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Evaluation of tuberculosis clinical characteristics by gender

Tüberküloz klinik özelliklerinin cinsiyet farlılıkları açısından değerlendirilmesi

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SUMMARY

Objective: The aim of this study was to evaluate the clinical features of tuberculosis (TB) in terms of gender differences over a ten-year period.
Method: This retrospective cohort study was performed using Sivas Tuberculosis Dispensary 2010- 2019 TB patient records. TB incidence, mortality, drug sensitivity percentages and some clinical characteristics of patients were determined.
Results: The rate of female new patients was 51.4 % and the female to male ratio was 1.05. The gender difference in rates was highest in the 0-19 age group. Most of the cases (49.9 %) were extra-pulmonary tuberculosis (EPTB) and this rate in female (66.6 %) was significantly higher than in male (33.4 %). The most common extra-pulmonary involvement was the lymphatic system (39.7 %). Complete the disease as a cure (65.7 %), treatment failure (100.0 %) and deaths (66.7 %) due to TB were significantly higher in male. We recorded the drug resistance 9 % for ethambutol, 8.6 % for isoniazid, 4.5 % for streptomycin and 2.8 % for rifampicin and there was no significant difference by gender. The incidences of all TB forms, pulmonary tuberculosis (PTB) and EPTB showed a decreasing trend in both genders and age groups except for those aged 60 and over in male. TB mortality rate and drug sensitivity percentages were in an increasing trend in both genders.
Conclusions: Significant changes were found in some clinical features of TB according to gender. It is thought that situations arising from gender changes in TB control programs should be considered.
Keywords: Tuberculosis, gender identity, epidemiology

ÖZET

Amaç: Bu çalışmanın amacı, on yıllık bir dönemde tüberkülozun klinik özelliklerini cinsiyet farklılıkları açısından değerlendirmekti.
Yöntem: Bu retrospektif kohort tipteki çalışma Sivas Verem Savaş Dispanseri 2010-2019 tüberküloz hasta kayıtları kullanılarak gerçekleştirildi. Hastaların tüberküloz insidansı, mortalitesi, ilaç duyarlılık yüzdeleri ve bazı klinik özellikleri belirlendi.
Bulgular: Kadın yeni hasta oranı %51.4, kadın/erkek oranı 1.05'ti. Oranlardaki cinsiyet farkı en yüksek 0-19 yaş grubunda görüldü. Vakaların çoğu (%49.9) akciğer dışı tüberkülozdu ve bu oran kadınlarda (%66.6) erkeklerden (%33.4) anlamlı olarak yüksekti. En sık görülen akciğer dışı tutulum lenfatik sistemdi (%39.7). Hastalığı kür olarak tamamlama (%65.7), tedavi başarısızlığı (%100.0) ve tüberküloza bağlı ölümler (%66.7) erkeklerde anlamlı olarak daha yüksekti. İlaç direnci etambutol için %9, izoniazid için %8.6, streptomisin için %4.5 ve rifampisin için %2.8'di ve

cinsiyete göre anlamlı bir fark yoktu. Tüm tüberküloz formları, akciğer ve akciğer dışı tüberküloz insidansları her iki cinsiyette ve erkeklerde 60 yaş ve üzeri olanlar dışında tüm yaş gruplarında azalma eğilimi gösterdi. Tüberküloz mortalite oranı ve ilaç duyarlılık yüzdeleri her iki cinsiyette de artış eğilimindeydi.
Sonuç: Cinsiyete göre tüberkülozun bazı klinik özelliklerinde önemli farklılıklar bulundu. Tüberküloz kontrol programlarında cinsiyet farklılığından kaynaklanan durumların dikkate alınması gerektiği düşünülmektedir.
Anahtar sözcükler: Tüberküloz, cinsiyet kimliği, epidemiyoloji

