Original Paper

Outcome of tuberculosis treatment at the pulmonary - tuberculosis department of A.U.TH. during the three-year period 2012-2014

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SUMMARY

INTRODUCTION: Tuberculosis remains a serious threat to public health and one of the leading causes of death among infectious diseases. Monitoring treatment outcome is necessary in order to assess the effectiveness of the therapeutic intervention and to identify possible obstacles to disease control. In that setting outcome is an important indicator of the effectiveness of TB control programs. **MATERIAL AND METHODS:** This is a retrospective study of TB patients registered at the Department of Pulmonary Medicine Aristotle University of Thessaloniki (AUTH), in the period from January 1st, 2012 to December 31st, 2014. **RESULTS:** 89 patients aged 49.5±19.20 years were recorded. 67.5 % were men. 68.5% of patients were of Greek origin and 91% suffered from pulmonary TB. In 78.7% of patients the diagnosis was confirmed microbiologically. 11.2% presented with monoresistance or polydrug resistance to anti-TB drugs. The positive outcome rate of the TB treatment was 67.5%, of which 38.2% were cured and 29.3% completed the treatment. The outc ome was negative in 32.5% of patients and rates that corresponded specifically to death, treatment failure, loss to follow-up and lack of evaluation were 4.5%, 1.1%, 2.2% and 24.7% respectively. **CONCLUSION:** The positive outcome rate of TB among patients was lower than the WHO global target of 85%. There is a clear need for a comprehensive management of problems in TB monitoring in Greece, both in terms of its impact and its outcome.

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INTRODUCTION

Despite the ongoing medical progress, tuberculosis (TB) is still a serious threat to public health and one of the leading causes of death among infectious diseases[1]. It is estimated that in 2015, the incidence of TB was

10.4 million cases worldwide, with 60% of them occurring in six countries (India, Indonesia, China, Nigeria, Pakistan and South Africa). In addition, about 480,000 new cases of multidrug-resistant TB and 100,000 cases with rifampicin resistance were recorded[2].

In the European Region of the World Health Organization (WHO) it is estimated that in 2015 there were 323,000 cases of TB that correspond to 35.5 cases per 100,000 people, and this accounts for about 3.0% of the global burden of TB, with 85% of all cases occurring in 18 countries[3].

In 2015, 482 cases were reported in Greece and as a result, the average incidence of the disease is approximately 4.4 per 100,000 people[3]. Over the four years 2010-2014, Greece was one of the few countries in Europe that showed an increasing trend in TB incidence, with this increase being mainly related to the native population and not to foreign patients[4], while 2015 a small decrease in the incidence of the disease[3] was observed. In Greece the disease is underreported and it has been shown that only 1/3 of treated TB cases are recorded[5-7].

In 1994 the WHO declared TB a "global emergency" because of the concern over the disease's extent in most of the developing world[8]. Over the last 22 years, strategies for the control of TB have been proposed at a global level. In 1995, the implementation of the Directly Observed Therapy (DOTS) program was proposed[9,10]. In 2001-2005 the "first global plan to stop TB" was launched and in 2002 a global fund was created favoring access to international funding[11]. In 2006 the WHO launched an enhanced strategy called "Stop TB Strategy" in order to achieve universal access to health services for people with TB, while the second "global plan to stop TB" covered the period 2006-2015[1]. The new "global TB strategy after 2015" adopted by the 67th World Health Assembly (WHA) in May 2014 has set itself the objective of ending by 2035 the TB epidemic, "the end TB strategy", by decreasing deaths from TB by 95% compared to 2015 and the incidence of the disease by 90% compared to 2015 [12].

All those measures led to a slow and steady decrease in the incidence of the disease from 1997 to 2001, with an increase in 2001, when the number of cases among HIV-infected patients in Africa increased[13]. Since then, TB incidence has been decreasing[13]. TB mortality has been diminished by 47% between 1990 and 2015 and it is estimated that 43 million lives have been saved from 2000 to 2014[14,15].

Treatment outcome is an important indicator of the effectiveness of TB control programmes[16]. Monitoring the outcome of treatment is necessary to assess the effectiveness of treatment but also to identify possible obstacles to disease control[17]. Sadly, there is no systematic recording of the treatment's outcome in Greece. Greece was not included in the study on the outcome of TB treatment in the European Union and the European Economic Area for the period from 2002 to 2011 because it was one of the countries that did not provide any data for any year of that decade[17].

In this context, this study aims to record the outcome of TB treatment at the Department of Pulmonary Medicine, AUTH, at "G. Papanikolaou" General Hospital of Thessaloniki and to identify the factors potentially associated with a negative outcome.

MATERIAL AND METHODS

This is a retrospective study of patients with TB registered at the Department of Pulmonary Medicine, AUTH, between January 1st, 2012 and December 31st, 2014. Data were collected from patients' records and include social and demographic factors and data related to both the disease itself and treatment outcome.

The Department of Pulmonary Medicine, AUTH started its operation in 1966[18]. The TB out-patient clinic has been operating in its current form since July 2011, twice a week.

