RESEARCH ARTICLE

Tuberculosis treatment outcome in Thessaloniki, Greece - a single center study

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Abstract
Background: Greece is one of the few countries in the European Union/European Economic Area, which do not report tuberculosis (TB) treatment outcome. This study aimed to assess treatment outcomes and identify possible intervening factors in patients with TB in Thessaloniki, Greece, over the period 2012-2017.
Methods: All patients diagnosed with TB -excluding rifampicin-resistant/multidrug-resistant (RR/MDR)-TB- during 2015-2017 were included in the study. Data on demographic characteristics, localization, diagnostic methods, resistance, and treatment outcome were recorded and compared to the period 2012-2014.
Results: During the period 2015-2017, 82 patients (48 men) with a mean age of 53.8 ± 15.6 years were diagnosed with TB. No significant differences in demographics, microbiological, or treatment characteristics were detected between the two three-year periods, except for the percentage of immunocompromised patients, which was higher during 2015-2017 (15.9 % vs 5.6 %, p =0.029). In the total number of patients, two factors were significantly different between patients with a positive and negative outcome. The percentage of favorable outcome was higher for patients with extrapulmonary compared to pulmonary TB (90.9 % vs 70.5 %, p =0.044). Furthermore, the percentage of immunocompetent patients with a positive outcome was significantly higher in the second treatment period compared to the first (treatment success rate 66.7 % in 2012-2014 vs 84.1 % in 2015-2017, p =0.014). This difference was attributed to the presence of a social nurse who joined the center in 2015.
Conclusions: TB treatment success rate in Greece is below the World Health Organization standards. Interventions such as appropriate multidisciplinary staffing of TB centers may prove valuable in improving TB care in Greece.
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Keywords: Tuberculosis, treatment success rate, outcome, Greece

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Introduction

Tuberculosis (TB) is a much-neglected issue in Greece. According to the recent report from the European center for disease prevention and control, notification rates have declined from 5/100,000 in 2012 to 4.1/100,000 in 2016, and the estimated incidence was 5.2 for 2012, which is below the mean European incidence of 14.5[1]. However, there is evidence of severe underreporting of the disease. Jelastopulu et al showed that in 2000-2003 only 38.7 % of TB cases identified in major hospitals and 70 % of cases identified by public health departments of western Greece were admittedly reported to the National Public Health Organization (NPHO) resulting in an estimated case detection rate of 14/100,000[2]. Lytras et al calculated the number of treated cases based on the consumption of anti-TB drugs in the period 2004-2008 and estimated underreporting at 80 % and annual incidence at 30/100,000[3]. Finally, Ibarz-Pavon et al applied record linkage and the capture-recapture method on 2012 data from the NPHO, the national reference laboratory for mycobacteria and Sotiria Chest Diseases Hospital, the largest chest diseases hospital in the country and calculated the observed and estimated TB underreporting rates at a national level at 55 % and 75 %, respectively. Based on their data, the estimated TB incidence rate is 15/100,000[4].

Even more alarmingly, there are no data on the outcome of TB treatment, since Greek health services are not required to report TB outcome to NPHO. As a consequence, Greece is one of the few countries in the European Union/European Economic Area (EU/EEA) for which the outcome is unknown[1]. According to the "End TB Strategy" launched by the World Health Organization (WHO), TB treatment success rate should increase to 90 % by 2025, and TB deaths should be reduced by 95 % compared to 2015 by 2025 in order to end the global TB epidemic[5]. It is needless to say that monitoring and accurately reporting treatment outcomes is necessary to achieve these goals. Recording outcome is essential in assessing the effectiveness of treatment and identifying

possible obstacles to disease control since the outcome is an important indicator of the effectiveness of TB control programs[6]. In this setting, the present study aimed to assess treatment outcomes and identify possible intervening factors in a cohort of patients diagnosed with TB in the pulmonary department, Aristotle University of Thessaloniki, Greece, over the period 2015-2017 in comparison with the previous period (2012-2014).