INTRODUCTION

Tuberculosis (TB) is a global pandemic that poses a serious threat to public health around the world [1]. *Mycobacterium tuberculosis* bacillus is the cause of the disease and is spread by TB patients, for example, by coughing and throwing bacteria into the air and it typically affects the lungs (pulmonary TB- PTB), but can also affect other organs (extra-pulmonary TB- EPTB) [2]. Approximately a quarter of the world's population is at risk of developing TB disease as they are infected with *M. tuberculosis* [2]. According to the 2020 global tuberculosis report, an estimated 10 million people worldwide became ill with TB in 2019, and 1.2 million people died from TB [3]. TB affects people of both genders of all age groups, but is most common in male (≥15 years), who also accounted for 56 % of all TB cases in 2019 and this rate is 32 % for female and 12 % for children (<15 years) [3].

The total number of TB patients diagnosed in 2017 in Turkey was 12 046, of which were determined as 92.2 % new cases, 7.8 % patients previously treated with, 42.3 % female, 57.7 % male, 66.1 % those with PTB, 33.9 % those with EPTB [4]. TB incidence has dropped by an annual average of 5% for th last 10 years, and the incidence was found to be 14.6 per hundred thousand in 2017 [4].

TB epidemiology is significantly affected by age and gender throughout life [5]. Male and female have different combinations of risk factors for TB and different pathways are followed in their diagnosis and treatment [5]. Among the reasons for the more prevalence of TB in male are male's higher exposure to infectious tuberculosis cases outside the home, higher prevalence of disease risk factors in male (e.g. smoking, alcohol use), and more difficult diagnosis (low volume or quality expectorated sputum) or access to care in female [6–10]. TB mainly affects female when they are economically and reproductively active, and the impact of the disease is strongly felt by their children and families [11].

Controlling TB requires understanding which epidemiological and medical factors put individuals at a higher risk of TB and which are protective [12]. Although TB is reported to be seen twice as often in male as in female worldwide, gender differences may vary in different parts of the world and in different age groups. The aim of this study is to evaluate the clinical features of TB in terms of gender differences over a ten-year period (2010-2019).

MATERIAL AND METHODS

This retrospective cohort study was performed using Sivas Tuberculosis Dispensary 2010-2019 TB patient records. Sivas is located in the Turkey's Central Anatolia region. TB incidence, mortality, drug sensitivity percentages and clinical characteristics of patients (case definition, disease location, disease outcomes, therapy duration, extra-pulmonary involvement, drug resistance) were determined by years and evaluated in terms of gender differences. The study protocol was approved by the Institutional Review Board of Cumhuriyet University (IRB no. 2020-02/27). Informed consent was confirmed by the IRB.

The data obtained from our study were evaluated with SPSS 22.0 program and Joinpoint regression program 4.8.0.1. Descriptive statistics such as mean, standard deviation and percentage distribution were calculated. The normality of the data was measured with the Kolmogorov-Simirnov test. Since the data did not provide parametric conditions, Mann Whitney U test was used for two independent groups. Chi-square test and Joinpoint regression analysis were used. The level of error was taken as 0.05.

RESULTS

Distribution of some clinical characteristics and age groups of tuberculosis patients by gender is given in Table 1. The total number of cases included in the study was 918 and 819 (89.2%) of these were new TB cases. The total number of female new patients was 421 (51.4 %) and the female to male ratio was 1.05. Although not significant, female was in the majority in cases in the 0-19 and ≥60 age group, while male was in the 20-59 age group. The gender difference in rates was highest in the 0-19 age group. 49.9 % of the cases were EPTB and EPTB rate in female was significantly higher than in male ($p< 0.001$). The most common extra-pulmonary involvement was the lymphatic system with 182 cases (39.7 %).

