DOI: 10.4274/forbes.galenos.2022.58672
Forbes J Med 2023;4(2):148-54

Original Article / Orijinal Araştırma

Using Sociodemographic and Clinical Characteristics to Distinguish Between Drug-sensitive and Drug-resistant Tuberculosis

İlaca Duyarlı ve İlaç Dirençli Tüberkülozun Ayrımında Sosyodemografik ve Klinik Özelliklerin Önemi

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Cite as: Varol Y, Karaman O, Biçmen C. Using Sociodemographic and Clinical Characteristics to Distinguish Between Drug-sensitive and Drug-resistant Tuberculosis. Forbes J Med 2023;4(2):148-54

ABSTRACT

Objective: The purpose of this study was to investigate the significance of sociodemographic and clinical characteristics in multidrug-resistant tuberculosis (MDR-TB) and drug-sensitive tuberculosis (DS-TB) patients treated in an inpatient tuberculosis clinic.

Methods: Retrospective analyzes of demographic, clinical, side effect, treatment effectiveness and mortality data were performed on MDR-TB and DS-TB patients diagnosed and treated in the chest disease and tuberculosis inpatient clinics hospitalized between 2010 and 2018.

Results: There were a total of 218 tuberculosis patients, of whom 75.2% were males. When we compared the MDR-TB versus DS-TB patients, we found no statistically significant difference in terms of age, gender, marital status, and nationality ($p<0.05$ for all). There was a statistically significant difference in educational status between two groups ($p=0.007$). Also, occupational history was statistically significantly different between the MDR-TB and DS-TB population ($p<0.001$). MDR-TB patients had more recurrence rates than DS-TB patients (42.2-11%, respectively) and new cases were statistically significantly more in DS-TB patients (57.8-89%). The number of defeated patients was statistically higher in MDR-TB patients ($p=0.045$).

Conclusion: In this study, we showed that patient type combined with clinical and demographic features may help to distinguish MDR-TB patients, which is a public health problem in our country.

Keywords: Tuberculosis, treatment, drug-sensitive, multidrug-resistant tuberculosis

ÖZ

Amaç: Bu çalışmanın amacı, yatarak tedavi edilen çok ilaca dirençli tüberküloz (MDR-TB) ve ilaca duyarlı TB (DS-TB) hastalarında sosyodemografik ve klinik özelliklerin önemini araştırmaktır.

Yöntem: 2010-2018 yılları arasında göğüs hastalıkları ve TB kliniğinde yatarak tedavi gören MDR-TB ve DS-TB hastalarının demografik, klinik, ilaç yan etki, tedavi etkinliği ve mortalite verilerinin retrospektif analizleri yapıldı.

Bulgular: %75,2'si erkek olan toplam 218 TB hastası çalışmaya alındı. MDR-TB ile DS-TB hastalarını karşılaştırdığımızda yaş, cinsiyet, medeni durum ve uyruk açısından istatistiksel olarak anlamlı bir fark olmadığı görüldü (hepsi için $p<0,05$). İki grup arasında eğitim durumu açısından istatistiksel olarak anlamlı fark vardı ($p=0,007$). Ayrıca meslek öyküsü açısından MDR-TB ve DS-TB grupları arasında istatistiksel olarak anlamlı derecede fark saptandı ($p<0,001$). MDR-TB hastaları, DS-TB hastalarına göre

Received/Geliş: 18.08.2022
Accepted/Kabul: 03.10.2022

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daha fazla nüks oranlarına sahipti (sırasıyla %42,2-11) ve yeni olgu sayısı DS-TB hastalarında istatistiksel olarak anlamlı derecede daha fazlaydı (%57,8-89). Ölen hasta sayısı MDR-TB hastalarında istatistiksel olarak daha yüksekti (p=0,045).

Sonuç: Bu çalışmada, ülkemizde önemli bir halk sağlığı sorunu olan MDR-TB hastalarının ayırt edilmesinde klinik ve demografik özelliklerle birleştirilmiş hasta tipinin yardımcı olabileceğini gösterdik.