Materials and methods

This is a retrospective cohort study with continuous sampling, including all adult patients (inpatients and outpatients) who were diagnosed with TB in the Pulmonary Department, Aristotle University of Thessaloniki, one of the two largest pulmonary departments of northern Greece, between January 1st, 2015 and December 31st, 2017. Patients were excluded if they had rifampicin-resistant/multidrug-resistant (RR/MDR)-TB. The patients with RR/MDR-TB cannot be categorized with other TB patients when yearly treatment outcome is investigated since definitions for treatment outcome are different for RR/MDR patients, and the duration of treatment lasts longer than 12 months[7]. Thus, treatment outcome, for RR/MDR patients, is usually reported separately[8-9]. In total, seven patients with RR/MDR-TB were excluded from the present study (two from the period 2012-2014 and five from the period 2015-2017). Due to the small number of patients with RR/MDR-TB, a comparison of their outcomes with those of non-RR/MDR-TB was not considered appropriate.

Data regarding patients' demographic characteristics, co-morbidities, anatomical site of disease, method of diagnosis (smear, culture, nucleic acid amplification test-Xpert MTB/RIF, Cepheid, Sunnyvale, California, USA), resistance profile, time to smear and culture negativity, side effects of anti-TB drugs, and treatment outcome were recorded.

These data were compared to corresponding data from the period 2012-2014, which had been published previously[10]. Predictors of outcome were analyzed for the total number of patients, i.e., 2012-2017. Bacteriological vs clinical diagnosis, pulmonary vs extrapulmonary TB, and treatment outcomes were defined according to the WHO 2013 criteria[11]. Besides patients receiving standards of care as per institutional approved guidelines, this retrospective collection and usage of data was approved by the Ethical Committee of the General Hospital of Thessaloniki "G. Papanikolaou", and all participants gave informed consent regarding this work.

Statistical analysis was performed using the IBM SPSS Statistics for Windows, Version 20 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean value ± standard deviation and categorical variables as number and percentage (% in brackets) values. To distinguish parametric from non-parametric variables, normality assessment was performed, using the Kolmogorov-Smirnov normality test, as the number of patients was more than 50. The independent samples T-test and the Mann Whitney U test were respectively used for parametric and non-parametric variables to detect significant differences between the two three-year periods in continuous variables. The chi-square test (χ^2) was used for the comparison of categorical variables between the two three-year periods. A difference was considered statistically significant when $p < 0.05$.

Results

During the period 2015-2017, 82 patients, 48 men and 34 women with mean age 53.8 ± 15.6 years, were diagnosed with TB (excluding RR/MDR-TB) in the pulmonary department, Aristotle University of Thessaloniki, Greece. Sixty patients (73.2 %) were of Greek origin, and the remaining 22 (26.8 %) were from Georgia (eight), Albania (two), Bulgaria (two), Russia (two), Kirgizstan (one), Pakistan (one), Armenia (one), Moldova (one), Romania (one), Senegal (one), Serbia (one), and unknown origin (one). Pulmonary TB was diagnosed in 68 (82.9 %) patients, with six of them presenting with miliary TB and 12 showing extrapulmonary involvement as well. Extrapulmonary TB was present in 14 (17.1 %) patients, the most prevalent being lymphadenitis in 11 patients and involvement of pleura, kidneys, and pericardium in one each. Eight (9.8 %) patients had a history of previous anti-TB treatment, while the rest 74 (90.2 %) were new cases. Out of 82 patients, only one was living with human immunodeficiency virus (HIV), while 11 were drug users. Co-morbidities were present in 54 (65.9 %) patients, out of whom 25 presented with one co-morbidity and 29 with more than one. Thirteen patients (15.9 %) were immunocompromised [nine due to anti-tumor necrosis factor-alpha (TNF-a) agents, two due to chemotherapy, and two due to other immunosuppressants]. Regarding smoking habit, 31 (37.8 %) were current smokers, six (7.3 %) were ex-smokers, 23 (28.0 %) had no history of smoking and for the remaining 22 (26.8 %) the smoking habits were not recorded.

TB diagnosis was established microbiologically in 68 (82.9 %) patients and clinically in 14 (17.1 %) cases. Thirteen out of 14 patients without microbiological confirmation had compatible histopathology. Regarding microbiological confirmation, 36 patients presented with positive smear, 61 positive culture, and 57 positive nucleic acid amplification test). Resistance to at least one first-line anti-tuberculosis drug excluding rifampicin was recorded in 15 (18.3 %) patients (six with mono-resistance and nine with poly-resistance). The mean period to smear negativity for pulmonary TB patients was 39.3 ± 41.1 days and to culture negativity 63.9 ± 48.6 days. Ten (12.2 %) patients presented side effects leading to drug cessation to one anti-TB drug, and five (6.1 %) presented side effects to more than one.