In the present study patients' gender, age, somatometric characteristics, country of origin, smoking habits, and co-morbidities were recorded.

TB cases were classified according to WHO's 2013 definitions that were revised in December 2014 as follows:

- based on the method of diagnosis a) bacteriologically confirmed TB cases -cases in which a biological specimen is positive by smear microscopy, culture or nucleic acid amplification tests-NAATs and b) clinically diagnosed TB cases - cases that have been diagnosed with active TB by a clinician who has decided to initiate a full course of TB treatment. This definition includes cases diagnosed on the basis of X-ray abnormalities or suggestive histology and extrapulmonary cases without laboratory confirmation.[19].
- based on anatomical site of disease a) pulmonary TB - any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree as well as miliary TB and b) extrapulmonary TB- any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs, e.g. pleura, lymph nodes, ab-

domen, genitourinary tract, skin, joints and bones, meninges[19]. In case of coexistence of pulmonary and extrapulmonary localization, the case is classified as pulmonary TB[19].

- based on the history of previous TB treatment, cases are classified as (a) new patients - patients who have never been treated for TB or have taken anti-TB drugs for less than 1 month and (b) Previously treated patients - patients who have received 1 month or more of anti-TB drugs in the past.[19]
- based on the resistance to anti-TB drugs, cases are classified as: a) monoresistance - resistance to one first-line anti-TB drug only, b) polydrug resistance-resistance to more than one first-line anti-TB drug (other than both isoniazid and rifampicin), c) multidrug resistant TB, MDRTB - resistance to at least both isoniazid and rifampicin and e) extensively drug resistant TB (XDRTB)-resistance to any fluoroquinolone and to at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin), in addition to multidrug resistance[19].

Regarding TB outcome, WHO definitions were used:

Cured - A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion[19].

Treatment completed - A TB patient who completed treatment without evidence of failure but with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable[19].

Treatment failure - A TB patient whose sputum smear or culture is positive at fifth month or later during treatment[19].

Death - A TB patient who dies for any reason at starting or during the course of treatment[19].

Lost to follow-up - A TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more[19].

Not evaluated - Refers to patients for whom an exact outcome of treatment has not been defined, for example because they were transferred to another center and the result is unknown[19].

This study includes bacteriologically confirmed cases but also clinically diagnosed cases, cases of pulmonary and extrapulmonary TB, newly diagnosed cases but also patients with a history of TB and cases of monoresistance and poly resistance. The study excluded patients with multidrug-resistant TB (MDRTB) and those with extended resistant TB (XDRTB). Favorable-positive outcome of the antiTB therapy means the cure and completion of treatment. In contrast, negative outcome was considered that of patients whose treatment failed, those who died, patients lost to follow-up and the group of patients who were not evaluated.

An Excel spreadsheet was used to process and study the data, and all the data gathered were recorded therein. Then, the χ^2 test was applied by the use of the Chi-Square Calculator freeware. (http://www.socscistatistics.com/tests/chisquare/Default2.aspx).

RESULTS

As evidenced by this study's data, 89 patients aged 49.5 ±19.20 years were recorded in the TB clinic in the three-year period 2012-2014. The distribution of patients per year was 21 patients (23.6%) in 2012, 34 (38.2%) in 2013 and 34 (34.8%) in 2014. Most were men (67.5%) and of Greek origin (68,5%). 31.5% of all patients were foreigners, specifically: 8 from Georgia, 6 from Albania, 4 from Pakistan, 2 from Bulgaria and 1 patient from each of the following countries: Armenia, China, Moldova, Bangladesh, Romania, Russia, Ghana and one of unknown origin. The demographic characteristics are presented in detail in Table 1.

91% of the patients suffered from pulmonary TB and only 9% from extrapulmonary TB, especially of the

TABLE 1. Social and demographic data

Patients characteristics	2012-2014 (n,%)	2012 (n,%)	2013 (n,%)	2014 (n,%)
Number of patients	89 (100%)	21 (23,6%)	34 (38,2%)	34 (38,2%)
Men	60 (67,5%)	13 (61,9%)	25 (73,5%)	22 (64,7%)
Women	29 (32,5%)	8 (38,1%)	9 (26,5%)	12 (35,3%)
Greek	61 (68,5%)	18 (85,7%)	21 (61,8%)	22 (64,7%)
Foreigners	28 (31,5%)	3 (14,3%)	13 (38,2%)	12 (35,3%)

pleura (Table 2). Most (86.5%) of the cases were new. In 78.7% of patients (70 persons) the diagnosis was microbiologically confirmed, of which 46 patients showed positive AFB (acid-fast bacilli) smears, and 14 were NAATs positive and AFB-negative. 11.2% had monoresistance or polydrug resistance to anti-TB drugs, of which 50% were of Greek origin (Table 3). 58.4% were negative for HIV co-infection, while in 41.6% testing was not recorded. 62.9% of all patients presented with co-morbidities (Table 4). Regarding smoking, 35.9% were active smokers, 4.5% were ex-smokers, 22.5% were non-smokers, and 37.1% provided no data on their smoking habits.