Lymphatic system, genitourinary system (GUS), skin, gastrointestinal system (GIS), peritoneum, bone, joint, vertebra, central nervous system (CNS) and breast involvements were significantly higher in female than in male ($p< 0.001$) while pleura and cardiovascular system involvements were significantly higher in male than in female ($p< 0.001$). Complete the disease as a cure, treatment failure and deaths due to TB were significantly higher in male than in female ($p< 0.001$). Drug resistance test was applied to only 290 patients, and we recorded drug resistance 9 % for ethambutol (EMB), 8.6 % for isoniazid (INH), 4.5 % for streptomycin (SM) and 2.8 % for rifampicin (RIF) and there was no significant difference by gender (Table 1).

The annual incidence and the mortality rates of TB cases stratified by gender and age groups are given in Table 2. The annual TB incidence was higher in female in all TB cases, in EPTB cases, and in P-EPTB cases. The annual TB mortality was higher in male in all TB cases, and in PTB cases. The annual TB incidence and annual TB mortality in all TB cases, PTB cases and EPTB cases were higher in those aged 60 and over (Table 2).

In 2010- 2019, in TB incidence, there was an annual 3.73 % (95 % Confidence Interval [CI]= -7.7; 0.4) non-significant ($p= 0.070$) decrease in male and an annual 6.98 % (95 % CI= -10.3; -3.6) significant ($p= 0.002$) decrease in female (Fig 1). TB mortality rate showed a significant increase of 12.63 % (95 % CI= 2.9; 23.3, $p= 0.016$) annually in female, while it showed a non-significant increase of 0.62 % (95 % CI= -7.5; 9.4, $p= 0.869$) annually in male (Fig 1).

Between 2010 and 2019, the incidence of TB in male showed a decreasing trend in the 0-59 age range (significantly in the 20-59 age range) (Annual Percent Change [APC]= -6.97 %, 95 % CI= -13.2; -0.3, $p= 0.042$ for the 20-39 age group; APC= -6.36 %, 95 % CI= -11.8; -0.6, $p= 0.034$ for the 40-59 age group). For those aged 60 and over, in TB incidence, there was an annual 23.50 % significant decrease (95 % CI= -37.9; -5.8, $p= 0.035$) between 2012 and 2016, and an annual 45.79 % significant increase (95 % CI= 24.1; 71.2, $p= 0.008$) between 2016 and 2019 (Fig 2). On the other hand, in female, the incidence of TB was in a decreasing trend in all age groups, being significant only in the 40-59 age group (APC= -10.33 %, 95 % CI= -18.8; -1.0, $p= 0.035$) (Fig 2).

In the years examined, the incidences of PTB and EPTB were in a downward trend for both genders (APC= -2.23 %, 95 % CI= -7.3; 3.1, $p = 0.353$ for PTB- male; APC= -3.45 %, 95% CI= -9.9; 3.4, $p = 0.272$ for EPTB- male; APC= -6.86 %, 95 % CI= -13.3; 0.0, $p= 0.051$ for PTB- female). This downward trend was significant only in the 6.72% annual decline in EPTB incidence in female (95 % CI= -10.7; -2.5, $p= 0.007$) (Fig 3).

The number of cases of lymphatic system and pleural involvement, where extra-pulmonary involvement was the most common in males, was in a non-significant decreasing trend in the years examined (APC= -3.44 %, 95 % CI= -11.2; 5.0, $p = 0.361$ for Pleura- male; APC= -3.06 %, 95 % CI= -10.1; 4.5, $p = 0.367$ for Lymphatic system - male) (Fig 4). In female, a significant decrease was observed in the number of cases for lymphatic system involvement by annual 9.74 % (95 % CI= -15.2; -4.0, $p= 0.005$) and for Genitourinary system (GUS) involvement by annual 12.63 % (95 % CI= -21.8; -2.4, $p= 0.022$). On the other hand, although not significant, there was an increase in the number of cases with pleural involvement, and a decrease in the number of cases with Gastrointestinal system (GIS) and peritoneum involvement (APC= 1.49 %, 95 % CI= -5.5; 8.9, $p= 0.643$ for Pleura- female; APC= -0.66 %, 95 % CI= -4.7; 3.6, $p = 0.724$ for GIS, peritoneum- female) (Fig 4).