Patients' characteristics, in comparison with the previous three-year period, are shown in Table 1. No significant differences in demographics, microbiological or treatment characteristics were detected between the two three-year periods, except for the percentage of immu-

nocompromised patients, which was higher during 2015-2017 (15.9 % vs 5.6 %, p =0.029).

Regarding outcome, out of the 82 patients in the 2015-2017 period, 65 (79.3 %) had a favorable outcome [35 (42.7 %) cured, and 30 (36.6 %) treatment completed]. Seven patients died during treatment (8.5 %); three died due to causes unrelated to TB and after showing improvement, while the remaining four (three immunocompromised patients and one aged 85 years) died within ten days from diagnosis, due to TB. The treatment outcome for the two periods is presented in Table 2 and Figure 1.

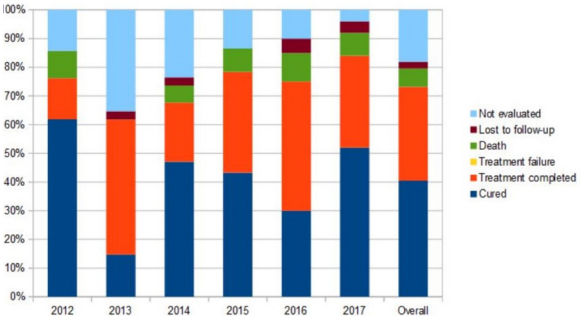

Figure 1: Bar diagram presenting annual and total treatment outcome during the years 2012-2017.

Overall treatment success during the two treatment periods was achieved in 125 out of the 171 patients (73.2 %). In the sum of 171 patients from the two periods together, several factors -time period (2012-2014 vs 2015-2017), age, country of origin, site of infection, history of anti-TB treatment, co-morbidities, smoking status, smear and culture positivity, presence of resistance to anti-TB drugs, development of side effects- were investigated in relation to treatment outcome (Table 3). Only two factors were significantly different between patients with a positive and negative outcome. The percentage of favorable outcome was higher for patients with extrapulmonary vs pulmonary TB (90.9 % vs 70.5 %, p =0.044). Furthermore, the percentage of immunocompetent patients who had a positive outcome was significantly higher in the second treatment period compared to the first (treatment success rate 66.7 % in 2012-2014 vs 84.1 % in 2015-2017, p =0.014). For the total number of patients regardless of immune status, the outcome did not reach statistical significance between the two treatment periods, although 79.3 % of patients showed a favorable outcome in 2015-2017 vs 67.4 % in 2012-2014 (p =0.081).

Table 1: Baseline characteristics of the 171 patients diagnosed with tuberculosis during the two periods (2015-2017 and 2012-2014) who were included in the study.

Baseline characteristics	2012-2014 (n =89)	2015-2017 (n =82)	Total (n =171)	p-value
Age (years)	49.5 ± 19.2	53.8 ± 15.6	51.6 ± 17.8	0.130
Male gender	60 (67.5)	48 (58.5)	108 (63.2)	0.229
Greek origin	61 (68.5)	60 (73.2)	121 (70.8)	0.476
History of anti-TB treatment	12 (13.5)	8 (9.8)	20 (11.7)	0.449
Smear positive	46 (51.7)	36 (43.9)	82 (48)	0.592
Culture positive	61 (68.5)	61 (74.4)	122 (71.4)	0.205
Site of infection (pulmonary)	81 (91)	68 (82.9)	149 (87.1)	0.115
Co-morbidities	55 (61.8)	54 (65.9)	109 (63.7)	0.582
Immunocompromisation	5 (5.6)	13 (15.9)	18 (10.5)	**0.029**
Resistance to any drug*	9 (10.1)	15 (18.3)	24 (14)	0.218
Side effects[#]	11 (12.4)	15 (18.3)	26 (15.2)	0.280
Time to smear conversion (days)	29.4 ± 30.3	39.3 ± 41.1	34.25 ± 36	0.242
Time to culture conversion (days)	61.3 ± 41.9	63.9 ± 48.6	62.7 ± 45.2	0.922
Weight difference[$]	5.1 ± 4.8	5.4 ± 5.7	5.22 ± 5.2	0.868

Values are presented as mean ± standard deviation or number and percentage (%) in brackets, n: number, TB: Tuberculosis, *: patients with rifampicin-resistant/multidrug-resistant tuberculosis were not included, [#]: that led to drug discontinuation, [$]: after-before treatment.

