiografske promene u gornjim poljima pluća bile su značajni indicatori tuberkuloze pluća. Bol u grudima, visoka tempeartura i ra-

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diografske promene u donjim poljima pluća bile su značajno češće kod pneumonije.

Ključne reči:
tuberkuloza pluća; pneumonija; znaci i simptomi; faktori rizika.

Introduction

Tuberculosis (TB) in the second decade of the 21st century is an infectious disease with the highest mortality rate. During 2015, TB affected 9.4 million people, with a fatal outcome in 1.4 million patients that were treated. There has been a decline in incidence in most areas around the world, but the scale of this decline is far smaller than expected. The current global TB incidence rate continues to fall by around 2% per year which is insufficient to achieve the goal of eliminating TB by year 2050 [1]. The existing recommendations for an early detection of TB appear to be insufficient. This is particularly true for the high-risk groups with clearly expressed symptoms that do not seek medical advice. The potential health, social and/or economic benefits, would probably be higher if not for the delayed diagnosis in the high-risk groups [2]. Particular attention should be paid to people with bad life habits (cigarette smoking, alcohol consumption) and the high-risk groups: HIV positive, diabetics, refugees, prisoners, the homeless and the elderly. For any given risk group, an early treatment provides less severe clinical manifestations and less economic costs, and in epidemiological sense, prevents the spread of the epidemic [3].

The diagnosis of pulmonary TB (PTB) is based on the presence of respiratory symptoms and characteristic signs, laboratory parameters, a direct microscopy examination of sputum, sputum culture and chest radiography [4]. In countries with a limited health infrastructure, the diagnosis of PTB, and especially a sputum smear-negative PTB (SNPT), can present a challenge [5]. Symptom screening is a key component in fight against TB and is one of the main strategies for the eradication of this contagious disease. The significant symptoms include a prolonged cough that lasts more than 2 weeks, a productive cough, hemoptysis, fever, night sweats, weight loss and chest pain [6]. Symptom screening is appealing because it is simple, does not require expensive equipment and can be used in general medical practice. Cough is the main symptom of TB and is considered a positive symptom if it lasts longer than two weeks. It could be accompanied by sputum production or haemoptysis [7]. Productive cough is more common in sputum positive TB and is associated with 4–5 times higher level of disease transmission compared with sputum negative TB [5]. Risk factors for developing PTB are malnutrition and low body mass index (BMI) which make symptoms such as weight loss and poor appetite particularly important [8]. TB patients report night sweats as one of the characteristic symptoms [9], while chest pain is rarely reported [10]. However, it is necessary to confirm the diagnosis in a fast and systematic way as these signs are also indicative of a number of other respiratory diseases.

Respiratory diseases such as PTB and pneumonia induce a series of laboratory abnormalities such as anemia and accelerated erythrocyte sedimentation rate. Numerous studies documented anemia in patients with PTB. Anemia, caused by chronic infections such as TB, results from the suppression of erythropoiesis by inflammatory mediators [11, 12].

Symptom screening is the first step in diagnosing PTB, although the symptoms themselves have relatively little significance. Detecting suspicious symptoms provides a timely suspicion of disease while chest radiography, culture and/or findings of sputum positive for Koch bacillus will lead to a definite diagnosis. A direct microscopy examination of sputum should be a routinely applied analysis in all patients who have manifested symptoms of PTB. Late diagnosis of TB largely influences the low rate of incidence decline and leads to poorer medical outcomes [13].

In developed countries, pneumonia is the major cause of morbidity and mortality in adults [14] and it leads to a high level of hospitalization, especially in the elderly. The onset is sudden, accompanied by the characteristic respiratory symptoms. Lifestyle factors (cigarette smoking, alcohol abuse, social determinants) and associated diseases (cardiovascular diseases, diabetes mellitus, HIV) are high risk factors for developing TB and pneumonia. Patients can also exhibit multiple risk factors at the same time [15].

The aim of our study was to point out the differences and similarities between symptoms, laboratory parameters and clinical indicators in patients with PTB and patients with pneumonia in the general population and in people belonging to the high risk groups for developing TB.

