

Available online at www.sciencerepository.org

Science Repository



Research Article

Changing Pattern of Tuberculosis: Clinical Presentation Within a Decade - Analysis from South-East Europe

Sanja Popović Grle^{1,2}, Vesna Trkeš¹, Matea Škoro^{1*}, Marina Lampalo¹ and Marija Alilović¹

¹University Hospital Centre Zagreb, Clinical Department for Lung Diseases Jordanovac, Zagreb, Croatia

²Medical School University of Zagreb, Zagreb, Croatia

ARTICLE INFO

Article history:

Received: 14 May, 2020

Accepted: 23 May, 2020

Published: 30 May, 2020

Keywords:

Tuberculosis

mycobacterium tuberculosis

epidemiology

comorbidity

acid-resistant bacilli

ABSTRACT

Introduction: Tuberculosis (TB) is an infectious disease from which people suffer even in the 21st Century. According to official data for Croatia, the number of cases in the last decade has been decreasing.

Aim: Due to the triple reduction in incidence in the last ten years in Croatia, the purpose of this study is to investigate whether patient characteristics have been changed, along with their comorbidities.

Material and Methods: This was a cross-sectional study where we treated 230 patients (62.1% male and 37.8% female) age 40-60 years with tuberculosis in 2003 and in 2013, we treated 70 patients (54.9% of men and 45% women). Tuberculosis was diagnosed by direct microscopy of sputum, catheter aspirate, tumor tissue, lymph node puncture, swab wound in 2003 and by direct microscopy of sputum samples, catheter aspirates and bronchial washing samples in 50% of cases in 2013.

Results: In 2003, 95.2% of patients had pulmonary tuberculosis. Comorbidities were found in 63.8%. 51.3% were smokers, 36.5% were alcoholics, diabetes and chronic obstructive pulmonary disease (COPD) was found in 12.2% and tumors in 6.5%. After 10 years, 91.4% of patients had pulmonary tuberculosis. 90% of them had comorbidities - 14.2% of patients had diabetes mellitus, 10% were treated for malignancies, COPD was present in 8.5%. 31.4% were smokers, while alcoholism was found in 11.4%.

Conclusion: After 10 years tuberculosis has changed its face in South-East Europe. TB occurs more often in the elderly population with comorbidities in 90% of cases (mostly diabetes mellitus, malignancies and COPD). Men are no longer a risk group because women are affected almost equally. Clinical awareness of the possibility of TB should be considered in patients with comorbidities, and active screening and prevention should be undertaken.

© 2020 Matea Škoro. Hosting by Science Repository.

Introduction

Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis*. It belongs to a group of granulomatous diseases of well-known aetiology. Around 8 million people are in contact with tuberculosis every year, and 3 million die. Around one-third of the world's population is infected with tuberculosis, of which 5-10% will suffer from tuberculosis immediately after infection or after several years [1].

The global incidence of tuberculosis in 2016 is 140/100.000 (range 118-164). Estimated epidemiological burden of TB for the American region amounted 27/100.000 (range 26-29), for the African region 254/100.000 (range 227-284), East Mediterranean 114/100.000 (range 86-147), Europe 32/100.000 (range 27-36), South-East Asia 240 (range 164-331) and the Western Pacific 95/100.000 (range 79-113) [2].

After year 1955, when the number of registered TB cases in Croatia was the highest ever (20.000 TB patients), number of TB cases was in

*Correspondence to: Matea Škoro, pulmonology resident at University Hospital Centre Zagreb, Clinical Department for Lung Diseases Jordanovac, Jordanovac 104, 10000 Zagreb, Croatia; Tel: 385994025755; E-mail: skoro.matea@gmail.com

constant decrease. In 1991, the incidence went up to 45/100.000 and continued to increase during 1992 and 1993 due to the war. Namely, increase in tuberculosis cases was attributed to the migration of inhabitants from regions with a higher number of cases of tuberculosis, the increased number of drug and alcohol addicts and also the increase in the population of the homeless [3]. During the year 2002, the incidence of tuberculosis in Croatia amounted to 33/100.000 and mortality 4.1/100.000. There were significant differences concerning the number of cases with a higher incidence of tuberculosis in the northern regions compared to the southern regions. In 2002 the greatest number of cases was registered in the Sisačko-Moslavačka County (57.2/100.000) in the middle continental part of Croatia, and the lowest in the Dubrovačko-Neretvanska County (12.2/100.000) in the south Mediterranean part of Croatia [4].

