Factors Affecting Sputum Conversion Time in Patients with Smear-Positive Tuberculosis

Yayma-Pozitif Tüberküloz Hastalarında Balgamda Konversiyon Süresini Etkileyen Faktörler

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ABSTRACT Objective: To determine the possible factors affecting the sputum conversion time in patients with sputum smear-positive tuberculosis. **Material and Methods:** Files of 163 smear positive lung tuberculosis patients who had been treated at the Umraniye Tuberculosis Dispensary in 2006 were retrospectively examined. A p value of <0.05 was considered significant for the statistical analyses. Pearson Chi-Square test was applied for the cathegorical variables and the frequency analyses. The Mann Whitney-U Test was used for variables without a normal distribution. **Results:** The age of patients ranged between 16 and 70 years (mean: 33.6±13.3 years); 124 (76.1%) of the patients were male and 39 (23.9%) of were female. The conversion time was 2 months or shorter in 127 (77.9%) patients (mean conversion time: 1.96±1.04 months). We found no relationship between the conversion time and gender, smoking status, hospitalization, comorbidity and extent of radiological findings. The conversion time was 3 months or longer in 28 (31.8%) of 88 patients who displayed a cavity on chest X-ray and in 8 (10.8%) of 74 patients who displayed no cavity. This was statistically significant (p=0.001). The median value of the body mass index was determined as 21.4 kg/m^2 (interquartile range:19.2-22.9) in patients in whom the conversion time was 2 months or shorter, and 19.6 kg/m^2 (interquartile range:18.1-20.9) in patients in whom the conversion time was 3 months or longer. This result was statistically significant (p=0.015). **Conclusion:** The presence of a cavity on chest X-ray and low body mass index are factors that increasing time of sputum smear conversion.

Key Words: Tuberculosis, pulmonary; body mass index; sputum

ÖZET Amaç: Yayma-pozitif akciğer tüberkülozu hastalarında balgamda konversiyon süresini etkileyen olası faktörleri belirlemek. **Gereç ve Yöntemler:** 2006 yılında Ümraniye Verem Savaş Dispanserinde tedavi edilen toplam 163 yayma-pozitif akciğer tüberkülozlu hastanın dosyaları geriye dönük olarak incelendi. İstatistiksel analizler için p<0,05 anlamlı kabul edildi. Kategorik değişkenler ve sıklık analizleri için Pearson ki-kare testi uygulandı. Normal dağılım göstermeyen değişkenler için Mann Whitney-U testi kullanıldı. **Bulgular:** Yaşları 16 ile 70 yıl arasında (ortalama: 33,6±13,3 yıl) değişen hastaların, 124 (%76,1)'ü erkek, 39 (%23,9)'u kadın olup, 127 (%77,9) hastada konversiyon süresi 2 ay ve altında idi (ortalama konversiyon süresi 1,96±1,04 ay). Konversiyon süresi ile cinsiyet, sigara içme durumu, hastanede yatış, komorbidite varlığı ve radyolojik bulguların yaygınlığı arasında ilişki saptamadık. Akciğer grafisinde kavite olan 88 hastanın 28 (%31,8)'inde, kavite olmayan 74 hastanın ise 8 (%10,8)'inde konversiyon süresi 3 ay ve üstünde olup, bu durum istatistiksel olarak anlamlı bulundu (p=0,001). Konversiyon süresi 2 ay ve altında olan hastalarda vücut kitle indeksi ortanca değeri 21,4 kg/m^2 (%25-19,2/%75-22,9) iken, 3 ay ve üstünde olan hastalarda ise 19,6 kg/m^2 (%25-18,1/%75-20,9) saptandı, bu sonuç istatistiksel olarak anlamlı idi (p=0,015). **Sonuç:** Akciğer grafisinde kavite varlığı ve düşük vücut kitle indeks değeri, balgamda konversiyon süresini uzatan faktörlerdir.