Methods

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

A prospective study was conducted at the Department of Pulmonology of the Health Center in Kosovska Mitrovica, the reference hospital for TB treatment. The study included patients with TB and pneumonia treated in the period between 2011 and 2015. All hospitalized patients (145) were divided into 2 groups: 70 patients with PTB and 75 patients with pneumonia.

On admission, the patients' data regarding demographics, age, gender, residence, marital status, education, employment status and social determinants was gathered. We also processed risk factors for developing TB and pneumonia, including smoking, alcohol consumption, 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.

All of the patients exhibited positive symptoms of cough, expectoration, haemoptysis, chest pain, fever, night

sweats and asthenia. Clinical signs of the disease included weight loss, anemia and high blood sedimentation rate. Weight loss was defined as a positive symptom if it exceeded 10% of the total body weight in the last three months. Hemoglobin below 12 g/dL in women and 13 g/dL in men was taken as the reference value for the confirmation of anemia. Haemoptysis were positive if it occurred only once.

Clinical follow-up included an examination of the sputum before the treatment (negative and positive results), the type of TB (new or relapse) and the outcome of the treatment. The results of chest X-rays were categorized according to the scale of the changes, their localization and their morphological structure.

Sputum samples were taken from all the patients for a direct microscopy of the preparations stained according to the 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 Löwenstein-Jansen medium. PTB was bacteriologically confirmed if the two sputum findings confirmed bacillus and/or in a case of positive sputum cultivation. The final diagnosis of pulmonary TB was made based on the M+ in sputum and/or chest X-rays. The diagnosis of pneumonia was made based on clinical findings, bacteriological sputum findings and chest X-rays. The interpretation of chest X ray abnormalities was performed by a radiologist. Chest postero-anterior X-rays in both groups focused on pulmonary parenchyma and caverns. The interpretation of abnormalities in the pulmonary parenchyma included unilateral or bilateral changes and location changes in the lower, medium and upper fields.

Statistical analysis

The data were analyzed by the descriptive statistical methods and presented as frequencies and relative numbers. For the analysis of frequency differences between the groups, the chi-square test was used. Binary logistic regression was the technique used to analyze the dependencies between activities. The multiple logistic regression model included all the predictors that had statistical significance at 0.05 in the single logistic regression model. The criterion for a statistical significance was $p < 0.05$.

For the statistical data analysis we used the SPSS Statistics 22 software program SPSS Statistics 22. Inc., Chicago, IL, USA).

Results

The study included the TB and pneumonia patients treated at the Pulmonology Department in the period from 2011 to 2015. Out of 145 patients, 70 were treated for PTB and 75 for pneumonia. There were significant differences in demographic characteristics between the two groups of patients. There was a significantly higher incidence of PTB in the males ($p < 0.001$), middle-aged and older, while the patients suffering from pneumonia were older than 60 years of age ($p = 0.0012$). In relation to their place of residence, patients from the rural areas were significantly more prone to TB infection ($p < 0.001$). Family status had no significant influence on the onset of these two diseases. The TB patients belonged to lower-educational level groups ($p = 0.025$). Patients' occupation did not influence the onset of these respiratory infectious diseases and there was no significant difference of incidence between the patients with TB and the patients with pneumonia ($p = 0.394$) (Table 1).

Lifestyle and comorbidity impact the morbidity of both TB and pneumonia. In the patients with the TB bad habits, such as cigarette smoking ($p = 0.002$) and alcohol consumption ($p = 0.050$), were dominant. Associated diseases were equally present in both groups of patients, except for diabetes mellitus which was significantly more frequent in the patients with pneumonia ($p = 0.024$). The social determinants were important in the patients with PTB ($p = 0.001$) (Table 1).

The respiratory symptoms were characteristic for both groups of patients. The onset of the symptoms in the patients suffering from TB was longer than 2 weeks before visiting a doctor ($p < 0.001$). Cough, expectoration, hemoptysis and fatigue symptoms did not differ significantly. The patients with TB frequently reported weight loss and night sweats ($p < 0.001$). In the patients with pneumonia, chest pain was prevalent ($p < 0.001$) as well as a high temperature ($p = 0.036$). The laboratory variables, hemoglobin values, hematocrit and erythrocyte sedimentation rate did not differ significantly between the two groups of patients. Positive bacteriological culture of sputum also did not differ (Table 2).