Around twenty-fold decrease of incidence during a period of 50 years during second half of the XX century in Croatia was due to a better socio-economic conditions, which were slowly and continuously improving, introduction of obligatory BCG vaccinations for all newborns, with excellent compliance rate, as well as better TB cases diagnostics and therapy. Now the situation in Croatia is stable for many years. Because of that, we expected that incidence after the decade (from 2003-2013) should be also lower, but we hypothesized that the type of patients has been changed, together with comorbidities. Known facts are that TB in organs other than lungs is increasing with immunocompromising diseases and therapy, with more of those patients around the world each day. Extrapulmonary tuberculosis is more difficult to diagnose and is less familiar to most clinicians. Beside clinical point of view, we were interested in TB strain characteristics in our TB patients during investigating years, also about resistance to antituberculous drugs during a 10-year followed period. Namely, TB drugs resistance was traditionally low in Croatia, with the incidence lower than in neighbouring countries. We also find it is important to identify the latest trends in antituberculosis resistance.

Patients and Methods

We have conducted a study on a group of patients with proven tuberculosis (weathen microbiologically or histologically) in the year 2003 and 2013 at the University Hospital Centre Zagreb, Clinical Department for Lung Diseases Jordanovac, Zagreb, Croatia. With the analysis of case histories, we got information about age, gender, habits, comorbidities and clinical manifestations of tuberculosis (pulmonary/extrapulmonary). From the register of the microbiology laboratory, we have found the types of clinical samples that were analysed, their smear-positive or smear-negative microbiological results as well as sensitivity to antituberculous drugs.

Tuberculosis was diagnosed by direct microscopy in sputum, catheter aspirate, tumorous tissue, lymph node puncture, wound swab and from bronchial washing. During 2003, year two hundred and thirty (230) patients were treated for tuberculosis, while in 2013 there were seventy patients (70) with tuberculosis at the University Hospital Centre Zagreb, Clinical Department for Lung Diseases Jordanovac, Zagreb, Croatia.

Results

I Age and Sex

In the year 2003, two hundred and thirty (230) patients were treated for tuberculosis at the University Hospital Centre Zagreb, Clinical Department for Lung Diseases Jordanovac, Zagreb, Croatia. Out of the total number, 62.1% (143) were men and 37.8% (87) women. The male-female ratio was 1.6:1. In the age group from 20-29 years, 11.2% were men and 11.1% women, and in the age group 30-39 years 13.2% men and 8% women. The majority of the men (54%) were in the age group 40-60 years, which is the most productive working age for men, as well as 33% of women. In total, there were 43.5% of patients in this age group. More men than women were treated in the age group 20-65 years. After 65 years, the largest number of treated were women. Of the 87 women, 47% of them were older than 65 years (41).

Recurrence of the disease had 23.6% of patients. In 2012 there were a total of 70 patients in whom we diagnosed TB. The male-female ratio was 1.2:1, 54.9% (39) of patients were men and 45% (32) were women. We have noticed a correlation between age and number of patients. The lowest number of patients, only 4 patients (5.7%), were in the age group between 20-29, 11.4% (8 patients) were in the age between 30-39, 37.1% (26 patients) were in the age between 40-60. The largest number of patients, 44.2% (31) were older than 60 years. Of all these patients, 21.4% had a history of previous tuberculosis.

In ten years, we have noticed a decline in patients with recurrent tuberculosis. Patients smoke and drink alcohol significantly less, and the percentage of COPD patients is also lower (Table 1). Reduction in alcohol and cigarettes use among the TB patients could be related to a lower incidence of tuberculosis recurrence.

Table 1: Comorbidities in patients with tuberculosis in the study sample.

TB and comorbidities	Patients 2003 (n=230)	Patients 2013 (n=70)
Smoking	118 (51.3)	22 (31.4)
Alcoholism	84 (36.5)	8 (11.4)
Diabetes mellitus	28 (12.2)	10 (14.2)
COPD	28 (12.2)	6 (8.5)
Malignant diseases	15 (6.5)	7 (10)
AIDS	1 (0.4)	0 (0)

COPD: Chronic obstructive pulmonary disease; AIDS: Acquired immunodeficiency syndrome. Values expressed as n (%).

I Bacteriologic Evaluation

In 2003, direct microscopy of material (sputum, catheter aspirate, tumorous tissue, lymph node puncture, wound swab) for acid-resistant bacilli was positive in 73.5% of cases whereas in 58 patients (26.5%)

acid resistant bacilli were not found in the material by direct microscopy. In 17% of patients, *M. tuberculosis* was confirmed by cultivation, and in only 8.3% of patients tuberculosis bacilli were not found. Treatment was commenced with antituberculous (ATL) on the basis of the clinical and radiographic status by pulmonology specialist, without microbiological confirmation. Of these 58 patients, *M. tuberculosis* grew in 39 (67.2%) cultures, while 19 (32.8%) cultures were negative. The majority of these patients had pleural effusion and lymphadenitis. The treatment was mostly based on the dominance of lymphocytes in the pleural liquid or cytological results of epithelioid cells in the impression of the biopsy of the pleura and puncture of the lymph node. In nine patients acid-resistant bacilli were found directly microscopically in the material (sputum, pleural effusion, lymph node puncture, pus obtained by incision, tumour tissue), but *Mycobacterium tuberculosis* did not grow in the cultures.