Anahtar Kelimeler: Tuberküloz, akciğer; vücut kitle indeksi; balgam

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The tranmission of tuberculosis caused by *Mycobacterium tuberculosis*, is essentially airborne. Hence, only patients with pulmonary sputum smear-positive tuberculosis transmit the disease.[1]

World Health Organization (WHO) declared an emergency situation in 1993 to take necessary precautions for tuberculosis (TB).[2] There were an estimated 9.2 million new cases of tuberculosis (TB) in 2006 (139 per 100 000 population), including 4.1 million new smear positive cases (44% of the total).[3] The main source of infection is a patient with active pulmonary tuberculosis (PTB) and positive sputum smears, who is excreting tubercle bacilli.[1,4] The available data suggest that once patients with TB begin to receive effective chemotherapy, they rapidly become less infectious.[1,5]

Turkey's National Tuberculosis Programme recommends the following treatment regimens: for new PTB cases and extra-pulmonary cases: a 6-month treatment regimen consisting of 2 months of isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E) or streptomycin (S), followed by 4 months of HR; for relapse and defaulter cases: an 8-month treatment regimen consisting of HRZES for 2 months, followed by HRZE for 1 month and HRE for 5 months; for failure and chronic cases: an individualised treatment regimen with second-line drugs under the supervision of a specialised centre.[6] In new patients with smear-positive PTB, the sputum smears are examined at the end of the initial phase of treatment (2 months) and on two more occasions during the continuation phase of treatment. For new PTB patients, negative sputum smears at 2 months are indicate that treatment should change from the initial to the continuation phase. If the smear is positive the intensive phase is extended by one more month for that patient.[7,8] Sputum smear and culture conversion are important indicators for the effectiveness of treatment and the patient's infectivity.[9-13]

In this study we aimed to determine predictors of the sputum smear conversion time among patients with PTB.

MATERIAL AND METHODS

SETTING

Umraniye is a rapidly urbanizing region of Istanbul with a continuously growing population. It has a surface area of 153 km^2 and a population of 501 260, according to the count in 2007. The Umraniye Tuberculosis Dispensary was founded in 1996 and a total 3142 patients with TB have been treated for 10 years. Of a total of 409 patients, 117 had extrapulmonary TB in 2006. One-hundred and sixty-three smear-positive cases with PTB that had been treated in 2006 were included in the study. Patients with smear-negative PTB and those who had extrapulmonary TB were excluded from the study.

PROCEDURES

The demographic characteristics of all the smear-positive patients in one year period were recorded. The age, sex, smoking status, presence of comorbidity and diabetes mellitus (DM), additional drug use, presence of hospitalization and the application of directly observed treatment (DOT) were scanned. The types of the patients were defined as "new", "had previous treatment" and "relapsed". When a patient had never received treatment for TB or had taken antituberculosis drugs for less than 1 month, the patient was considered as a new patient. A "relapsed" patient was described as one who had previously been treated for TB, had been declared cured or treatment had been completed, and who was diagnosed with bacteriologically positive (smear or culture) tuberculosis. Patients who had been treated as default (a bacteriologically-positive patient, who had returned to treatment following interruption of treatment for 2 months or longer) and those who had been treated after failure (a patient for whom a re-treatment regimen had been begun after the previous treatment having failed) were grouped under the heading of "had previous treatment".

Conventional chest X-ray was used for radiological evaluation. The penetration and the location of the radiological findings (unilateral or bilateral), the presence and the number of cavi-

ties were assessed. The sputum smears were examined for acid fast bacilli (AFB) by microscopy and the specimens were cultured on the Lowenstein-Jensen (LJ) medium. The presence of drug resistance was noted in culture positive cases. Due to the fact that not all patients displayed sputum culture results, the smear examination by microscopy was based for conversion. The conversion time was expressed as month. The body mass index (BMI) values were calculated in all the patients.

All new patients received standard chemotherapy including H, R, E or S, and Z for 2 months and HR for 4 months. The relapse and default cases received an 8-month treatment regimen consisting of HRZES for 2 months, followed by HRZE for 1 month and HRE for 5 months. Microscopic examination of the sputum with 2 samples was performed monthly during initial phase of therapy and on 2 more occasions during the continuation phase of treatment. Delayed sputum smear conversion was considered when 2 positive sputum smear results were obtained in the second month of anti-tuberculosis treatment.