The positive outcome rate of the TB treatment was 67.5% (60 patients), of whom 34 patients (38.2%) were cured and 26 patients (29.3%) completed their treatment. Negative outcome was recorded in 32.5% of patients (29 patients). More specifically, the rates that correspond to death, treatment failure, lost to follow up and not evaluated were 4.5% (4 patients), 1.1% (1 patient), 2.2% (2 patients) and 24.7% (22 patients) respectively (Figure 1). The annual outcome of patient treatment is shown in Figure 2.

As shown in Table 5, no statistically significant factors were found that could be implicated in the negative treatment outcome. Patients who died during TB treatment were two men and two women aged over 70 years, of Greek origin with pulmonary drug-susceptible TB and with co-morbidities (three patients with cardiovascular problems and one with chronic obstructive pulmonary disease). Death in the first three patients occurred on the 13th, 30th, 42nd day of treatment and was attributed to TB. The fourth patient died of an unrelated to TB cause in the 9th month of treatment while showing significant clinical and radiological improvement.

TABLE 3. Number of patients with drug resistance

	Patients with resistance (n,%)	Country of origin
Isoniazid	3 (3,4%)	Greece (1), Albania(1), Pakistan(1)
Rifampicin	1 (1,1%)	Georgia
Streptomycin	3 (3,4%)	Greece (1), Georgia (1), Russia (1)
Ethambutol	1 (1,1%)	Greece
Pyrazinamide	1 (1,1%)	Greece

TABLE 4. Co-morbidities of patients with tuberculosis

	Number of patients (%)
Number of patients with co-morbidities	56 (63%)
Patients with one concomitant disease	27 (48,2%)
Patients with more than one concomitant disease	29 (51,5%)
Central nervous system diseases	1 (1,8%)
Cardiovascular system diseases	24 (42,9%)
Respiratory diseases	6 (10,7%)
Gastrointestinal disorders	7 (12,5%)
Diseases of the genitourinary system	8 (14,3%)
Diseases of the musculoskeletal system	5 (8,9%)
Diabetes mellitus and metabolic diseases	7 (12,5%)
Patients with mental disorders	5 (8,9%)
Autoimmune Diseases	7 (12,5%)
Patients with immunosuppression	5 (8,9%)
Patients with neoplastic disease	2 (3,6%)
Viral hepatitis	5 (8,9%)
Alcoholism	3 (5,4%)
Users of intravenous substances	6 (10,7%)

DISCUSSION

Based on the results of the present study, the positive outcome rate in TB patients at the Department of Pulmonary Medicine, AUTH, during the three-year period 2012-2014 was 67.5% in total, and specifically 76.2%, 61.7% and 67.6% in the years 2012, 2013 and 2014 respectively. This rate is certainly lower than the recommended WHO

TABLE 2. Anatomical site of disease

Anatomical site	(n,%)	2012 (n,%)	2013 (n,%)	2014 (n,%)
Pulmonary	81 (91%)	19 (90,5%)	29 (85,3%)	32 (94,2%)
Extrapulmonary	8 (9%)	2 (9,5%)	5 (14,7%)	1 (2,9%)
Pleura	5 (5,6%)	2 (9,5%)	3 (8,9%)	
Lymph nodes	2 (2,3%)		1 (2,9%)	1 (2,9%)
Spine	1 (1,1%)		1 (2,9%)	

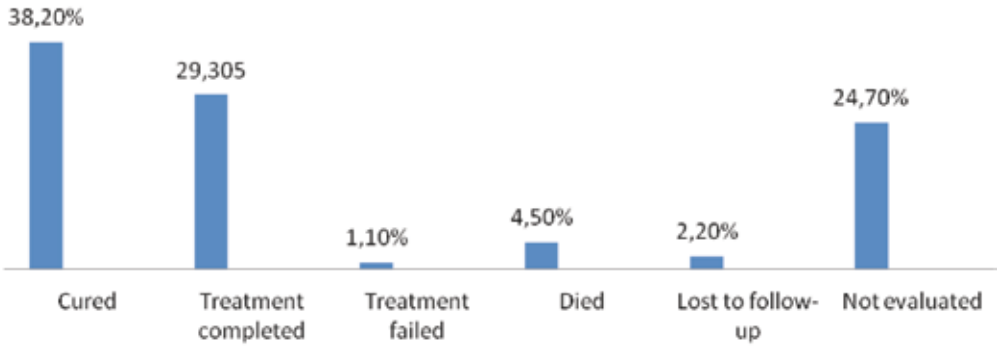

FIGURE 1. Tuberculosis treatment outcome for the three year period 2012-2014.