There were significant differences in radiographic changes between the groups. In the patients with the TB X-ray changes were more common in the upper lung fields ($p < 0.001$) and both lungs were significantly more likely to have been affected by the changes ($p = 0.004$). The incidence of a relapse in the patients with TB was 7%, while in the patients with pneumonia there was no relapse recorded. The relapse of the disease was significantly more frequent in PTB ($p = 0.018$). The hospital treatment of the patients with TB was significantly longer than in the patients with pneumonia ($p < 0.001$) (Table 2).

Night sweats were typical and statistically highly significant symptom in the patients with TB. In the simple logistic models, the variables associated with an increased risk of developing night sweats were: the PTB diagnosis ($p = 0.001$), 30–39 years of age ($p = 0.001$) and 40–49 years of age ($p = 0.004$) compared to the over-60 years of age group taken as the reference value, life in the city ($p = 0.022$) and diabetes mellitus ($p = 0.009$). The variables associated with a reduced risk of developing night sweats are the X-ray changes in the upper ($B = -1.77$; $p = 0.022$) and middle lung fields ($B = -2.60$; $p = 0.007$). In the multiple logistic regression model, the strongest predictor associated with an increased risk of night sweats was a diagnosed PTB ($p < 0.001$; OR = 30.0 (6.56–137.0) which indicated that those suffering from PTB had 30 times higher risk of developing night sweats (Table 3).

Chest pain is an important symptom in the patients with pneumonia. The univariate and multivariate logistic regres-

sion model indicated that chest pain was not a predictor for developing PTB (p = 0.002; OR = 0.006 (0.009–0.35). Also, there was no significant relation between chest pain as an important symptom of pneumonia and smoking habits (p = 0.05; OR = 0.30 (0.09–1.0). The pain predictors were unilateral changes (p = 0.028; OR = 4.65 (1:19 to 18:21) in the lower lung fields (p = 0.003; OR = 0.08 (0:02 to 0:41) (Table 4).

Table 1

Sociodemographic characteristics and risk factors in the patients with pulmonary tuberculosis (PTB) and the patients with pneumonia

Characteristics	PTB (n = 70)	Pneumonia (n = 75)	*p*
	n (%)	n (%)	
Age (years)			
20–29	11 (15.7)	11 (14.7)	
30–39	6 (8.6)	7 (9.3)	
40–49	10 (14.3)	16 (21.3)	0.0012
50–59	26 (37.1)	7 (9.3)	
> 60	17 (24.3)	34 (45.3)	
Sex			
male	49 (70.0)	30 (40.0)	<0.001
female	21 (30.0)	45 (60.0)	
Residence			
rural	57 (81.4)	36 (48.0)	<0.001
urban	13 (18.6)	39 (52.0)	
Marital status			
single	30 (42.9)	28 (37.3)	0.497
married	40 (57.1)	47 (62.7)	
Education			
primary	41 (58.6)	30 (40.0)	
secondary	29 (41.4)	42 (56.0)	0.031
high	0 (0)	3 (4.0)	
Employment status			
unemployed	15 (21.4)	22 (29.3)	
toiler	20 (28.6)	13 (17.3)	0.394
office worker	11 (15.7)	13 (17.3)	
pensioner	24 (34.3)	27 (36.0)	
Smoking status			
never	23 (32.9)	43 (57.3)	
current	39 (55.7)	20 (26.7)	0.002
former	8 (11.4)	12 (16.0)	
Alcohol use	12 (17.1)	5 (6.7)	0.050
Social determinants	29 (41.4)	9 (12.0)	< 0.001
Cardiovascular diseases	15 (21.4)	23 (30.7)	0.206
Diabetes mellitus	9 (12.9)	21 (28.0)	0.024
COPD	11 (15.7)	8 (10.7)	0.368

COPD – chronic obstructive pulmonary disease.