STATISTICAL ANALYSIS

The analyses of the data were performed using the SPSS version 11.0 (Statistical Package for the Social Scienses, SPSS Inc., Chicago, IL, USA). The descriptive statistical data of the demographic and clinical variables were expressed as frequency, percentage, mean value and standart deviation (SD). The Pearson Chi-Square test was used for the cathegorical variables and the frequency analyses. The Mann Whitney-U Test was used for variables without normal distribution. For the statistical analyses, a p value of <0.05 was considered significant.

ETHICAL ASPECT

Due to the fact that all data analyses were retrospective and there was no possibility that any individual could be identified, the paper did not include a consent form nor an approval from the ethical committee.

RESULTS

The ages of patients were between 16 and 70 years (mean age: 33.6±13.3 years); 124 (76.1%) were male and 39 (23.9%) were female. One hundred and sixteen (71.2%) patients were smokers. The number of patients with comorbidity was 29 (17.8%), 12 (7.4%) of whom had diabetes mellitus. The other comorbidities were convulsion (n=1), rheumatoid diseases (n=2), leukemia (n=1), hepatitis (n=1), chronic renal failure (n=5), cardiac failure (n=6) and Crohn's disease (n=1). None of the patients were immunosuppressed, nor infected by human immunodeficiency virus (HIV).

The number of new patients was 144 (88.3%), 14 (8.6%) patients had relapsing disease and 5 (3.1%) patients had received previous treatment (Figure 1). The number of cases for whom therapy had begun at the hospital was 95 (58.3%), the mean time of hospital care was determined as 36.7±16.9 days. The radiological findings on chest X-ray were unilateral in 92 (56.4%) patients, bilateral in 71 (43.6%) patients and cavitary in 88 (54.0%) cases. DOT had been applied in 120 (73.6%) patients. While 10 (6.1%) patients were culture-negative, in 28 patients (17.2%) sputum culture had not been performed or sputum culture results were not available. Drug resistance was determined in 19 (15.2%) of 125 culture positive cases. Among all the patients, only H resistance (9 patients, 7.2%) was the most frequent drug resistance. Four patients (3.2%) displayed only S resistance, 2 (1.6%) patients displayed H and S resistance, 1 (0.8%) patient

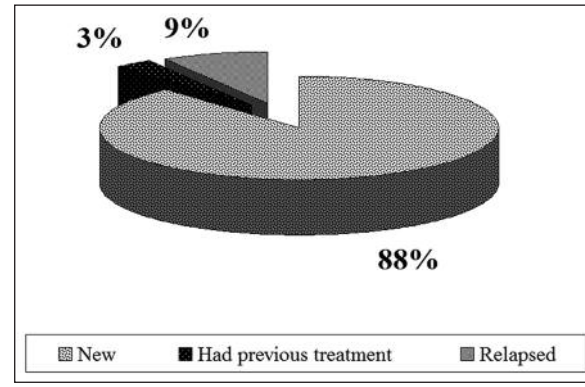

FIGURE 1: Distribution of patients according to the type of cases.

displayed H and R, 1 (0.8%) patient displayed R and S, 1 (0.8%) patient displayed H+R+S and 1 (0.8%) patient displayed H+R+E+S resistance (the type and frequencies of drug resistance have been presented in Table 1). The conversion time was 2 months or shorter in 127 (77.9%) patients and it was 3 months or longer in 36 (22.1%) patients (mean conversion time: 1.96±1.04 months) (Table 2). The type of the drug resistances and the conversion time in the initial culture-positive cases have been presented in the table (Table 3). In the statistical analyses (Pearson Chi-square test), we found no relationship between the conversion time and sex, smoking status, hospitalization, having comorbid diseases, extent of radiological findings, having previous TB, applying DOT and having drug resistance.