In 2013 detection of *M. tuberculosis* by microscopy was found in 50% (35) of patients in sputum samples, catheter aspirates and from bronchial washing. In other 50% of patients, the diagnosis was confirmed by culture-positive material (sputum, catheter aspirates, bronchial washing, urine, ascites, pleural fluid, lymph node biopsy). There were no patients where tuberculosis bacilli were not found.

III Pulmonary/Extrapulmonary Tuberculosis

In the year 2003, 6.5% of the men (15) and 5.2% of the women (12) a specific pleuritis was diagnosed in association with pulmonary tuberculosis or without it. In most cases in pleural liquid lymphocytic predominance was found. *M. tuberculosis* grew in the culture of the pleural effusion in nine patients, which amounts to 30% positive findings. This result represents a very high percentage of bacteriology confirmed tuberculosis for specific pleuritis. Three female patients had miliary tuberculosis, while in one male patient tuberculosis of the larynx was determined. Four women and two men had specific lymphadenitis on the neck and one woman mediastinal lymphadenitis. Diagnosis of specific lymphadenitis was confirmed by cytology, or histopathology methods and finding acid-resistant bacilli in the node puncture. In two patients (a man and a woman) *M. tuberculosis* grew in the urine culture.

Pulmonary tuberculosis had 64 patients in 2013. One patient also had tuberculosis of the larynx. Pleural tuberculosis with pulmonary TB was diagnosed in 2 women and 1 male. The diagnosis was established by analysis of pleural fluid and confirmed by positive culture. Two women had specific lymphadenitis established by lymph node biopsy with a histologic examination and positive culture for *M. tuberculosis*. One male patient had miliary tuberculosis. One man had a positive culture of ascites for *M. tuberculosis*. In one female patient tuberculosis of kidneys was diagnosed by positive culture of urine.

The ratio of pulmonary and extrapulmonary TB in 2003 was 7.2:1, and ten years later 5.6:1, indicating that extrapulmonary TB is becoming more frequent. Extrapulmonary tuberculosis is difficult to diagnose and less familiar to most clinicians. In the year 2013 detection of *M. tuberculosis* by microscopy was found only in 50% of cases, because of the increase in extrapulmonary forms. The diagnosis of this form of tuberculosis is challenging. Diagnosis of specific lymphadenitis is established by lymph node biopsy or aspiration with a histologic

examination, including stains for acid-fast organism and culture. Granulomas with caseous necrosis were seen in all biopsy specimens.

In genitourinary tuberculosis, the pathogens seem to be seeding on of the kidney. It should be collected at least three first early morning urine specimens and stained for acid-fast bacillus and cultured for mycobacteria. Abdominal tuberculosis can involve any intra-abdominal organ as well as the peritoneum. Acid-fast organisms are rarely seen on smears of the fluid, and cultures are positive in only 50%. Because of these, a laparoscopic biopsy is often needed to confirm the diagnosis.

IV Susceptibility Test

Out of the 230 patients treated during 2003 at the "Jordanovac" Hospital, in 10 patients (4.3%) resistance to one (n=3), two (n=3) or three (n=4) antituberculous was determined by resistance test. Multi-resistant tuberculosis (MDR) was found in four cases (1.7%) in which MDR-TB was defined as the resistance of the bacilli to the effects of two of the most important antituberculous: Isoniazid and Rifampicin (H and R). In the year 2013, in our patients, the conventional drug-susceptibility test did not show any drug-resistant organisms.

V Lifestyle

In 2003, 51.3 % of patients were smokers (118), 98 men and 20 women. Among them, 35.2% of the male patients (81) admitted to having consumed alcohol. At the same time, 28.2% (65) of men were smokers and alcoholics. Significantly fewer women smoked and consumed alcohol, only three women (1.3%). Among persons with tuberculosis in 2013, there were 31.4% smokers (22), 18 men and 4 women. At the same time, 11.4% of men (8) were taking alcohol. Two female patients were intravenous drug users, one with hepatitis B and C.