Anahtar Kelimeler: Tüberküloz, tedavi, ilaç duyarlı, çok ilaca dirençli tüberküloz

INTRODUCTION

Drug resistance in tuberculosis (TB) poses a threat to advancements in TB treatment and control, which is a concern for global public health.[1] In 2019, there are expected to be 10 million new cases of TB; of these, about 500,000 cases are rifampicin-resistant, with 78% being multidrug-resistant TB (MDR-TB).[2] Drug-resistant TB is a growing public health issue which is defined as a form of TB that has become resistant to at least isoniazid (INH) and rifampicin (R), the two first-line anti-TB medications, because it requires more expensive and complex treatment than drug-sensitive TB (DS-TB). According to projections, 3.3% of new (no prior treatment) TB infections and 17.7% of TB patients who have already received treatment will be due to MDR-TB in 2019.[2]

Drug resistance in TB is a very important health issue that jeopardizes progress in TB care and control programs. Early drug resistance detection is essential for the control of illness. It is still difficult to identify between patients with DS-TB and those with MDR-TB using readily available clinical information, particularly during the initial visit. Molecular testing and traditional culture-based phenotypic testing are the two forms of TB medication susceptibility tests now available. The former includes observing the behavior of the bacteria, which necessitates a laboratory facility with the necessary equipment and may take several weeks to obtain data.[3] The latter entails examining genetic alterations, which is quick but costly and can yield conflicting results.[4] Therefore, it would be ideal if clinical data from patient medical records could automatically predict the suspicion of MDR-TB.

Therefore, the aim of this study was to investigate the significance of sociodemographic characteristics in MDR-TB and DS-TB patients treated in an inpatient TB clinic.

METHODS

Patient Data

Retrospective analyzes of demographic, clinical, side effect, treatment effectiveness and mortality data were performed on MDR-TB and DS-TB patients diagnosed and treated in the chest disease and TB inpatient clinics hospitalized between 2010 and 2018. During this period, there were 109 inpatient MDR-TB patients, which were fully included in the analysis. For the comparison group, inpatient DS-TB patients (n=109) were included. The Ethical Committee of the University of Health Sciences Turkey, Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital with number 16 granted clearance for this study on July 22, 2020. The analysis of patient data was done using hospital archives. Chest X-rays and, if available, thorax computed tomography were evaluated for cases registered in the hospital imaging system. One- and two-lungs involvement were the two categories used to evaluate the radiological extent. Socioeconomic status is calculated over household disposable monthly net income.

Microbiological Data

Acid resistance staining with standard fluorochrome and/or Kinyoun technique was done on each sample as well as culture on BACTEC 960 (MGIT) (Becton Dickinson, Sparks, MD, USA) system and Löwenstein-Jensen medium. The BACTEC 960 (MGIT) equipment was used to evaluate the susceptibility of patient samples in line with the manufacturer's recommendations. Drug resistance in new samples was defined as resistance detected in patients who had not previously used TB medicines or had used them for less than a month. Drug resistance in cases that were successfully treated was described as resistance to a medication that the patient had previously used for more than a month.[5,6]

Treatment and Follow-up Data

The medications were classified in accordance with the World Health Organization (WHO) and the National Tuberculosis Guidelines, which were current throughout the period of the patients we included in the study (between 2010 and 2018).[1] DS-TB patients received the standard 4 drug regimen recommended by our National Tuberculosis Guidelines [isoniazid (H); rifampicin (R); ethambutol (E); pyrazinamide (Z)]. The MDR-TB patient's treatment plan had at least five active drugs, one of which was administered parenterally along with one quinolone. Drugs that were sensitive in the drug sensitivity test but had never been used before were classified as *active*, whereas drugs that had previously been used but were sensitive in the test were classified as *suspect*. Drugs that were both resistant and previously used were both regarded as *inactive*. The medications were introduced to the MDR-TB patient's treatment regimen one at a time, from the first to the fifth group.

According to the guidelines, a regimen of at least 5 active medicines from 5 medication classes was used to treat MDR-TB. The drugs were administered regularly as part of the directly observed treatment protocol. The treatment period was applied for 6-9 months for DS-TB. The treatment period was applied for 24 months for MDR-TB after the culture became negative.

When two groups of sputum obtained at least 30 days apart from one another's cultures and smear results were negative, the date of the first negativity was considered for the sputum conversion period. Three or more consecutive negative cultures that were obtained at least 30 days after the baseline period were considered proof of cure in patients who finished therapy without meeting the criteria for treatment failure. Therapy completion was defined as the absence of three or more consecutive, culture-negative results that were collected at least 30 days apart after the first period in patients who finished the treatment without exhibiting any symptoms of failure. The total number of patients with cure and completion of therapy was considered treatment success.