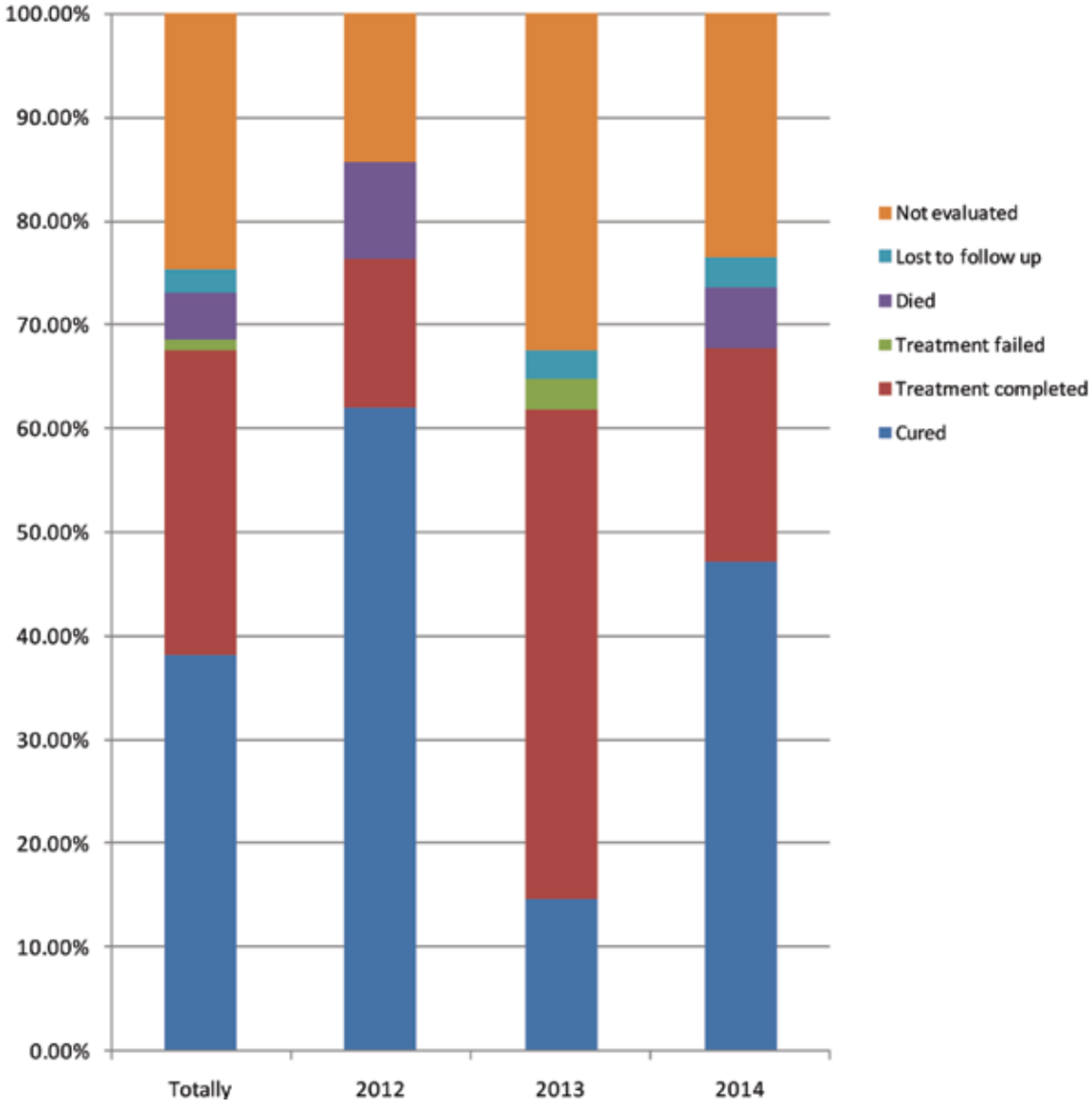

FIGURE 2. Annual and total tuberculosis treatment outcome.

TABLE 5. Clinical, social and demographic characteristics of patients and tuberculosis treatment outcome

		Number of patients (n, %)	Treatment success (n, %)	Treatment failure (n, %)	p value
Gender	Men	60 (67,5%)	39 (65%)	21 (35%)	0,4843
	Women	29 (32,5%)	21 (72,4%)	8 (27,6%)	
Age	≤64	69 (77,5%)	45 (65,2%)	24 (34,8%)	0,4111
	≥65	20 (22,5%)	15 (75%)	5 (25%)	
Country of origin	Greece	61 (68,5%)	45 (73,8%)	16 (26,2%)	0,0590
	Foreigners	28 (31,5%)	15 (53,6%)	13 (46,4%)	
Anatomical site	Pulmonary	81 (91%)	53 (65,4%)	28 (34,6%)	0,2039
	Extrapulmonary	8 (9%)	7 (87,5%)	1 (12,5%)	
History of previous TB treatment	Negative	77 (86,5%)	51 (66,2%)	26 (33,8%)	0,5467
	Positive	12 (13,5%)	9 (75%)	3 (23%)	
Co-morbidities	Absent	56 (62,9%)	40 (71,4%)	16 (28,6%)	0,2927
	Present	33 (37,1%)	20 (60,6%)	13 (39,4%)	
Smoking	Non smokers	20 (22,5%)	15 (75%)	5 (25%)	0,8279
	Active smokers	32 (35,9%)	21 (65,6%)	11 (34,4%)	
	Ex smokers	4 (4,5%)	3 (75%)	1 (25%)	
	No data	33 (37,1%)	21 (63,6%)	12 (36,4%)	
Resistance to antituberculosis drugs	Absent	79 (88,8%)	52 (65,8%)	27 (34,2%)	0,3674
	Present	10 (11,2%)	8 (80%)	2 (20%)	

target rate of 85%[13]. It is also evident that: 1) the highest number of patients with negative outcome corresponds to patients who were not evaluated, 2) TB remains a cause of mortality and 3) for a large number of patients testing for HIV co-infection was not recorded. No statistically significant factors that could be implicated in the negative treatment outcome were found. It is worth noting that the rate of microbiological confirmation of the disease was high (78.7% of all patients).