Table 2

Frequency of reported symptoms, clinical signs and radiological findings in the patients with pulmonary tuberculosis (PTB) and the patients with pneumonia

Parameters	PTB (n = 70)	Pneumonia (n = 75)	*p*
	n (%)	n (%)	
Simptom duration (weeks)			
< 2	11 (15.7)	53 (70.7)	< 0.001
> 2	59 (84.3)	22 (29.3)	
Cough	58 (82.9)	66 (88)	0.379
Productive cough	42 (60)	41 (54.7)	0.517
Hemoptysis	8 (11.4)	9 (12.0)	0.915
Chest pain	8 (11.4)	46 (61.3)	< 0.001
Fever	44 (62.9)	59 (78.7)	0.036
Night sweats	42(60.0	14 (18.7)	< 0.001
Asthenia	43 (61.4)	48 (64)	0.749
Weight loss	35 (50.0)	26 (34.7)	0.062
Anemia	22 (31.4)	18 (24.0)	0.317
Sedimentation rate	58 (82.9)	65 (86.7)	0.523
Culture			
negative	28 (40.0)	38 (50.7)	
positive	42 (60.0)	37 (49.3)	0.197
Location CXR abnormality			
upper field	54 (77.2)	1 (1.4)	
medium field	8 (11.4)	46 (61.3)	< 0.001
lower field	8 (11.4)	28 (37.3)	
Any CXR abnormality			
right	9 (12.8)	26 (33.3)	
left	24 (34.3)	25 (34.7)	0.004
bilateral	37 (52.9)	24 (32.0)	
Radiological severity			
initial	37 (52.9)	49 (65.3)	0.299
advanced TB	33 (47.1)	26 (34.7)	
Outcomes			
cured	65 (92.9)	75 (100.0)	0.018
retreatment	5 (7.1)	0 (0)	
Intra hospital therapy (days)			
< 30	17 (24.3)	70 (93.3)	
< 60	21 (30.0)	5 (6.7)	< 0.001
> 60	32 (45.7)	0 (0)	

CXR – chest x-ray.

Table 3

Uni- and multivariate logistic analysis of the association of night sweat and risk factor and clinical characteristics

Factors	Univariate OR (95% CI)	*p*	Multivariate OR (95% CI)	*p*
Diagnosis				
PTB	34.4 (4.07–290.9	0.001	30.0 (6.56–137.0)	< 0.001
pneumonia	Reference			
Age (years)				
20–29	15.0 (2.26–100.1)	0.005	5.51 (1.48–20.46	0.011
30–39	64.0 (5.1–798.9)	0.001	15.79 (2.67–93.54	0.002
40–49	14.8 (2.35–93.64)	0.004	6.18 (1.64–23.33)	0.007
50–59	9.0 (1.78–45.09)	0.008	4.47 (1.33–15.02)	0.016
> 60	Reference			
Sex	1.11 (0.35–3.55)	0.86		
Residence				
rural	Reference			
urban	4.30 (1.23–14.98)	0.022		
Education level				
primary	Reference			
secondary	0.29 (0.08–1.02)	0.054		
high	0 (0.0)	0.999		
Smoking status				
no	Reference			
yes	0.91 (0.27–3.06)	0.872		
former	1.63 (0.36–7.49)	0.528		
Any alcohol use	0.24 (0.03–1.84)	0.169		
Social determinants	0.70 (0.19–2.67)	0.606		
Diabetes Mellitus	8.59 (1.73–42.65)	0.009	4.80 (1.34–17.21	0.016
Cough duration				
< 2 weeks	Reference			
> 2 weeks	1.12 (0.34–3.70)	0.858		
Fever	1.52 (0.45–5.12)	0.499		
Location CXR abnormality				
upper field	0.17 (0.04–0.77)	0.022	0.17 (0.04–0.82)	0.027
medium filed	0.07 (0.01–0.49)	0.007	0.28 (0.08–0.98)	0.047
lower field	Reference			
Any CXR abnormality				
right	Reference			
left	2.19 (0.63–7.59)	0.218		
bilateral	2.85 (0.74–11.02	0.128		
Outcomes	8.62(0.59–126.6)	0.116		
Intra hospital therapy (days)				
< 30	Reference			
< 60	0.68 (0.14–3.22	0.623		
> 60	4.23 (0.72–24.7)	0.109		

OR – odds ratio; CI – confidence interval; PTB – pulmonary tuberculosis; CXR – chest x-ray.