Statistical Analysis

Statistical Package for Social Sciences 25.5 was used to perform statistically descriptive analyzes (IBM, NY, USA). The results are shown as the median (minimum-maximum), number, and percentage (%). The normality tests Shapiro-Wilk and Kolmogorov-Smirnov were performed to assess if the parameters used in the group comparison were normally distributed. To compare continuous variables, the Mann-Whitney U test and Student's t-test were employed, and to compare categorical data, the chi-square and Fisher's exact tests were used. The results are shown as the median (minimum-maximum), mean standard deviation, number, and percentage (%). Statistical significance was defined as a p value <0.05.

RESULTS

There were a total of 218 TB patients, of whom 75.2% were males. Demographic characteristics are shown in Table 1. The monthly income of the population was medium and low, and more than half of the population was an active smoker. Cough was the predominant symptom in our cohort with 70.6% (n=154), sputum production was 35.3% (n=77), and fever was 13.3% (n=29). One hundred-sixty (73.4%) patients were new TB cases, while 58 (26.6%) patients were recurrent TB. Clinical characteristics of the population are summarized in Table 2.

When we compared MDR-TB versus DS-TB patients, we found no statistically significant difference in terms of age, gender, marital status, and nationality. There was a statistically significant difference in educational status between two groups (p=0.007). Nearly 72% of the DS-TB patients graduated from middle or high school; however, this ratio is only 54% for MDR-TB. Also, occupational history was statistically significantly different between the MDR-TB and DS-TB population (p<0.001). In the DS-TB population, more than half of the patients were unemployed; however, this rate was only 33% in MDR-TB patients. There was no statistically significant difference between two groups regarding smoking history and comorbidity (Table 3). Besides, symptoms were similar between DS-TB and MDR-TB patients (p>0.05). There was a statistically significant difference in terms of TB history between two groups (p>0.001). MDR-TB patients had more recurrence rates than DS-TB patients (42.2-11%, respectively) and new cases were statistically significantly more in DS-TB patients (89%) (Table 3).

The duration of days between admission and treatment initiation was statistically significantly lower in the DS-TB

Table 1. Demographic characteristics of tuberculosis patients

Demographic characteristics	n (%)
Age at diagnosis (years) Mean±SD	46.7±16.2
Gender Female Male	 54 (24.8%) 164 (75.2%)
Natinality Turkish Republic Other	 208 (95.4%) 10 (4.6%)
Marital status Married Single	 158 (72.5%) 60 (27.5%)
Educational status Illiterate Primary school Middle-high school University	 4 (1.8%) 75 (34.4%) 137 (62.8%) 2 (0.9%)
Occupation Unemployed Employed Retired	 94 (43.1%) 77 (35.3%) 47 (21.6%)
Income (n=132) Low Medium High	 129 (59.2%) 3 (1.4%) -
Weight (kg) Mean±SD	59.6±10.4
Smoking status (n=213) Never smoker Active smoker Ex-smoker	 53 (24.3%) 139 (63.8%) 21 (9.6%)
Comorbidity	69 (31.7%)

SD: Standard deviation

group (p<0.001). The number of treatment interruptions was similar between DS-TT and MDR-TB patients; however, the amount of treatment interruption (calculated as days) was significantly higher in MDR-TB patients (p=0.003). As expected, drug groups, initial treatment period, and total treatment period were significantly different between two groups (Table 4). The culture conversion period was not statistically significantly different between two groups (p=0.6). The duration of hospitalization was significantly higher in the MDR-TB patients group (p<0.001). The number of defeated patients was statistically higher in MDR-TB patients (p=0.045). The cure rates were not statistically significantly different between the DS-TB and MDR-TB groups; however, it favors DS-TB (p=0.051) (Table 4).

DISCUSSION

Patients with MDR-TB had longer hospital stays and died more frequently than patients with DS-TB, but no demographic, clinical, laboratory, or radiological criterion was able to differentiate the scenario alone. Consistent with the literature, prior treatment history was the best predictor of DR-TB in our study (New or Relapse).[7-9]

Table 2. Clinical and microbiological characteristics of tuberculosis patients

Clinical properties	**n (%)**
Dyspnea	40 (18.3%)
Cough	154 (70.6%)
Sputum	77 (35.3%)
Fever	32 (14.7%)
Hemopthysis	29 (13.3%)
Chest pain	15 (6.9%)
Fatigue	59 (27.1%)
HIV positivity	2 (0.9%)
Pulmonary tuberculosis	214 (98.2%)
Extrapulmonary tuberculosis	19 (8.7%)
Prior treatment history New case Relapse	 160 (73.4%) 58 (26.6%)
Radiologic involvement Unilateral Bilateral	 43 (19.7%) 175 (80.3%)
Laboratory findings	**n (%)**
Sample kind Fasting gastric fluid Bronchoalveolar lavage Sputum Bronchial aspiration Byopsi Lenyh node Pleural biopsy Transthoracic fine needle aspiration biopsy	 1 (0.5%) 2 (0.9%) 183 (83.9%) 27 (12.4%) 1 (0.5%) 1 (0.5%) 2 (0.9%) 1 (0.5%)

Additionally, TB patients with lower levels of education, poorer incomes, and more consistent laboratory results may be an early sign of MDR-TB.