As described above, according to our data, 38.2% of patients were cured and 29.3% completed treatment, thus resulting in a total positive outcome of 67.5%. According to the WHO report published in 2017 regarding the surveillance and monitoring of TB in Europe, the positive outcome of TB treatment in our clinic was higher than in Cyprus (58.8% in 2014), Denmark (58.1% in 2014) and Germany (60.1% in 2014)[3] and lower than other European countries such as Albania (88.2% in 2014), Austria (73.1% in 2014), Belgium (79, 7% in 2014), Bulgaria (84.9% in 2014), the Former Yugoslav Republic of Macedonia (86.8% in 2014) and Turkey (86.9% in 2014)[3]. Moreover, the overall positive treatment outcome rate in our clinic was lower than the overall success rate of treatment in the European Union and the European Economic Area for the years 2002 to 2011, which amounted to 78.2%[17] and 76% for the year 2014[2]. Higher success rates were reported in the US in 2013 (89%)[20] and in Canada in 2012 (86%)[21]. Finally, at a global level the success rate of treatment for patients newly diagnosed with TB was 86% in 2013[15] and 83% in 2014[2].

Unfortunately, no data were found in the literature concerning the outcome of treatment in other TB clinics in Greece. The outcome is unknown in Greece, since its report is not mandatory. Ideally, in the context of an anti-TB program, the TB clinics across Greece could be integrated into a national network where it would be compulsory to report the course of the disease and the outcome of each patient's treatment. This of course requires adequate medical and paramedical staff as well as the appropriate electronic equipment. It is worth mentioning that our clinic was staffed by a specialized nurse only in June 2016, almost five years after the initiation of its operation.

Based on the present data, the percentage of patients whose treatment failed, died, lost to follow-up and those who cannot be evaluated were 1.1%, 4.5%, 2.2% and 24.7%, respectively. Therefore, it is clear that the negative outcome of treatment is mainly caused by the group of not evaluated patients for whom the outcome

is unknown. However, an unknown treatment outcome does not necessarily mean a negative outcome. In any case, the large number of the patients who do not show up for their follow up may be associated with the gap in the legislative framework and also the lack of incentives that would encourage them to complete their treatment under medical supervision. It is a fact that many of the patients do not come to the scheduled appointment, despite the systematic communication effort by the clinic's staff. Again, the lack of an appropriate legal framework and the lack of incentives (such as free tickets or financial support for the less well-off patients) make the control of attendance extremely difficult.

Death caused by TB remains a reality. As already mentioned, there were 1.8 million deaths from the disease[2] in 2015. Patients in this study who died were of Greek origin, with pulmonary TB, without history of previous treatment, or resistance to anti-TB drugs, but all of them were elderly patients with co-morbidities. Increased mortality in coexisting concomitant diseases was also noticed in other studies[22,23]. Many studies also suggested that elderly people in general show an increased death rate[24,25,26,27]. A study in South Africa suggested that older age is the most important independent factor associated with increased mortality[28]. The elderly are at risk for receiving a wrong diagnosis[29] mainly because disease at advanced age is manifested by non-specific symptoms and diagnosis may be confused by concomitant diseases. Therefore, the diagnosis is made at a more advanced stage leading to increased mortality[30,31]. The significance of the clinical suspicion of TB in the elderly is therefore evident. In Japan, early diagnosis is considered to be the most important measure for controlling TB in the elderly[32]. The history of previous TB[33,34] and the gender of patients[34] did not seem to have led to increased mortality as opposed to other studies[33,34].

According to this study, testing for HIV co-infection was not recorded for a significant number of patients (41.6%), although it is systematically pursued in our clinic. In 2014, it is estimated that there were about 1.2 million new cases of TB among HIV-positive people, of whom 74% lived in Africa and about 0.4 million people died of HIV and *Mycobacterium tuberculosis* co-infection[14]. People with HIV infection are 20-30 times more likely to develop active TB than the rest of the population[14] due to immunodeficiency and the coexistence of degraded social conditions[1,35]. All patients newly diagnosed with TB should know if they have HIV co-infection[36], therefore diagnosis of TB is an indication for HIV testing. Early diagnosis of TB/HIV infection reduces morbidity and mortality, costs of hospitalization and provides an opportunity for a better quality of life[37].