The conversion time was 3 months or longer in 28 (31.8%) of 88 patients who had a cavity on chest X-ray and in 8 (10.8%) of the 74 patients who had no cavity. This was statistically significant (p=0.001). The median value of BMI was determined as 21.4 kg/m^2 in an interquartile range (IQR) of 19.2-22.9 in patients who displayed a conversion time of 2 months or shorter, and the BMI was determined as 19.6 kg/m^2 in an IQR of 18.1-20.9 in patients who displayed a conversion time of 3 months or longer. This was found to be statistically significant (p=0.015).

TABLE 1: Type and frequencies of the drug resistance in culture positive cases.

Drug resistance	n	%
H	9	7.2
S	4	3.2
H+S	2	1.6
H+R	1	0.8
R+S	1	0.8
H+R+S	1	0.8
H+R+E+S	1	0.8
Total	19	15.2

TABLE 2: Distrubition of cases according to the conversion time.

Conversion time	n	%
≤ 2 months	127	77.9
≥ 3 months	36	22.1
Total	163	100.0

TABLE 3: Types of the drug resistances and conversion time in initial culture-positive patients.

Patient no	Type of the drug resistance	Conversion time (months)
1	H+R	2
2	S	1
3	S	2
4	H+R+E+S	1
5	S	2
6	H	2
7	H	4
8	H	3
9	S	2
10	H	1
11	H+R+S	1
12	H	1
13	H+S	3
14	H	2
15	H	2
16	H+S	2
17	H	2
18	H	2
19	R+S	2

DISCUSSION

In patients receiving anti-TB therapy, the smear conversion at the end of the initial phase of treatment is emphasized as an important early predictor of the treatment success.[4,6,8,14] Lienhardt et al. demonstrated that absence of sputum smear conversion after 2 months of chemotherapy was associated with default later during treatment.[15] There are different results regarding the relationship between sputum conversion and age, gender, smoking status and presence of DM. In a study, comprising 220 PTB patients in a South African population, while neither age and gender were associated with conversion, non-smoking was a predictor of a faster conversion time in smear and/or

culture.[14] Salihu et al. reported that age, sex, use of injectable drugs and alcohol abuse did not influence the sputum conversion rate.[13] In Spain, researchers determined that smoking habits were associated with delayed sputum conversion in patients with PTB.[16] Interestingly, Gullón et al. reported that in current smokers with PTB, the time to culture conversion was related only to the female gender.[17] Guler et al. found that old age, male sex, smoking and the presence of DM were associated with persistent sputum smear and culture positivity in 306 HIV-negative cases with PTB.[9] We found no relationship between the conversion time and gender, smoking status, comorbidity and DM. It has been shown that the severity of DM effects the risk of developing active TB. Similarly, the incidence of active TB is higher in insulin-dependent DM than non-insulin dependent DM.[18] In our retrospective study the type and the severity of DM could not be evaluated. Our study group consisted of 144 new patients and 19 patients who had previous TB. This is consistent with some prior studies in which no statistical difference was determined in the sputum smear conversion rate between patients with new PTB and cases that had previous TB.[1,13] It was shown that the hospitalization period should be cautiously determined, based on the disappearance of bacilli in the sputum.[19] In our cohort study, hospitalization rate was 58.3% and the mean time of hospital care was calculated to be 36.7±16.9 days. We established that the conversion time was not affected by hospitalization. Salihu et al. reported that DOT significantly enhanced the documented sputum conversion rates in 1735 cases.[13] Furthermore, Ciftci et al. found that DOT was more effective than self-administered therapy in patients with smear positivity, especially for shortening the bacteriological conversion time.[20] We determined in 120 (73.6%) of 163 patients in whom DOT was applied and there was no association between the conversion time and DOT. We think that the reason for this difference may have resulted from the limited number of cases in our study group.

Bilateral abnormal radiological findings on chest X-ray were seen in 71 (43.6%) patients and cavitary lesions were occured in 88 (54.0%) cases. Despite the determination of no relationship between the conversion time and lung cavitation in some previous studies, it has been determined in most studies that cavitary disease is the risk factor that most prolongs the period for the sputum to become negative.[1,5,8,12,13,16,19,21] In the multivariate analysis, Dominquez Castellano et al. showed that the radiographic pattern (cavitation) was one of the independent factor associated with time to conversion.[1] In Spain, cavitary lung lesions were found to be associated with slower sputum culture conversion rates in the early treatment period.[5] Accordingly, we found that having cavitary disease is associated with prolonged smear conversion time.