VI Tuberculosis and Comorbidities

Other chronic diseases were also found in 63.8% of the patients treated for TB in the University Hospital for Lung Diseases "Jordanovac" in 2003. The most frequent was tuberculosis associated with diabetes mellitus and chronic obstructive pulmonary disease (COPD). In both cases, in 28 patients (12.2%), tuberculosis with malignant diseases was found in 15 patients (6.5%), and tuberculosis and ulcer disease in 13 patients (5.7%). Tuberculosis was also diagnosed in 9 (3.9%) of mental patients treated. AIDS was only diagnosed in one patient (0.4%) with tuberculosis in 2003.

With detailed analysis of comorbidities, we found that in 2013 diabetes mellitus was represented in 14.2% of patients (10) which was an increase compared to the period from 10 years ago. The same percentage, patients were receiving immunosuppressive therapy like corticosteroids, methotrexate, biological therapy and cytostatics. Malignant diseases have been increasing and amounted to 10% of patients (7). The patients had neoplasms (lungs, leukaemia CLL, prostatic cancer, cervix uteri cancer) and received chemotherapy, radiotherapy, hormonal therapy, and some even undergo surgery. Unexpectedly, the number of patients suffering from COPD was in decline after 10 years and was 8.5% of patients (6).

Discussion and Conclusion

Despite modern medicine, tuberculosis is still a significant clinical problem in the world. Comparing the ten-year period (2003 and 2013) at the University Hospital Centre Zagreb, Clinical Department for Lung Diseases Jordanovac, Zagreb, Croatia, we detected almost three times smaller number of patients with tuberculosis. In 2003 disease was the most frequent in middle age, between 40 and 60 years. After ten years we have noticed a correlation between age and number of patients. The lowest number of patients was in the age group between 20-29 years and the largest number were patients older than 60 years. Another important fact is that men are no longer a risk group because women are affected almost equally.

As we expected, pre-existing comorbidities also contributed to the risk of developing tuberculosis. In 2003, other chronic diseases in patients with TB were found in 63.8% of the patients, but in 2013 comorbidities were presented in 90% of cases, indicating their importance.

Relapse of tuberculosis in 2003 was determined in 23.6% of patients and ten years after still occurs in 21.4% TB patients. In 2013 patients significantly less smoke and drink alcohol. Also, the percentage of patients with COPD was smaller (Table 1). All considered, alcohol, smoking and COPD could be risk factors for recurrence of tuberculosis. The largest number of TB patients in 2013 got tuberculosis after 60 years of age, in a significantly older age than TB patients from the year 2003. Because of that, it is unexpected that in 2013 relapse of tuberculosis was reduced only by 2.2%.

In 2003, in 73.5% of patients, acid-resistant bacilli were found by direct microscopy in investigated samples (sputum, catheter aspirate, lymph node puncture, wound swab, tumour tissue). In Croatia, in the 2002 year, 69.5% of patients were directly microscopically positive [4]. The percentage of microbiological positivity in the investigated group was above average. Few facts probably have an influence on that good result. In Croatia, there are hospitals specialized for lung diseases, where tuberculosis is frequently a differential diagnosis. Also in those years, the medical community in Croatia was sensitized to the problem of tuberculosis, because the Project "Improvement of tuberculosis control in Croatia – an educational programme for chest physicians, general practitioners and community service providers" was running.

The Project was leading by pulmonologists, in cooperation with Institute Open Society Croatia, and the World Health Organization, Regional Office Europe. Many health care workers, physicians with different specializations (epidemiologists, microbiologists, paediatricians), not only chest physicians and general practitioners, together with nurses and community service providers were educated through many seminars form 2003-2006 year. All participants receive the book written by physicians running the Project: "Tuberculosis-Renewed Challenge for Medicine at the Beginning of the Third Millennium", what they find useful. All these activities lead to better diagnostic and treatment procedures with TB patients. Possibly lower incidence of TB patients, increased number of bacteriology confirmed TB cases, no drug resistance and a lower rate of TB relapses could be also the result of better education of health professionals on TB problem.

All of the above indicates that awareness and knowledge of the presence of tuberculosis raise the standard of work and approaches the results of the goals set by DOTS. One of the main goals of DOTS is the isolation of tubercular bacilli in 70% of patients, for which the treatment of patients in the "Jordanovac" Hospital entirely accomplished this task with 73.5% microbiologically proved tuberculosis [5]. In nine patients acid-resistant bacilli were found in material directly microscopically, and *M. tuberculosis* did not grow in cultures. This is explained in the literature as non-viability of the bacilli in the sample due to previous treatment with antibiotics with devitalising effect [6]. There is also the possibility of failing to adhere to the protocol for the treatment of the sample (overlong exposure to reagents for homogenisation and decontamination, or greater concentration, which damages the acid-resistant bacilli and reduces the ability to grow in the culture) or failure to adhere to the rules of microscopy (transfer of acid-resistant bacilli from previously positive material and contact of the preparation with the applicator of the bottle or objective) [7]. It can also be due to atypical *Mycobacteria* with specific requirements for cultivation (different incubation temperature, the addition of specific substances in the culture), *Mycobacteria* with incubation of longer than 12 weeks or particularly sensitive species, which are detected by molecular technique [8].