This study did not reveal any statistically significant factors that may have adversely affected treatment outcome, although the small total number of patients does not allow safe conclusions. The origin of patients seems to have a marginal effect on the outcome of the disease, the Greek patients showing a higher positive outcome than foreigners (73.8% and 53.6%, respectively). The rate of successful treatment was higher for natives than for foreigners in other studies as well[17,38,39]. In Italy and Switzerland treatment discontinuation has been associated with foreign patients[40,41]. On the other hand, it has been reported that migrants in the European Union do not receive the same level of healthcare at the level of prevention, diagnosis and treatment, possibly because of their social exclusion and financial situation[42]. The gender of patients does not seem to have affected the outcome of the treatment as opposed to other studies that reported lower rates of TB treatment success in male patients, a fact that was attributed to social and environmental factors[17,27,34,35,43,44]. A study conducted in South Africa suggested that male sex was an independent risk factor for treatment discontinuation[45]. However, biological factors may also play a role as shown by a study in mice, where male mice developed a more severe form of TB[46]. Patients with resistance to anti-TB drugs seemed to have a successful treatment rate equivalent to the success rates of drug sensitive TB regardless of whether they had mono or poly-drug resistance. Resistance to pyrazinamide did not seem to adversely affect the therapeutic effects in a California study[47]. In contrast, in other studies, pretreatment resistance[39,48-51], acquired resistance[49] (new drug resistance during or at the end of treatment), but also any resistance to isoniazid other than MDR-TB[48], rifampicin resistance[48,49,52] and streptomycin resistance[49] were associated with therapeutic failure. Increased mortality was found with rifampicin resistance in a Peruvian study. The presence of concomitant diseases does not seem to have affected the outcome of the treatment in the present study. In contrast, other studies have shown that the presence of any concomitant disease is associated with an adverse outcome[22,23,53,54]. In China diabetes mellitus seemed to result in therapeutic failure[55]. In some studies therapeutic failure seemed to be caused by the intravenous use of illicit drugs[56-59] as well as by alcohol dependence[58,59]. This study also shows that 34.4% of active smokers, 25% of ex-smokers and 36.4% of patients that provided no

data on their smoking habits had a negative outcome. Smoking has been associated with adverse treatment outcome[34]; it significantly increases the risk of TB, and in particular more than 20% of TB cases worldwide are caused by smoking[14].

The rate of bacteriologically confirmed diagnosis of the disease in this study amounted to 78.7%. In 2015 the rate of bacteriological diagnosis of TB in Greece was 86.9%[3]. However, it should be taken into account that this rate probably does not reflect the reality because of the significant lack of reporting, since it is more likely that there is no microbiological confirmation in unreported cases. In Europe, the disease's bacteriological confirmation varies considerably between countries, from 34% to 96% in Uzbekistan and Slovenia respectively, with four countries having a bacteriologically confirmed diagnosis rate of less than 50%, thus highlighting the need to improve diagnostic methods[3]. The microbiological diagnosis of TB is lower in general in countries outside the European Union and the European Economic Area, (EU/EEA) compared to that of the EU/EEA countries (57% and 79.5%, respectively)[3].

The most significant restriction of the study is the small number of patients that did not allow conclusions about the factors that may have adversely affected the outcome of the treatment. At the same time, the large number of patients who cannot be evaluated raises numerous questions about the actual outcome of TB.

In conclusion, this study shows that the positive outcome rate of TB patients at the Department of Pulmonary Medicine, AUTH, from 2012 to 2014 was lower than the WHO global target of 85%, whereas death from TB is still a reality. Since the outcome of TB is an indicator of the effectiveness of healthcare services, there is a clear need for a comprehensive response to the problems of recording and monitoring TB in Greece in terms of both its impact and its outcome. This could be achieved by developing, implementing and continuously evaluating an integrated anti-TB program and a clear underlying legislative framework for the safe management, and the precise description of the obligations and rights of the TB patients.