Table 2: Treatment outcomes during the two 3-year periods (2012-2014 and 2015-2017) included in the study.

Treatment outcome	2012-2014 (n =89)	2015-2017 (n =82)	Total (n =171)
Cured	34 (38.2)	35 (42.7)	69 (40.4)
Treatment completed	26 (29.3)	30 (36.6)	56 (32.8)
Treatment failure	1 (1.1)	0 (0.0)	1 (0.6)
Death	4 (4.5)	7 (8.5)	11 (6.4)
Lost to follow up	2 (2.2)	2 (2.4)	4 (2.3)
Not evaluated	22 (24.7)	8 (9.8)	30 (17.5)

Values are presented as number and percentage (%) in brackets, n: number.

Table 3: Predictors of treatment outcome. Demographic and clinical parameters investigated in relation to the treatment outcome.

	Positive outcome (%)		Negative outcome (%)		p-value
Period with healthcare visitor	Yes	79.27	Yes	20.73	0.081
	No	67.42	No	32.58	
Period with healthcare visitor (adjusted for immune status)	Yes	84.06	Yes	15.94	**0.014**
	No	66.67	No	33.33	
Gender	Male	69.44	Male	30.56	0.158
	Female	79.37	Female	20.63	
Age (years)	< 65	71.88	< 65	28.12	0.585
	>= 65	76.19	>= 65	23.81	
Country of origin	Greeks	75.83	Greeks	24.17	0.189
	Foreigners	66.00	Foreigners	34.00	
Site of infection	Pulmonary	70.47	Pulmonary	29.53	**0.044**
	Extrapulmonary	90.91	Extrapulmonary	9.09	
History of anti-TB treatment	Yes	70.00	Yes	30.00	0.739
	No	73.51	No	26.49	
Co-morbidities	Yes	73.40	Yes	26.60	0.908
	No	72.58	No	27.42	
Smoking	Yes	76.71	Yes	23.29	0.368
	No	83.72	No	16.28	
Smear	Positive	73.17	Positive	26.83	0.506
	Negative	70.89	Negative	29.11	
Culture	Positive	73.77	Positive	26.23	0.696
	Negative	68.42	Negative	31.58	
Any resistance	Yes	79.17	Yes	20.83	0.320
	No	68.93	No	31.07	
Resistance to Isoniazid	Yes	85.71	Yes	14.29	0.673
	No	69.75	No	30.25	
Any side effects	Yes	86.21	Yes	13.79	0.081
	No	70.42	No	29.58	

TB: Tuberculosis.

Discussion

To our knowledge, this is the first report of treatment outcome for TB in Greece. In our center, a favorable outcome was reached in 73.2 % of patients for the years 2012-2017, which is lower than the global and the European treatment success rate for 2016 (82 % and 77 %, respectively) and certainly much below the recommended target level of ≥90%[12]. In our view, there are mainly two explanations for this discrepancy. First, the severity of the disease, i.e., our patients are almost always symptomatic patients visiting a tertiary health care facility with extended disease, since no screening protocols for high-risk groups are currently implemented in Greece. Second -and probably more important- the absence of an organized network of social and medical support, in combination with the absence of a national tuberculosis program in Greece, compared with other countries in EU/EEA[13].

Interestingly, our success rate for 2015-2017 of 79.3 % is comparable with global[12], and European figures[6], as opposed to the period 2012-2014, during which a lower (by nearly 12 %) percentage of favorable outcomes was detected. This difference reached statistical significance when immune-compromised patients were excluded from the analysis. Despite the rise in deaths, negative outcomes lowered in the second period, mainly due to the decrease in the "not-evaluated" group from 24.7 % in 2012-2014 to 9.8 % in 2015-2017. The only difference in the management of TB patients between the two three-year periods was the participation of a social nurse in the outpatient clinic during 2015-2017. Therefore, this decrease can be attributed to the presence of a social nurse who joined the outpatient clinic in February 2015. In our view, this intervention changed patient management facilitating access to medication and medical care in general and setting an example regarding how to improve TB care in Greece. A recently published thorough systematic review has also pointed out the beneficial role of social nurses in many aspects of TB management in low-incidence countries, including, among others, individualized support, psycho-emotional support, socio-economic support, and possibly directly observed therapy[14].