Although pulmonary tuberculosis is the dominant form, Tuberculosis was smear or culture positive in pleural discharge/extravasation samples of 9 patients (3.9%), lymph nodes of 7 (3%), urine samples of 2 (0.9%), wound swab of 1 and tumour tissue of 2 patients. According to data from the Epidemiology Service in the Republic of Croatia in 2002 *M. tuberculosis* was identified in 3% of pleural punctures, 12.9% of lymph node punctures, 16.3% of wound swabs and 5% of tissue samples [9].

In 2013 detection of *M. tuberculosis* by microscopy was found in 50% of the patients in sputum samples, catheter aspirates and from bronchial washing. In other 50% of patients, diagnosis was confirmed by culture-positive samples (sputum, catheter aspirates, bronchial washing, urine, ascites, pleural fluid, lymph node biopsy).

I Tuberculosis and Resistance to Antitubercotics

Multi-resistant tuberculosis (MDR) has become a great world problem. Multi-resistance is the resistance to the two most powerful agents against tuberculosis: Isoniazid and Rifampicin, with or without resistance to other antitubercotics. It is associated with the inadequate application of antitubercotics, HIV seropositivity, drug addiction and even amplifying effect of short-course chemotherapy [10].

In 2003, resistance to one or more antitubercotics was determined in 10 patients (4.3%) treated at the "Jordanovac" Hospital. In the Republic of Croatia during 2002 resistance was determined in 4.8% of patients [9]. In 2003 multi-resistant tuberculosis (MDR-TB) at the "Jordanovac" Hospital was found in four cases (1.7%) of the hospitalized population. There were 28 cases (0.6%) of multi-resistant patients in the whole of Croatia during 2001, which amounts to a significantly smaller percentage of multi-resistant patients with tuberculosis than in other neighbouring countries.

In 2013, resistance to one or more antituberculars was not found at the "Jordanovac" Hospital in the hospitalized population. According to data from Croatian Institute of Public Health, the number of resistant *M. tuberculosis* strains in 2013 in Croatia has shown that 62.6% were monoresistant, and 37.4% were resistant to two or more first-line antituberculars. Monoresistance to isoniazid was found in 48.3% of cases, and monoresistance to streptomycin in 13.2% isolated cases [11].

II Tuberculosis and Alcoholism

A combination of tuberculosis and alcoholism, which is considered by many to be the most widespread disease of mankind, represents a medical, social and epidemiological problem. Decreased resistance arises because of the irregular lifestyle of alcoholics and alcohol intoxication. The incidence of alcoholism among first-time patients with tuberculosis is 8-10%, and in the case of recurrence significantly greater. Tuberculosis in alcoholics is detected in the advanced stage with a high percentage of direct microscopically BK positives which indicates diffusion of the disease.

Mortality in alcoholics with tuberculosis is considerably higher compared to mortality in other tubercular patients. Tubercular alcoholics represent a significant social and epidemiological problem due to the fact that they are often in places where there are many people, such as waiting-rooms and restaurants [12, 13]. Of the patients treated for tuberculosis in the "Jordanovac" Hospital in 2003, 36.5% of patients (male and female) were alcoholics. In 2013, a significant drop in the number of patients with a history of alcohol intake. Among sexes, male alcoholic patients were more prevalent (11.4%), than woman (1.3%).

III Tuberculosis and Smoking

A large number of patients with tuberculosis are smokers. According to recent literature, tuberculosis occurs more frequently and tuberculosis-related mortality rates are significantly higher in smokers than in never-smokers [12, 14]. Not only does tuberculosis occur more frequently in smokers, but also there is increased risk of death in this group, due to respiratory diseases, particularly of tuberculosis, which was demonstrated in a comprehensive investigation carried out in India, and published in the European Journal of Clinical Microbiology & Infectious Diseases in 1994 [15]. Of the patients treated for tuberculosis at the "Jordanovac" Hospital in the year 2013 1.3% of male and female patients were smokers. In 2013, smoking among Croatian adult population was decreasing and amounted to 31% [16].

IV Tuberculosis and Immunodeficiency

The treatment of chronic and malignant diseases has become more successful with the application of new, more sophisticated methods in medicine. The life span of many patients has been extended and with it the development of immunocompromising conditions, which is the greatest risk factor for the development of tuberculosis. Immunodeficiency conditions can occur in a large number of diseases. Patients with impaired cellular and humoral immunity (malignant diseases, granulomatosis, fibrosis, systemic diseases of connective tissue, ulcerous colitis, Crohn's disease, Addison's disease), metabolism disorders (diabetes mellitus, renal insufficiency, hyperthyroidism,

malnutrition) on immunosuppressive therapy (corticosteroids, cytostatics and radiation), suffer from tuberculosis more frequently.