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REFERENCES

1. Sulis G, Roggi A, Matteelli A, et al. Tuberculosis: Epidemiology and Control. Mediterranean Journal of Hematology and Infectious Diseases 2014; 6:e2014070.
2. World Health Organization- WHO. Global tuberculosis report 2016.
3. European Centre for Disease Prevention and Control/WHO Regional Office for Europe (ECDC/WHO EURO). Tuberculosis surveillance and monitoring in Europe 2017.
4. European Centre for Disease Prevention and Control, WHO Regional Office for Europe. Tuberculosis surveillance and monitoring in Europe 2016. Stockholm: ECDC; 2016.
5. Jelastopulu E, Alexopoulos EC, Venieri D, et al. Substantial underreporting of tuberculosis in West Greece: implications for local and national surveillance. Euro Surveill 2009; 14:pii:19152.
6. Lytras T, Spala G, Bonovas S, et al. Evaluation of Tuberculosis Underreporting in Greece through Comparison with Anti-Tuberculosis Drug Consumption. Dowdy DW, ed. *PLoS ONE*. 2012; 7:e50033.
7. Ibarz-Pavón AB, Papaventsis D, Kalkouni R, et al. Pilot study of the completeness of notification of adult tuberculosis in Athens, Greece. Int J Tuberc Lung Dis 2016; 20:920-5.
8. World Health Organization (WHO). TB: a global emergency, WHO report on the TB epidemic. WHO/TB/94.177. Geneva, 1994.
9. World Health Organization (WHO). WHO tuberculosis programme: framework for effective tuberculosis control. WHO/TB/94.179. Geneva, 1994.
10. International Union Against Tuberculosis and Lung Disease (IUATLD). Tuberculosis Guide for Low Income Countries, 4th ed. IUATLD, Paris, 1996.
11. World Health Organization (WHO)/Stop-TB Partnership. The Global Plan to Stop TB: Phase 1: 2001–2005. WHO/CDS/STB/2001.16. WHO, Geneva, 2001.
12. World Health Organization (WHO). Global strategy and targets for tuberculosis prevention, care and control beyond 2015. Geneva, 2013.
13. World Health Organization (WHO). Global Tuberculosis Report 2013. Geneva, 2013.
14. World Health Organization: WHO Fact sheets on tuberculosis. Fact sheet N°104. Reviewed March 2016.
15. World Health Organization (WHO). Global Tuberculosis Report 2015.
16. World Health Organization. Treatment of Tuberculosis Guidelines. 4th editionWHO/HTM/TB/2009.40. Geneva: WHO; 2009.
17. Karo B, Hauer B, Hollo V, van der Werf MJ, Fiebig L, Haas W. Tuberculosis treatment outcome in the European Union and Europen E conomic Area: an analysis of surveillance data from 2001-2011. Euro Surveill 2015; 20:pii:30087. doi: 10.2807/1560-7917.ES.2015.20.49.30087.
18. Moschota K, 2016. Sanatorium Asvestochori where the present meets the past. Thessaloniki.
19. World Health Organization (WHO). Definitions and reporting framework for tuberculosis – 2013 revision (updated December 2014).