The presence of a social nurse was the factor most strongly associated with outcome in our cohort, the other one being TB localization, which was lymphadenitis in the majority of cases. In our cohort, there were only 22 patients with extrapulmonary TB, and lymph nodes were the most common site of infection. In a much larger cohort from Denmark, including 450 cases of extrapulmonary TB, lymph nodes were also the most common site of infection with figures similar to ours (55.4 % vs 50.0 %). In that cohort, the percentage of favorable outcomes also reached 90.9 %, as in ours[15]. Extrapulmonary TB is a much more heterogeneous form of the disease compared to pulmonary TB, as it can affect any organ

or system. However, the majority of the cases concern lymph node or pleural TB, which are less threatening localizations than pulmonary TB and can be treated more effectively, thus the favorable outcome is much higher in these cases[15].

Negative predicting factors such as increasing age, male sex, foreign origin, non-infective co-morbidities, and sputum positivity, which have been highlighted in large-scale studies[6,16-17], were not identified in ours, possibly due to the small number of our patient cohort. HIV co-infection, drug abuse, and retreatment are also factors related to unfavorable outcome[18]. However, our cohort included only one patient who was living with HIV co-infection, 11 patients with drug abuse, and 20 patients with previously treated TB. Therefore, possibly lacked the statistical power to confirm those factors as significant predictors for an unfavorable outcome.

Particular emphasis should be paid in the rapidly increasing reception of refugees from countries with a high incidence of TB. The proportion of foreign-born TB patients has increased significantly in the last 20 years[19]. Previous studies have shown that being foreign-born and being in congregate settings at treatment initiation was related to unfavorable outcomes[20]. Screened asylum seekers had poorer treatment outcomes and were more often lost to follow-up compared to cases identified by passive case finding[21], a phenomenon also observed in our outpatient clinic. Nevertheless, in our cohort, even though patients of foreign origin had less often favorable treatment outcomes compared to patients of Greek origin (66.0 % vs 75.8 %) the difference was not significant, probably due to the small number of our cohort. It is important to point out that the majority of foreign-born patients with TB up to 2017 were from the ex-Soviet Union countries, and good communication was possible since no significant language barrier existed. It would be interesting to explore how TB's outcome is affected by country of origin in the more recent period when the majority of foreign-born patients are form Asia and Africa, and a significant percentage of them are minors with no family support [22].

As previously reported[6,17], one reason behind the suboptimal treatment success rate is the high mortality. Indeed 6.4 % of patients died during treatment, which is close to the European average[6,23]. All eleven patients who died during the 2012-2017 period had significant co-morbidities, five were above 80 years of age, and three were immunocompromised. Interestingly all were of Greek origin, which corresponds to their advanced age since immigrants with TB are typically younger in Greece.

Very little is known about TB treatment success rate in Greece since it is one of the few countries across Europe that does not report outcome[1,12]. Although it would probably be risky to extrapolate our single-center success rate to the entire country, we consider our results to be similar to that of other TB centers in the public sector. In Greece, TB patients can be diagnosed and treated both in the public and the private sector. In the public sector, only a few centers such as ours follow up patients on a regular basis across the country; these account for the vast majority of patients, especially more severe cases and also cases among immigrants and refugees. Isolated patients can be followed up either in the private sector or in regional public hospitals; these are usually patients in a better condition, but their number is low; therefore, their contribution to the total country treatment success rate is considered minimal.

Based on the reported results, TB treatment success rate in Greece is below the WHO standards, and given the country's immigration rates and financial crisis, it is not expected to improve in the following years. In this setting, it is essential to establish a system of credible reporting of both TB incidence and treatment success rate in order to best identify and address factors associated with poor outcome. Interventions such as appropriate and multidisciplinary staffing of TB centers may prove valuable in improving TB care in Greece.

Conflict of interest

Authors declare no conflict of interest.

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