Apart from immunodeficiency a large number of additional factors also participate in the occurrence of tuberculosis: malnutrition, social-economic status, age (neonates, small children, older age), and mental disease. In such conditions, tuberculosis occurs in altered clinical and radiographic form, which represents difficult circumstances for diagnosis. Symptoms of the basic disease are mainly dominant, which can mask the appearance of the specific process. Because of the suppression of cellular immunity the tuberculin skin test (TST) is negative in the majority of patients, and weakly positive in a small number of patients. In the case of diabetics atypical forms of tuberculosis are frequent in the form of an infiltrate or abscess of the middle and lower lung lobe. Apart from tuberculosis co-morbid diseases were also determined in 63.8% of the patients treated during 2003 in the "Jordanovac" Hospital, while in 2013, 90% of patients with tuberculosis had one or more comorbidities.

V Tuberculosis and Diabetes Mellitus

Some studies have found that a diagnosis of DM triples the risk of developing tuberculosis (relative risk = 3.11; 95% CI: 2.27-4.26) [17]. Tuberculosis has long been the leading cause of death in diabetics as it leads to worsening of the basic disease. The introduction of insulin in therapy significantly reduced mortality. The development of tuberculosis in unregulated diabetes is facilitated by malnutrition with a fall in body weight. In such cases, severe forms of tuberculosis develop with the intoxication of the organism [18, 19]. Diabetes mellitus was also present in 12.5% of the patients treated for tuberculosis in the "Jordanovac" Hospital during 2003. This percentage is slightly higher than the expected 10% of patients with diabetes who contract tuberculosis according to world statistics. In 2013, a diabetes continues to increase among those suffering from tuberculosis and was 14.2% of the investigated hospitalized population.

VI Tuberculosis and COPD

The occurrence of tuberculosis in COPD is most probably caused by long-term application of corticosteroids, because of their anti-inflammatory effect. The prolonged use of corticosteroids is particularly dangerous in older patients who have previously suffered from tuberculosis. Particular care should be taken with regard to febrile conditions in patients with COPD, who are often on corticosteroid therapy for a longer period, together with antibiotic therapy. Of the patients treated for tuberculosis in the "Jordanovac" Hospital during 2003, 9.8% of the men and 16.1% of the women suffered from COPD, which together amounts to 12.2%.

A different percentage of patients with COPD and TB has been reported in recent studies, from airflow obstruction in 11% and 29.97% of new TB cases to 30.7% of those with a past medical history of TB as registered in population-based PLATINO study [20-22]. PLATINO study shows that not only the association between TB and airflow obstruction was significant and strong but the medical history of TB is also associated with more severe grades of obstruction by the GOLD classification. The next possible cause of COPD occurrence in TB

patients recurrence of tuberculosis and repeated destruction of lung tissue by *M. tuberculosis* induced inflammation. It is also well known that tuberculosis with sequels is one of the most frequent causes of COPD in non-smokers. Obstruction of the respiratory pathways, because of the effect of tuberculosis, has a similar clinical course as smokers COPD. Bronchodilation therapy can be useful, and the method of lung rehabilitation is strongly recommended [23-25].

Our results have shown that COPD among TB patients in 2013 fell by 3.7% so the total amount of patients having both TB and COPD was 8.5%, among them 7.1% of men and 1.4% of women (in absolute number – only one woman).

VII Tuberculosis and Malignant Diseases

Malignant diseases represent one of the frequent factors of risk for the occurrence of tuberculosis. Apart from deteriorated cellular immunity due to malignant disease, immunosuppressive therapy, cytostatics and radiation are incorporated, which inhibit cellular and humoral immunity. Prolonged febrile conditions in malignant diseases, particularly with scar tissue lesions after recovering from tuberculosis should arouse suspicion of reactivation of tuberculosis. According to the literature, tuberculosis occurs in 5-13% of patients with malignant diseases [26, 27].

In our patients in 2003 tuberculosis was diagnosed in 6.5% of patients with malignant diseases (lung carcinoma, lymphomas) which is consistent with the expected connection of tuberculosis and malignant diseases. In 2013, the occurrence of malignancies with tuberculosis was increasing and amounted to 10% of the investigated hospitalized population.