Table 4

Uni- and multivariate logistic analysis of the association of chest pain and risk factor and clinical characteristics

Factors	Univariate	*p*	Multivariate	*p*
	OR (95% CI)		OR (95% CI)	
Diagnosis				
PTB	0.01 (0.001–0.15)	0.001	0.06 (0.009–0.35)	0.002
pneumonia	Reference			
Age (years)				
20–29	1.79 (0.266– 12,025)	0.549		
30–39	4.37 (0.422–45,251)	0.216		
40–49	2.06 (0.344–12,785)	0.435		
50–59	2.06 (0.376–11,314)	0.404		
> 60	Reference			
Sex	0.66 (0.231–1,937)	0.459		
Residence				
rural	Reference			
urban	1.45 (0.449–4,713)	0.532		
Education level				
primary	Reference			
secondary	0 (0.0)	0.999		
high	1.81 (0.501–6,546)	0.366		
Smoking status				
no	Reference			
yes	0.30 (0.09–1.0)	0.050	0.39 (0.15–1.0)	0.050
former	0.11 (0.02–0.68)	0.018	0.13 (0.03–0.55)	0.006
Any alcohol use	0.95 (0.130–7,036)	0.964		
Social determinants	2.17 (0.491–9,650)	0.306		
Diabetes mellitus	0.701 (0.168–2,933)	0.627		
Cough duration				
< 2 weeks	Reference			
> 2 weeks	2.45 (0.742–8,140)	0.141		
Fever	0.62 (0.181–2,171)	0.461		
Location CXR abnormality				
upper field	0.23 (0.029–1,921)	0.177	0.38 (0.07–2.03)	0.255
medium field	0.18 (0.05–0.71)	0.014	0.45 (0.15–1.33)	0.148
lower field	Reference			
Any CXR abnormality				
right	Reference			
left	4.65 (1.19–18.21)	0.028	2.53 (0.83–7.73)	0.102
bilateral	1.83 (0.459–7,362)	0.390	1.14 (0.37–3.49)	0.819
Outcomes	1.56 (0.068–35,668)	0.781		
Intra hospital therapy (days)				
< 30	Reference			
< 60	7.13 (1.07–47.64)	0.043		
> 60	4.14 (0.360–47,607)	0.254		

OR – odds ratio; CI – confidence interval; PTB – pulmonary tuberculosis; CXR – chest x-ray.

Discussion

The diagnosis of TB can be established through examining clinical symptoms [1], chest radiography [3], sputum culture, sputum microscopy and the combinations of these [6]. In our study, we evaluated the symptoms, laboratory parameters and clinical signs of the disease in the patients with PTB and pneumonia in Northern Kosovo. These can contribute to determining the diagnostic value of symptoms and provide the support for improving strategies for the detection and diagnosis of new cases of PTB. Symptom screening contributes to an early detection and reduces the spread of PTB [3].

Anti-TB dispensary (ATD) in Kosovska Mitrovica is a very well organized medical institution for a complete diagnosis of TB. Most patients with suspected symptoms are referred to ATD, where the diagnosis is quickly given after a direct microscopic examination of sputum for Koch's bacillus and the chest X-ray. Due to similar initial symptoms of pneumonia and TB, it can happen that a general practitioner does not recognize TB which postpones anti-TB treatment, and such a patient becomes potentially contagious to the environment and can expect a worse outcome.

One of the major causes of morbidity and mortality in adults in developed countries is pneumonia [13]. It is, also, a frequent cause of hospitalization in the elderly. The main risk factors for the incidence of pneumonia, besides older age, are associated diseases. In people older than 60 years of age, the most common comorbidities are diabetes mellitus [16], a metabolic syndrome, cardiovascular diseases and chronic obstructive pulmonary diseases [13]. There is a high prevalence of pneumonia in patients with multiple lifestyle risk factors and comorbidities. Pneumonia often affects older men while, in our study, the women were more likely to be afflicted (60%) [17].