In total of 125 culture positive cases, drug resistance was determined in 19 (15.2%) patients. While only H resistance (5.5%) was the most frequent resistance, the rate of H and R resistance rate was 2.4%. Pulmonary multidrug-resistant TB is defined as having a positive sputum culture for *M. tuberculosis* with in vitro resistance to at least H and R.[11] Several published studies reported that drug susceptibility was a factor that was correlated with a longer conversion time in patients with PTB.[5,19] Conversely, Rekha et al. reported in their series that the presence of pre-treatment H or R resistance did not affect the smear conversion.[8] In our study, we determined no relationship between the drug resistance and the conversion time, either. The most likely explanation for this is that we had 19 patients with any drug resistance and had only 3 patients with both H and R resistances in culture positive cases.

The association between TB and nutritional status has been studied for decades. A bidirectional relationship between the two conditions has been reported: on one hand, it has been proposed that TB leads to malnutrition, while on the other, a poor nutritional status has been postulated to be a risk factor for acquiring TB.[12,22] For this reason we decided to investigate the relationship between BMI and the sputum smear conversion time. In patients in whom the conversion time was 2 months or

shorter, the median value of BMI was calculated as 21.4 kg/m^2 (IQR: 19.2-22.9). The rate of prolonged conversion time was 22.1% among 163 patients with PTB; in this group the BMI of the patients was determined 19.6 kg/m^2 (IQR:18.1-20.9). This was statistically significant.

Our study has several limitations. First, because this was a retrospective cohort study, some data of the patient files could not be accessed, such as the degree of sputum smear positivity, initial sputum culture results and the culture follow-ups. Therefore, the factors that could have affected the sputum culture conversion time could not be evaluated. Second, without a doubt we need a larger cohort to analyze the association between the conversion time and comorbid factors such as DM, DOT effect, having previous TB and multi-drug resistance. In spite of these limitations, we could not find a published similar study in the literature disclosing the relationship between BMI and sputum smear conversion time.

In conclusion, the presence of cavity on chest X-ray and low BMI are factors that affect the sputum smear conversion time in patients with PTB. Due to the fact that sputum smear and culture conversion are indicators for the patient's infectivity, close monitoring of these patients is important to decrease the transmission of disease in the community.