VIII Tuberculosis and AIDS

The association of tuberculosis and AIDS ("the dammed duet") represents a considerable problem which has led to an increased rate of the incidence of tuberculosis. AIDS is caused by the human immunodeficiency virus (HIV). AIDS was first seen in 1979 in homosexuals in the USA, and in Croatia, where it was first registered in 1986. Croatia is a country with low risk of contracting AIDS and consequently, no significant effect of suffering from AIDS is expected on the epidemiology of tuberculosis in this country [28].

According to WHO, an estimated 10% of the incident TB cases in 2016 were among people living with HIV and the percentage of TB cases coinfecting with HIV was highest in countries in the African Region, exceeding 50% in parts of southern Africa [2]. A recent meta-analysis has also shown that pooled RR for unsuccessful outcome in people living with HIV compared to those without HIV infection was higher (1.41; 95% CI: 1.15–1.73) with a greater effect of HIV on unsuccessful treatment outcomes in low-income regions (RR 2.23; 95% CI: 1.60–3.11) compared with high income regions (RR 1.22; 95% CI: 0.97–1.53) [13].

AIDS occurs in persons infected with HIV after a period of several years. Tuberculosis may be the first sign that the person is infected with HIV [29, 30]. Determination of HIV-antibodies in patients with tuberculosis is not a routine examination in the University Hospital Centre Zagreb,

Clinical Department for Lung Diseases "Jordanovac". During 2003 only one patient at the "Jordanovac" Hospital was diagnosed with AIDS. The patient was transferred to the University Hospital for Infectious Diseases "Dr Fran Mihaljević" in Zagreb, where he died. In 2013 we didn't have any TB patient with AIDS.

Conclusion

After 10 years, tuberculosis in Croatian patients has changed its "face". It occurs more often in the elderly population usually followed by comorbidities (in 90% of cases). The most common are diabetes mellitus, malignancies and COPD - a disease of modern civilization. Men are no longer a risk group because women are affected almost equally. Smoking and alcoholism are still highly represented but significantly decreased. Clinical awareness of the possibility of TB should be considered in patients with these risk factors, then an active screening and prevention should be undertaken.

Tuberculosis is a disease, which still represents a world problem. According to the World Health Organisation, in a further increase of tuberculosis is expected. Listed reasons are the influence of HIV infection, immigration of inhabitants from regions with a high prevalence of tuberculosis to developed countries. In East Europe, there has been a deterioration in the social-economic status and an increase in the number of the poor population. In some countries of West Europe, there has been an increase in the prevalence of tuberculosis because programmes for the control of tuberculosis have been abandoned.

Tuberculosis can only be conquered by complete control of the disease. National programmes should be continued in countries which have them and renewed in countries which have abandoned them and should be organised in those countries which do not have them. New medications should be produced and methods of rapid diagnosis developed [31].

REFERENCES

1. H J Milburn (2001) Primary tuberculosis. *Curr Opin Pulm Med* 7: 133-142. [[Crossref](#)]
2. WHO (2017) Global Tuberculosis Report 2017.
3. Ministarstvo zdravstva Republike Hrvatske - Naputak za suzbijanje i sprječavanje tuberkuloze. Zagreb 1998.
4. Gjenero-Margan I. Kretanje tuberkuloze u Republici Hrvatskoj. U: Hrvatski zdravstveno-statistički ljetopis 2002.godina. Hrvatski zavod za javno zdravstvo. Zagreb, 2002.
5. WHO, Tuberculosis Control Programmes on the Introduction and Use. 2002.
6. Laam Li, Nilmini Mendis, Hana Trigui, James D Oliver, Sebastien P Faucher (2014) The importance of the viable but non-culturable state in human bacterial pathogens. *Front Microbiol* 5: 258. [[Crossref](#)]
7. D B Giller, A D Kostenko, B M Giller, G V Giller (2002) Treatment of patients with destructive pulmonary tuberculosis with concomitant diabetes mellitus. *Probl Tuberk* : 18-21. [[Crossref](#)]
8. F Yamagishi, Y Sasaki, T Yagi, H Yamatani, F Kuroda et al. (2000) [Frequency of complication of diabetes mellitus in pulmonary tuberculosis]. *Kekkaku* 75: 435-437. [[Crossref](#)]