It was found that drug sensitivity percentages in both male and female were in an increasing trend in the years examined. Of these, those that showed a significant increase were observed in isoniazid sensitivity with an annual increase of 1.63 % (95 % CI= 0.1; 3.1, $p= 0.036$) in male and in rifampicin sensitivity with an annual increase of 0.89 % (95 % CI= 0.1; 1.7, $p= 0.032$) in female (Fig 5).

Table 1. Distribution of some clinical characteristics and age groups of tuberculosis patients by gender

Characteristics		**Total[†] (n=918)**	**Male (n= 458, 49.9%)**	**Female (n=460, 50.1%)**	
Age groups (years) (n, %)					
0-19		120 (13.1)	55 (45.8)	65 (54.2)	$x^2 = 1.884$ p = 0.597
20-39		269 (29.3)	135 (50.2)	134 (49.8)	
40-59		285 (31.0)	150 (52.6)	135 (47.4)	
≥60		244 (26.6)	118 (48.4)	126 (51.6)	
Case definition (n, %)					
New		819 (89.2)	398 (48.6)	421 (51.4)	$x^2 = 7.689$ p = 0.092
From a transport		48 (5.2)	30 (62.5)	18 (37.5)	
Relapse		42 (4.6)	23 (54.8)	19 (45.2)	
Returning from treatment		6 (0.7)	4 (66.7)	2 (33.3)	
From treatment failure		3 (0.3)	3 (100)	0 (0.0)	
Disease location (n, %)					
Extra-pulmonary		458 (49.9)	153 (33.4)	305 (66.6)	$x^2 = 102.047$ p < **0.001**
Pulmonary		436 (47.5)	293 (67.2)	143 (32.8)	
Pulmonary and extra-pulmonary		24 (2.6)	12 (50.0)	12 (50.0)	
Disease outcomes (n, %)					
Completing treatment		663 (72.2)	311 (46.9)	352 (53.1)	$x^2 = 23.651$ p < **0.001**
Cure		108 (11.8)	71 (65.7)	37 (34.3)	
Abandon treatment		55 (6.0)	23 (41.8)	32 (58.2)	
Death		48 (5.2)	32 (66.7)	16 (33.3)	
Transplant outgoing		41 (4.5)	18 (43.9)	23 (56.1)	
Treatment failure		3 (0.3)	3 (100.0)	0 (0.0)	
Therapy duration (months) (Mean ± SD)		6.95 ± 2.93	6.84 ± 2.84	7.06 ± 3.01	U = 109654.0 p = 0.251
Extra-pulmonary involvement (n, %)		**(n=458)**	**(n= 153)**	**(n= 305)**	
Lymphatic system		182 (39.7)	46 (25.3)	136 (74.7)	$x^2 = 48.134$ p < **0.001**
Pleura		87 (19.0)	53 (60.9)	34 (39.1)	
Genitourinary system		48 (10.5)	14 (29.2)	34 (70.8)	
Skin		42 (9.2)	15 (35.7)	27 (64.3)	
Gastrointestinal system, Peritoneum		45 (9.8)	9 (20.0)	36 (80.0)	
Bone, Joint, Vertebra		23 (5.0)	6 (26.1)	17 (73.9)	
Central nervous system		15 (3.3)	7 (46.7)	8 (53.3)	
Breast		11 (2.4)	0 (0.0)	11 (100.0)	
Cardiovascular system		3 (0.7)	2 (66.7)	1 (33.3)	
Larynx		2 (0.4)	1 (50.0)	1 (50.0)	
Drug resistance (n, %)[‡]		**(n=290)**	**(n=176, 60.7%)**	**(n=114, 39.3%)**	
Ethambutol	Sensitive	264 (91.0)	162 (61.4)	102 (38.6)	$x^2 = 0.020^*$ p = 0.888
	Resistant	26 (9.0)	14 (53.8)	12 (46.2)	
Isoniazid	Sensitive	265 (91.4)	160 (60.4)	105 (39.6)	$p = 1.000^{**}$
	Resistant	25 (8.6)	16 (64.0)	9 (36.0)	
Streptomycin	Sensitive	277 (95.5)	167 (60.3)	110 (39.7)	$x^2 = 0.290^*$ p = 0.590
	Resistant	13 (4.5)	9 (69.2)	4 (30.8)	
Rifampicin	Sensitive	282 (97.2)	171 (60.6)	111 (39.4)	$x^2 = 0.126^*$ p = 0.723
	Resistant	8 (2.8)	5 (62.5)	3 (37.5)	