The link between MDR-TB and age has not been fully established in previous findings because different studies use different cut-off criteria for age groups. According to a Chinese study on MDR-TB, the 30-to 59-year-old age bracket is associated with MDR-TB. However, according to European MDR-TB research, MDR-TB patients are more likely to be under 65 years old.[7-11] In our study, there was no difference in age groups between MDR-TB and DS-TB patients and represent an average adult population.

In males, TB is more prevalent.[12-14] Men are more likely to get resistant TB in Western Europe than in the Eastern part, according to research.[7] Contradicting that finding, it was shown in another study that being a woman had a significant relationship with MDR-TB.[10] The authors of the article made the assumption that this link was due to the local preponderance of female health care personnel. Our data revealed that there was male dominance in both groups, not significantly different from each other. Gender might be considered a major geographical risk factor for MDR-TB.

The history of treatment is a well-known potential risk factor for the occurrence of drug resistance in TB. According to the WHO Global Report on MDR-TB and extensively drug-resistant TB, instances of TB with a prior history of TB treatment are substantially more likely to develop DR-TB.[15] Such a predictor can be used to screen DR-TB patients early on, especially in clinical settings with limited resources. For instance, a patient who relapsed would suggest that medication susceptibility testing should be performed at the beginning of treatment.

Radiological examinations are used to distinguish between resistant and sensitive patients with TB. Yang et al.[16] demonstrated that clinical features may identify DR-TB patients with an accuracy of approximately 61% and relatively low sensitivity. Also, radiological characteristics based on the number of affected measured areas can do so with an accuracy of about 67% and a poor specificity. Additionally, combining radiological and clinical characteristics may enhance the outcomes. Regarding the combined characteristics, the automated classifier has a 72.34% average accuracy rate and an average area under the curve value of 78.42%. According to another research, people with drug resistance TB used to have big lesions, whereas lesions that are tiny or medium in size are more prevalent in persons with DS-TB.[17] Nearly 80% of the patients in the current research had bilateral lesions, and there was no difference in the groups. We believe that because our DS-TB patients were hospitalized due to their

Table 3. Comparison of the MDR-TB versus DS-TB patients in terms of demographic and clinical characteristics			
	MDR-TB n (%)	**DS-TB n (%)**	**p value**
Demographic data			
Age at diagnosis (year) Mean±SD	46.3±16.3	47.2±16.3	0.678
Gender Female Male	 26 (23.9%) 83 (76.1%)	 28 (25.7%) 81 (74.3%)	0.754
Nationality Turkish Republic Other	 101 (92.7%) 8 (7.3%)	 107 (98.2%) 2 (1.8%)	0.052
Marital status Married Single	 79 (72.5%) 30 (27.5%)	 79 (72.5%) 30 (27.5%)	1.000
Educational status Illiterate Primary school Middle-high school University	 1 (0.9%) 47 (43.1%) 59 (54.1%) 2 (1.8%)	 3 (2.8%) 28 (25.7%) 78 (71.6%) 0 (0.0%)	**0.007**
Occupation Unemployed Employed Retired	 36 (33.0%) 53 (48.6%) 20 (18.3%)	 58 (53.2%) 24 (22.0%) 27 (24.8%)	**<0.001**
Weight (kg) median (min-max)	60 (35-80)	60 (35-92)	0.321
Smoking status (n=213) Never smoker Active smoker Ex-smoker	 26 (24.3%) 67 (62.6%) 14 (13.1%)	 27 (25.5%) 72 (67.9%) 7 (6.6%)	0.283
Comorbidity	33 (30.3%)	36 (33.0%)	0.662
Clinical features			
Dyspnea	20 (18.5%)	20 (18.5%)	1.000
Cough	80 (74.1%)	74 (69.2%)	0.424
Sputum	36 (33.3%)	41 (38.3%)	0.472
Fever	16 (15.0%)	16 (15.0%)	1.000
Hemopthysis	11 (10.4%)	18 (16.8%)	0.170
Chest pain	10 (9.3%)	5 (4.7%)	0.187
Loss of weight	25 (23.4%)	34 (31.8%)	0.169
Pulmonary tuberculosis	105 (96.3%)	109 (100.0%)	**0.044**
Extrapulmonary tuberculosis	8 (7.3%)	11 (10.1%)	0.471
Prior treatment history New case Relapse	 63 (57.8%) 46 (42.2%)	 97 (89.0%) 12 (11.0%)	**<0.001**
Radiologic involvement Unilateral Bilateral	 26 (23.9%) 83 (76.1%)	 17 (15.6%) 92 (84.4%)	0.126
MDR-TB: Multidrug-resistant tuberculosis, DS-TB: Drug-sensitive tuberculosis, SD: Standard deviation, min-max: Minimum-maximum			