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REFERENCES

1. Domínguez-Castellano A, Muniain MA, Rodriguez-Baño J, Garcia M, Rios MJ, Galvez J, et al. Factors associated with time to sputum smear conversion in active pulmonary tuberculosis. Int J Tuberc Lung Dis 2003;7(5):432-8.
2. Gümüş S. [Epidemiology of tuberculosis in the world and in Turkey]. Turkiye Klinikleri J Pulm Med-Special Topics 2011;4(2):1-6.
3. Summary. Global Tuberculosis Control: Surveillance, Planning, Financing: WHO Report 2008. Geneva: WHO Press; 2008. p.1-3.
4. Özsöz A. [Management of smear positive patient]. Turkiye Klinikleri J Thorax Dis 2003; 1(2):50-4.
5. Fortún J, Martín-Dávila P, Molina A, Navas E, Hermida JM, Cobo J, et al. Sputum conversion among patients with pulmonary tuberculosis: are there implications for removal of respiratory isolation? J Antimicrob Chemother 2007;59(4):794-8.
6. Sevim T, Ataç G, Güngör G, Törün I, Aksoy E, Gemci, et al. Treatment outcome of relapse and defaulter pulmonary tuberculosis patients. Int J Tuberc Lung Dis 2002;6(4):320-5.
7. Harries AD, Gausi F, Salaniponi FM. When are follow-up sputum smears actually examined in patients treated for new smear-positive pulmonary tuberculosis? Int J Tuberc Lung Dis 2004;8(4): 440-4.
8. Banu Rekha VV, Balasubramanian R, Swaminathan S, Ramachandran R, Rahman F, Sundaram V, et al. Sputum conversion at the end of intensive phase of Category-1 regimen in the treatment of pulmonary tuberculosis patients with diabetes mellitus or HIV infection: An analysis of risk factors. Indian J Med Res 2007;126(5):452-8.
9. Güler M, Unsal E, Dursun B, Aydin O, Capan N. Factors influencing sputum smear and culture conversion time among patients with new case pulmonary tuberculosis. Int J Clin Pract 2007; 61(2):231-5.
10. Patel N, Deshpande MM, Shah M. Effect of an immunomodulator containing Mycobacterium w on sputum conversion in pulmonary tuberculosis. J Indian Med Assoc 2002;100(3):191-3.
11. Holtz TH, Sternberg M, Kammerer S, Laserson KF, Riekstina V, Zarovska E, et al. Time to sputum culture conversion in multidrug-resistant tuberculosis: predictors and relationship to treatment outcome. Ann Intern Med 2006;144(9):650-9.
12. Krapp F, Véliz JC, Cornejo E, Gotuzzo E, Seas C. Bodyweight gain to predict treatment outcome in patients with pulmonary tuberculosis in Peru. Int J Tuberc Lung Dis 2008; 12(10):1153-9.
13. Salihu HM, Aliyu MH, Ratard R, Pierre-Louis BJ. Characteristics associated with reported sputum culture conversion in the era of re-emergent Mycobacterium tuberculosis in the State of North Carolina, 1993-1998. Int J Tuberc Lung Dis 2003;7(11):1070-6.
14. Babb C, van der Merwe L, Beyers N, Pheiffer C, Walzl G, Duncan K, et al. Vitamin D receptor gene polymorphisms and sputum conversion time in pulmonary tuberculosis patients. Tuberculosis (Edinb) 2007;87(4):295-302.
15. Lienhardt C, Manneh K, Bouchier V, Lahai G, Milligan PJ, McAdam KP. Factors determining the outcome of treatment of adult smear-positive tuberculosis cases in The Gambia. Int J Tuberc Lung Dis 1998;2(9):712-8.
16. Gullón Blanco JA, Suárez Toste I, Lecuona Fernández M, Galindo Morales R, Fernández Alvarez R, Rubinos Cuadrado G, et al. [Tobacco smoking and sputum smear conversion in pulmonary tuberculosis]. Med Clin (Barc) 2007;128(15):565-8.

17. Gullón JA, Suárez I, Lecuona M, Fernández R, Rubinos G, Medina A, et al. Time to culture conversion in smokers with pulmonary tuberculosis. Monaldi Arch Chest Dis 2009;71(3): 127-31.

18. Dooley KE, Tang T, Golub JE, Dorman SE, Cronin W. Impact of diabetes mellitus on treatment outcomes of patients with active tuberculosis. Am J Trop Med Hyg 2009;80(4): 634-9.

19. Fujino T, Fusegawa H, Nishiumi M, Okubo Y, Kakizaki T, Maejima K, et al. [Epidemiological study on factors affecting the hospitalization period of patients with active tuberculosis]. Kekkaku 2008;83(8):567-72.

20. Çiftci F, Bozkanat E, Deniz Ö, Tozkoporan E, Okutan O, Ilvan A, et al. [Directly observed therapy versus self administered therapy for patients of new smear positive pulmonary tuberculosis during hospitalisation period]. Turkiye Klinikleri Arch Lung 2005;6(4):156-9.

21. Wang JY, Lee LN, Yu CJ, Chien YJ, Yang PC; Tami Group. Factors influencing time to smear conversion in patients with smear-positive pulmonary tuberculosis. Respirology 2009;14(7): 1012-9.

22. Kırkıl G, Özel E, Turgut T, Deveci F, Muz MH. [Evaluation of present risk factors of cases with pulmonary tuberculosis]. Turkiye Klinikleri Arch Lung 2006;7(1):30-3.