Several lifestyle factors are associated with an increased risk of PTB and pneumonia, including smoking and alcohol abuse [13, 14]. Smoking and excessive alcohol abuse are major health risks globally and are targets for interventions to reduce the global burden of this disease. Ensuring that patients make appropriate lifestyle changes would help reduce the overall burden of pneumonia. Similarly, being underweight may predispose patients to pneumonia due to the consequences of the undernutrition conditions on immune function, so assessment of the nutritional status of vulnerable patients might help identify those at increased risk of PTB and pneumonia [10, 17, 18].

The risk factors for PTB are: male gender, low BMI and alcohol consumption [19, 20]. The survey of 14 countries with the highest rate of TB incidence showed that the risk factors are more common in men than in women. Men of lower education, middle aged and older, were more likely to develop PTB. Also, men who consume alcohol and smoke cigarettes were significantly more predisposed to develop TB. There were less smokers among the affected women and they rarely consumed alcohol [17].

High-risk groups include people with a significantly higher incidence and prevalence of TB than the general population. They may be people with an individual risk of morbidity (such as HIV infection), or people from specific geographical locations or institutions. Smokers, alcohol consumers, diabetics or people with a BMI < 18.5 kg/m^2 are independently associated with the risk of developing TB. In most of the developed countries, diabetes is associated with a high BMI, where an associated obesity may be the cause of diabetes. Obesity and diabetes have a high prevalence in developed countries, and their possible interaction with smoking or heavy alcoholism in developing an active TB is a cause for worry [21, 22].

Smoking, alcohol consumption, diabetes and a low BMI can lead to a progression from a latent to an active form of TB. Possible mechanisms for smoking include the impaired clearance of secretions on the tracheobronchial mucosal surface, reduced phagocytic function of pulmonary alveolar macrophages, decreased production of tumor necrosis factor in pulmonary macrophages and increased iron overload in pulmonary macrophages [18, 23]. Chronic alcohol use has been shown to reduce a macrophage response and activate the immune system thus raising the risk of morbidity. The experimental studies showed that hyperglycemia may affect a host's immune response to the PTB. Malnutrition can reduce the host's protective immune response either by interfering in the interaction between monocyte-macrophages and T-lymphocytes and their cytokines, or by secondary immunodeficiency that increases the host's susceptibility to infection.

The important symptoms in the diagnosis of TB are: cough that persists for at least 2 weeks, expectoration, fever, night sweats, weight loss, asthenia, chest pain, and hemoptysis [24]. There is a possibility of only one symptom being present or a combination of several sensitive symptoms associated with TB. Cough is the main symptom of TB but also the main cause of the transmission of this disease. It occurs as a consequence of an inflammatory response to mycobacterial infection. An adequate response to therapy is manifested by the reduction of cough [7]. A cough that lasted for more than 2 weeks was present in 82.9% of our patients suffering from TB, while in 60% of the cases it was accompanied by sputum production, which coincides with the data of other studies [8, 12]. A cough that lasted longer than 2 weeks was significantly more frequent among sputum-positive TB [25], while a cough that lasts less than 2 weeks can be symptomatic of SNPT, but WHO recommends including a cough of any duration in the assessment of TB [24]. Early diagnosis and treatment of sputum-positive PTB (SPPT) in patients with a chronic cough is of high priority in reducing the transmission of TB [26, 27].

However, cough was equally frequent in patients with PTB and pneumonia. In our patients suffering from PTB, the symptoms started more than 2 weeks prior to visiting a doctor and they were manifested gradually, first with a cough and sputum production, and later with night sweats (60%), subfebrile temperature (62.9%) and weight loss (50%). In our patients suffering from pneumonia, the symptoms were sudden and fast developing and most of the patients were hospitalized in less than 2 weeks from the onset of symptoms. The patients suffering from pneumonia experienced a high temperature (78.7%) and chest pain that intensified during breathing (61.3%).

The symptoms that were particularly significant in patients with TB are night sweats and weight loss which, together with a persistent cough increase the specificity of these symptoms. Chest pain during breathing (11.4%) is not a significant symptom in the diagnosis of PTB [15]. Chest pain is one of the most common symptoms in the general population and can be the result of chest, abdomen and internal organs related diseases. One of the more common causes of chest pain are respiratory diseases, especially pneumonia [10]. Symptom screening is simple and is used in general medical practice. However, compared to the symptom screening, the chest radiography shows greater accuracy, while the combination of the two provides a far greater reliability [28]. Poor performance of symptom screening in the PTB detection was recorded in several studies, including the symptoms with the highest sensitivity, such as cough, fever, night sweats and weight loss [26].