Table 4. Comparison of the MDR-TB versus DS-TB patients in terms of laboratory, treatment and outcome characteristics

	MDR-TB	DS-TB	p value
Laboratory data	**Median (min-max)**	**Median (min-max)**	
Glucose	93.5 (40.0-490.0)	104.0 (57.0-474.0)	0.089
Urea	27.0 (10.0-91.0)	26.0 (8.0-90.0)	0.384
Creatinin	0.8 (0.4-6.1)	0.7 (0.4-1.9)	**0.008**
AST	21.0 (7.0-90.0)	20.0 (3.0-71)	0.941
ALT	13.0 (2.0-86.0)	15.5 (3.0-173.0)	**0.009**
Total bilirubin	0.5 (0.1-28.0)	0.5 (0.1-15.0)	0.409
Direct bilirubin	0.1 (0.0-8.0)	0.1 (0.0-4.6)	0.817
Treatment properties	**Median (min-max)**	**Median (min-max)**	
Number of drugs	5.0 (4.0-7.0)	4.0 (4.0-5.0)	**<0.001**
Duration (days) between admission and treatment initiation	12.0 (1.0-120)	1 (0.0-90.0)	**<0.001**
Amount of treatment interruption (days)	30.0 (0.0-195.0)	11.0 (2.0-90.0)	**0.003**
Initial treatment period (months)	6.0 (1.0-14.0)	2.0 (1.0-4.0)	**<0.001**
Culture conversion (months)	2.0 (1.0-12.0)	2.0 (1.0-3.5)	0.600
Total treatment duration (months)	24.0 (5.0-30.0)	6.0 (5.0-12.0)	**<0.001**
Duration of hospitalization (months)	5.0 (0.0-36.0)	1.5 (2.0-5.5)	**<0.001**
Drug information	**n (%)**	**n (%)**	
Drug groups ≤5 drugs ≥6 drugs	 76 (69.7%) 33 (30.3%)	 109 (100.0%) 0 (0.0%)	**<0.001**
Drug side effect	65 (59.6%)	36 (33.0%)	**<0.001**
Treatment interruption	22 (20.2%)	28 (5.7%)	0.334
Exitus	10 (9.2%)	3 (2.8%)	**0.045**
Cure	81 (77.9%)	95 (87.2%)	**0.051**

MDR-TB: Multidrug-resistant tuberculosis, DS-TB: Drug-sensitive tuberculosis, min-max: Minimum-maximum, AST: Aspartate transaminase, ALT: Alanine transaminase

severity, they may have higher radiological involvement than DS-TB patients who were treated as outpatients.

Study Limitations

The current study has some limitations. First, the study is retrospectiv ; nonetheless, due to the low number of MDR-TB patients, it is very difficult to make a prospective design. Since our clinic only treats MDR-TB patients who are hospitalized, we gathered DS-TB patients from inpatient settings to compare MDR-TB to DS-TB. However, this selection could not represent all DS-TB patients.

CONCLUSION

Compared to patients with DS-TB, patients with MDR-TB had more sophisticated treatment than DS-TB and incur higher expenses with higher mortality rates, but no single demographic, clinical, laboratory, or radiological factor could distinguish between the two situations. In this study, we showed that prior treatment history combined with clinical and demographic features may help distinguish MDR-TB patients.

Ethics

Ethics Committee Approval: The ethical committee of the University of Health Sciences Turkey, Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital with number 16 granted clearance for this study on July 22, 2020.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Y.V., O.K., C.B., Concept: Y.V., Design: Y.V., Data Collection or Processing: O.K., Analysis or Interpretation: O.K., C.B., Literature Search: O.K., C.B., Writing: Y.V.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare that this study received no financial support.

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