n Number; *SD* Standard deviation; [†] Colon percentage; [‡] Analysed the results of patients whose drug resistance was tested; [*]Continuity Correction; [**]Fisher's Exact Test

Table 2. Annual incidence and mortality rates of tuberculosis cases stratified by gender and age groups

Characteristics	Average population	Number of new cases over 10 years	Incidence rate /100 000 population/year	Number of deaths	Mortality rate /100 000 population/year
Overall tuberculosis cases					
Total	628646	819	13.02	48	0.76
Gender					
Male	314718	398	12.64	32	1.01
Female	313927	421	13.41	16	0.50
Age groups (years)					
0-19	196774	112	5.69	3	0.15
20-39	191009	241	12.61	3	0.15
40-59	139773	250	17.88	12	0.85
≥60	99617	216	21.68	30	3.01
Pulmonary tuberculosis					
Total	628646	378	6.01	36	0.57
Gender					
Male	314718	250	7.94	27	0.85
Female	313927	128	4.07	9	0.28
Age groups (years)					
0-19	196774	56	2.84	1	0.05
20-39	191009	114	5.96	2	0.10
40-59	139773	106	7.58	10	0.71
≥60	99617	102	10.23	23	2.30
Extra-pulmonary tuberculosis					
Total	628646	421	6.69	12	0.19
Gender					
Male	314718	139	4.41	5	0.15
Female	313927	282	8.98	7	0.22
Age groups (years)					
0-19	196774	55	2.79	2	0.10
20-39	191009	119	6.23	1	0.05
40-59	139773	137	9.80	2	0.14
≥60	99617	110	11.04	7	0.70
Pulmonary and extra-pulmonary tuberculosis					
Total	628646	20	0.31	0	0
Gender					0
Male	314718	9	0.28	0	0
Female	313927	11	0.35	0	0
Age groups (years)					
0-19	196774	1	0.05	0	0
20-39	191009	8	0.41	0	0
40-59	139773	7	0.50	0	0
≥60	99617	4	0.40	0	0