9. Gjenero-Margan I, Rudan I (2002) AIDS. U: Vorko-Jović A (ur). Priručnik za seminare i vježbe iz epidemiologije. Medicinska naklada, Zagreb: 59-78.
10. Kwon June J, Seung, Salmaan Keshavjee, Michael L Rich (2015) Multidrug-Resistant Tuberculosis and Extensively Drug-Resistant Tuberculosis. *Cold Spring Harb Perspect Med* 5: a017863. [[Crossref](#)]
11. Croatian national institute of public health, Croatian health service yearbook 2013. Zagreb, 2014.
12. Denise Rossato Silva, Marcela Muñoz-Torrico, Raquel Duarte, Tatiana Galvão, Eduardo Henrique Bonini et al. (2018) Risk factors for tuberculosis: diabetes, smoking, alcohol use, and the use of other drugs. *J Bras Pneumol* 44: 145-152. [[Crossref](#)]
13. Joel Philip Samuels, Aashna Sood, Jonathon R Campbell, Faiz Ahmad Khan, James Cameron Johnston (2018) Comorbidities and treatment outcomes in multidrug resistant tuberculosis: A systematic review and meta-analysis. *Sci Rep* 8: 4980. [[Crossref](#)]
14. Strong BE, Kubica GP. Isolation and identification of M. tuberculosis - a guide for the level laboratory. U.S. Department of Health and Human Services, CDC, Atlanta.
15. M Salfinger, G E Pfyffer (1994) The new diagnostic Mycobacteriology Laboratory. *Eur J Clin Microbiol Infect Dis* 13: 961-979. [[Crossref](#)]
16. WHO REPORT on THE global Tobacco Epidemic, 2015 Raising taxes on tobacco.
17. Christie Y Jeon, Megan B Murray (2008) Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. *PLoS Med* 5: e152. [[Crossref](#)]
18. Katalinić-Janković V. Služba za mikrobiologiju. U: XV Stručni sastanak Hrvatskih mikrobiologa, studeni 2003.godine. Hrvatski zavod za javno zdravstvo. Zagreb, 2003.
19. Crofton J, Home N, Miller F (2001) Klinička tuberkuloza, IBIS grafika, Zagreb.
20. M L Plit, R Anderson, C E Van Rensburg, L Page-Shipp, J A Blot et al. (1998) Influence of antimicrobial chemotherapy on spirometric parameters and pro-inflammatory indices in severe pulmonary tuberculosis. *Eur Respir J* 12: 351-356. [[Crossref](#)]
21. Dudnyk A, Blyzniuk S, Pavel O, Zakharchenko O, Butov D et al. (2017) ScienceDirect Initial airflow obstruction in new cases of pulmonary tuberculosis : Complication , comorbidity or missed ? 1-7.
22. A M B Menezes, P C Hallal, R Perez-Padilla, J R B Jardim, A Muiño et al. (2007) Tuberculosis and airflow obstruction: Evidence from the PLATINO study in Latin America. *Eur Respir J* 30: 1180-1185. [[Crossref](#)]
23. J Alcaide, M N Altet, P Plans, I Parrón, L Folguera et al. (1996) Cigarette smoking as risk for tuberculosis in young adults a case-control study. *Tuber Lung Dis* 77: 112-116. [[Crossref](#)]
24. Jotam G Pasipanodya, Thaddeus L Miller, Mauricio Vecino, Guadalupe Munguia, Robert Garmon et al. (2007) Pulmonary impairment after tuberculosis. *Chest* 131: 1817-1824. [[Crossref](#)]
25. T L Griffiths, M L Burr, I A Campbell, V Lewis-Jenkins, J Mullins et al. (2000) Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomized controlled trial. *Lancet* 355: 362-368. [[Crossref](#)]
26. Global tuberculosis Control. WHO Report 2000. WHO/CDS/TB 2000. Geneva 2000.
27. Popović-Grle S, UR. "Tuberkuloza-ponovni izazov medicini na početku trećeg tisućljeća", Zagreb: Klinika za plućne bolesti "Jordanovac", Ministarstvo zdravstva Republike Hrvatske, Institut Otvoreno društvo Hrvatska, 2004.
28. Giovanni Ferrara, Megan Murray, Kevin Winthrop, Rosella Centis, Giovanni Sotgiu (2012) Risk factors associated with pulmonary tuberculosis. *Curr Opin Pulm Med* 18: 233-240. [[Crossref](#)]
29. Ante Marusić, Vera Katalinić-Janković, Sanja Popović-Grle, Mateja Janković, Ivica Mazuranić et al. (2009) Mycobacterium xenopi pulmonary disease - epidemiology and clinical features in nonimmunocompromised patients. *J Infect* 58: 108-112. [[Crossref](#)]
30. Gompel Suwanpimolkul, Jennifer A Grinsdale, Leah G Jarlsberg, Julie Higashi, Dennis H Osmond (2014) Association between diabetes mellitus and tuberculosis in United States –Born and foreign-born populations in San Francisco. *PlosOne* 9: e114442. [[Crossref](#)]
31. Ragulan R, Subramanian S, Surendran Menon K, Arun Babu V (2015) A comparative study of clinico-radiological profile of pulmonary tuberculosis in diabetic and nondiabetic adults. *Int J Pharma Bio Sci* 6: 1341-1348.