20. Centers for Disease Control and Prevention (CDC). Reported Tuberculosis in the United States, 2013. Atlanta: CDC; October 2014.
21. Public Health Agency of Canada. Tuberculosis in Canada 2012-Pre-Release. Ottawa (Canada): Minister of Public Works and Government Services Canada; 2014.
22. Sengul A, Akturk UA, Aydemir Y, et al. Factors affecting successful treatment outcomes in pulmonary tuberculosis: a single-center experience in Turkey, 2005-2011. J Infect Dev Ctries 2015; 9:821-8.
23. Vasankari T, Holmström P, Ollgren J, et al. Risk factors for poor tuberculosis treatment outcome in Finland: a cohort study. BMC Public Health 2007; 7:291.
24. Lefebvre N, Falzon D. Risk factors for death among tuberculosis cases: analysis of European surveillance data. Eur Respir J. 2008; 31:1256-60.
25. Hauer B, Brodhun B, Altmann D et al. Tuberculosis in the elderly in Germany. Eur Respir J 2011; 38:467-70.
26. Kolappan C, Subramani R, Kumaraswami V, et al. Excess mortality and risk factors for mortality among a cohort of TB patients from rural south India. Int J Tuberc Lung Dis 2008;12:81-6.
27. Babalik A, Kilicaslan Z, Caner SS, et al. A registry-based cohort study of pulmonary tuberculosis treatment outcomes in Istanbul, Turkey. Jpn J Infect Dis 2013; 66:115-20.
28. Heunis JC, Kigozi NG, Chikobvu P, et al. Risk factors for mortality in TB patients: a 10-year electronic record review in a South African province. BMC Public Health 2017;17:38.
29. Rajagopalan S. Tuberculosis and aging: a global health problem. Clin Infect Dis 2001; 33:1034-9.
30. Packham S. Tuberculosis in the elderly. Gerontology 2001; 47:175-9.
31. Zevallos M, Justman JE. Tuberculosis in the elderly. Clin Geriatr Med 2003; 19:121-38.
32. Ohmori M, Wada M, Yoshiyama T, et al. Factors related to early case detection of tuberculosis in health service facilities for the elderly. Kekkaku 2003; 78:435-42.
33. Acuña-Villaorduña C, Ayakaka I, Dryden-Peterson S, et al. High mortality associated with retreatment of tuberculosis in a clinic in Kampala, Uganda: A retrospective study. Am J Trop Med Hyg 2015; 93:73–5.
34. Liew SM, Khoo EM, Ho BK et al. Tuberculosis in Malaysia: predictors of treatment outcomes in a national registry. Int J Tuberc Lung Dis 2015; 19:764–71.
35. Muñoz-Sellart M, Cuevas LE, Tumato M, et al. Factors associated with poor tuberculosis treatment outcome in the Southern Region of Ethiopia. Int J Tuberc Lung Dis 2010; 14: 973-9.
36. World Health Organization (WHO). WHO policy on TB/HIV collaborative activities: guidelines for national programmes and other stakeholders. Geneva, 2012.
37. Lima LM, Harter J, Tomberg JO, Vieirac DA, Antunesd ML, Cardozo-Gonzalese RI. Monitoring and assessment of outcome in cases of tuberculosis in a municipality of Southern Brazil. Rev. Gaúcha Enferm. Vol.37 no.1 Porto Alegre 2016 Epub Mar 01, 2016. doi.org/10.1590/1983-1447.2016.01.51467.
38. Van Hest, R, Ködmön, C, Verver, S, et al. Tuberculosis treatment outcome monitoring in European Union countries: systematic review. The European Respiratory Journal 2013; 41:635–43.
39. Farah MG, Tverdal A, Steen TW, et al. Treatment outcome of new culture positive pulmonary tuberculosis in Norway. BMC Public Health 2005; 5:14.
40. Faustini A, Hall AJ, Perucci CA. Tuberculosis treatment outcomes in Europe: a systematic review. European Respiratory Journal 2005; 26:503-10. Web. 13 Nov. 2016.
41. Helbling P, Medinger C, Altpeter E, et al. Outcome of treatment of pulmonary tuberculosis in Switzerland in 1996. Swiss Med Wkly 2002; 132:517–22.
42. Fernandes A, Miguel JP. Health and migration in European Union: better health for all in an inclusive society. 291173/09. Lisboa. Instituto Nacional de Saude Doutor Ricardo Jorge 2009.
43. Karim F, Ahmed F, Begum I, et al. Female-male differences at various clinical steps of tuberculosis management in rural Bangladesh. Int J Tuberc Lung Dis 2008; 12:1336-9.
44. Falzon D, Le Strat Y, Belghiti F, Euro TB. Correspondents. Exploring the determinants of treatment success for tuberculosis cases in Europe.Int J Tuberc Lung Dis 2005; 9:1224-9.
45. Connolly C, Davies GR, Wilkinson D. Who fails to complete tuberculosis treatment? Temporal trends and risk factors for treatment interruption in a community-based directly observed therapy programme in a rural district of South Africa. Int J Tuberc Lung Dis 1999; 3:1081-7.
46. Nhamoyebonde S, Leslie A. Biological differences between the sexes and susceptibility to tuberculosis. J Infect Dis 2014; 209(Suppl 3):S100-6.
47. Budzik JM, Jarlsberg LG, Higashi J et al. Pyrazinamide resistance, Mycobacterium tuberculosis lineage and treatment outcomes in San Francisco, California. PLoS One 2014;9:e95645.
48. Espinal MA, Kim SJ, Suarez PG et al. Standard short-course chemotherapy for drug-resistant tuberculosis: treatment outcomes in 6 countries. JAMA 2000; 283:2537-45.
49. Seung KJ, Gelmanova IE, Peremitin GG, et al. The effect of initial drug resistance on treatment response and acquired drug resistance during standardized short-course chemotherapy for tuberculosis. Clin Infect Dis 2004;39:1321-8.
50. Báez-Saldaña R, Delgado-Sánchez G, García-García L, et al. Isoniazid Mono-Resistant Tuberculosis: Impact on Treatment Outcome and Survival of Pulmonary Tuberculosis Patients in Southern Mexico 1995-2010. PLoS One 2016; 11:e0168955.
51. Villegas L, Otero L, Sterling TR, et al. Prevalence, Risk Factors, and Treatment Outcomes of Isoniazid- and Rifampicin-Mono-Resistant Pulmonary Tuberculosis in Lima, Peru. PLoS One 2016; 11:e0152933.
52. Meyssonnier V, Bui TV, Veziris N, et al. Rifampicin mono-resistant tuberculosis in France: a 2005-2010 retrospective cohort analysis. BMC Infect Dis 2014; 14:18.
53. Babalik A, Kilicaslan Z, Kiziltas S, et al. A retrospective case-control study, factors affecting treatment outcomes for pulmonary tuberculosis in Istanbul, Turkey. Balkan Med J 2013; 30:204-10.
54. Garrido Mda S, Penna ML, Perez-Porcuna TM, et al. Factors associated with tuberculosis treatment default in an endemic area of the Brazilian Amazon: a case control-study. PLoS One

2012; 7:e39134.
55. Mi F, Tan S, Liang L, et al. Diabetes mellitus and tuberculosis: pattern of tuberculosis, two-month smear conversion and treatment outcomes in Guangzhou, China. Trop Med Int Health 2013; 18:1379-85.
56. Deiss RG, Rodwell TC, Garfein RS. Tuberculosis and Drug Use: Review and Update. Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America, 2009; 48:10.1086/594126.
57. Valin N, Hejblum G, Borget I, et al. Management and treatment outcomes of tuberculous patients, eastern Paris, France, 2004. Int J Tuberc Lung Dis 2009; 13:881-7.
58. Diel R, Niemann S. Outcome of tuberculosis treatmentin Hamburg: a survey, 1997-2001. Int J Tuberc Lung Dis 2003; 7:124-31.
59. Working Group on Completion of Tuberculosis Treatment in Spain, Cayla JA, Caminero JA, Rey R, Lara N, Valles X, Galdos-Tanguis H. Current status of treatment completion and fatality among tuberculosis patients in Spain. Int J Tuberc Lung Dis 2004; 8:458-64.