Particular attention should be paid to the diagnosis of sputum negative TB. In areas with a higher prevalence of TB and HIV, the clinical signs and inexpensive tests, such as direct microscopy, tuberculin skin test and chest radiography, are of great importance in the diagnosis of PTB [29, 30]. Anorexia, asthenia and a less persistent cough are good predictors of SNPT. These symptoms thus deserve to be recommended as indicators of the SNPT diagnosis within an ATB dispensary. This strategy can help reduce morbidity and mortality associated with a late SNPT diagnosis [30]. Sputum-negative TB was present in 40% of those affected in Northern Kosovo, which is consistent with the results of other studies [5, 15, 30, 31], while the atypical radiographic changes occurred in 23% of the affected. The symptom screening had a significant role in these cases as it enabled the initial treatment until the disease was finally confirmed by Löwenstein-Jensen culture medium. Culture is the golden standard for laboratory confirmation of PTB [32].

PTB and pneumonia induce a series of laboratory abnormalities such as anemia, accelerated erythrocyte sedimentation rate, low serum albumin levels, hyponatremia, abnormal liver function, leukocytosis and hypocalcaemia. Numerous studies documented anemia in patients with TB. Anemia was present in 31.9% of our patients, but in most cases it was benign. Anemia, caused by chronic infections such as TB, results from the suppression of erythropoiesis by inflammatory mediators [33]. On the other hand, the disruption of iron homeostasis occurs with an increased absorption and retention of iron in the reticuloendothelial system in chronic infections such as TB [11]. Iron is an important growth factor. *Mycobacterium tuberculosis* and the retention of iron in the reticuloendothelial system are seen as defense mechanisms. Anemia improves with sputum conversion. Female gender and older age are risk factors for the concurrence of TB and anemia. Anemia is a common hematological abnormality in patients with PTB, it is usually mild and improves with the anti-TB treatment [34].

The symptom screening is the first step in early diagnosis of PTB both in the general population and high-risk groups. Patients who report symptoms indicating PTB should be referred to the microbiologic examination of sputum taken from three successive samples, sputum culture and chest X-ray. The confirmation of negative sputum smear results and the radiographic changes uncharacteristic of PTB further complicate an early diagnosis. In our patients that were treated for PTB night sweats were one of the characteristic symptoms which indicated 30 times greater risk of developing PTB; however, the radiographic changes were not in correlation with this symptom of the disease.

The univariate and multivariate logistic regression indicated chest pain as a significant predictor of pneumonia, accompanied by radiographic changes on the left or the right side and in the lower lung fields, which facilitated the diagnosis of pneumonia. Some symptoms in patients with PTB and pneumonia overlap and result in a late diagnosis of PTB. It is necessary to pay attention to the characteristic symptoms and clinical signs of the disease especially among high-risk groups, and refer the affected to appropriate centers for further diagnostic procedures. The bacteriological confirmation of sputum and chest radiography are important in the confirmation of suspected PTB. Early diagnosis of the disease is one of the first steps in its suppression.

Conclusion

TB incidence was more frequent in middle-aged and elderly men with bad life habits, smokers and alcohol abusers, people of low education and social status. Symptomatic cough lasted for more than 2 weeks before being reported to a doctor. The most pronounced symptoms were night sweats and weight loss. Patients treated for pneumonia at the same time were more frequently women, older than 60 years of age. Pneumonia and diabetes mellitus comorbidities were significant. The affected visited a doctor in less than 2 weeks from the onset of symptoms of the disease. A significantly higher number of patients with pneumonia had a high fever and chest pain during breathing.

The strongest predictor associated with an increased risk of night sweats was PTB. High fever and chest pain during breathing were correlated with the radiographic changes in middle or lower lung fields which indicated pneumonia. In conclusion, this study may help physicians understand the link between the symptoms, their duration, the risk factors and radiological findings in early diagnosis of PTB.

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Received on March 01, 2017.
Revised on April 29, 2017.
Accepted on May 22, 2017.
Online First May, 2017.