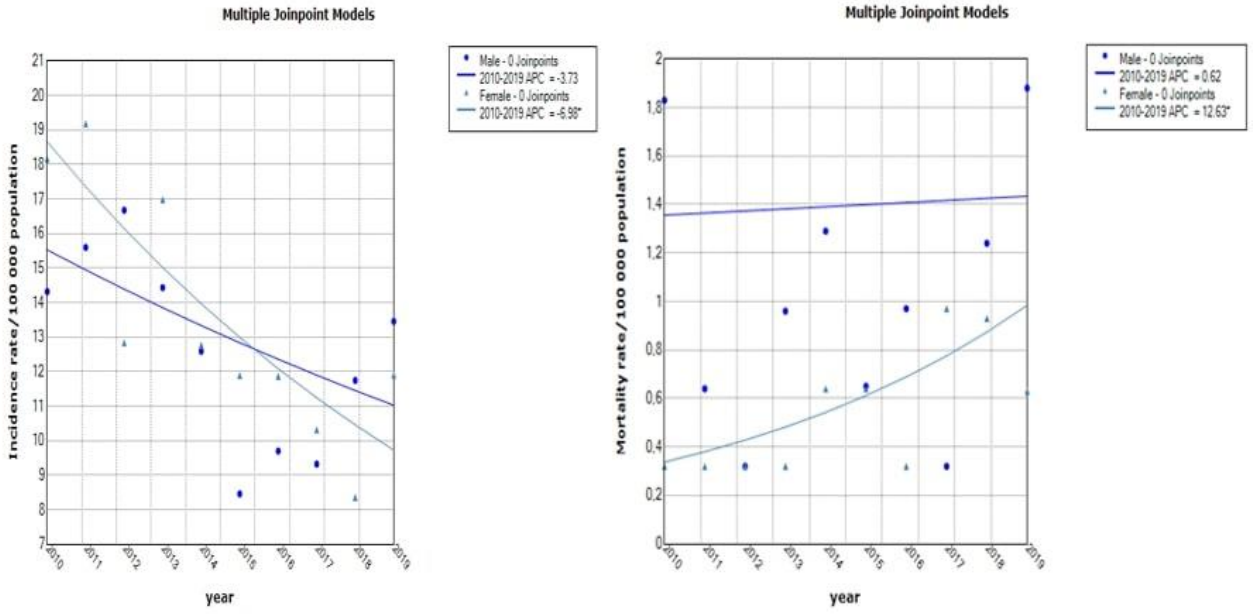

Fig 1: Joinpoint regression analysis of tuberculosis incidence and mortality rates by gender between 2010 and 2019.

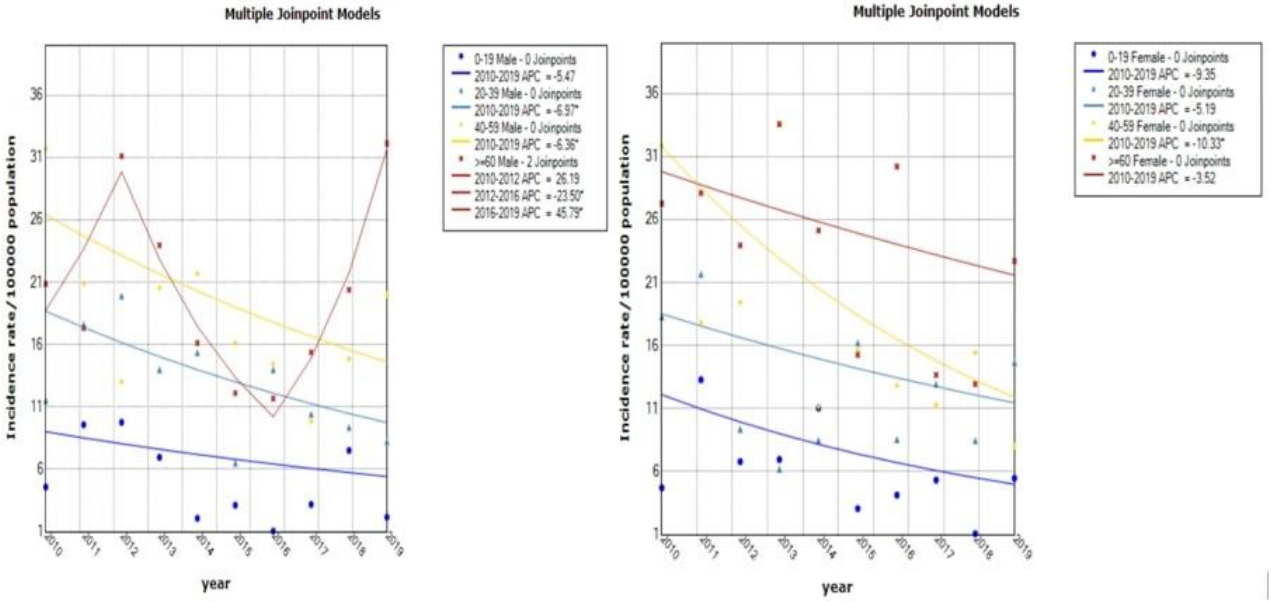

Fig 2: Joinpoint regression analysis of tuberculosis incidence rates by age groups and gender between 2010 and 2019.

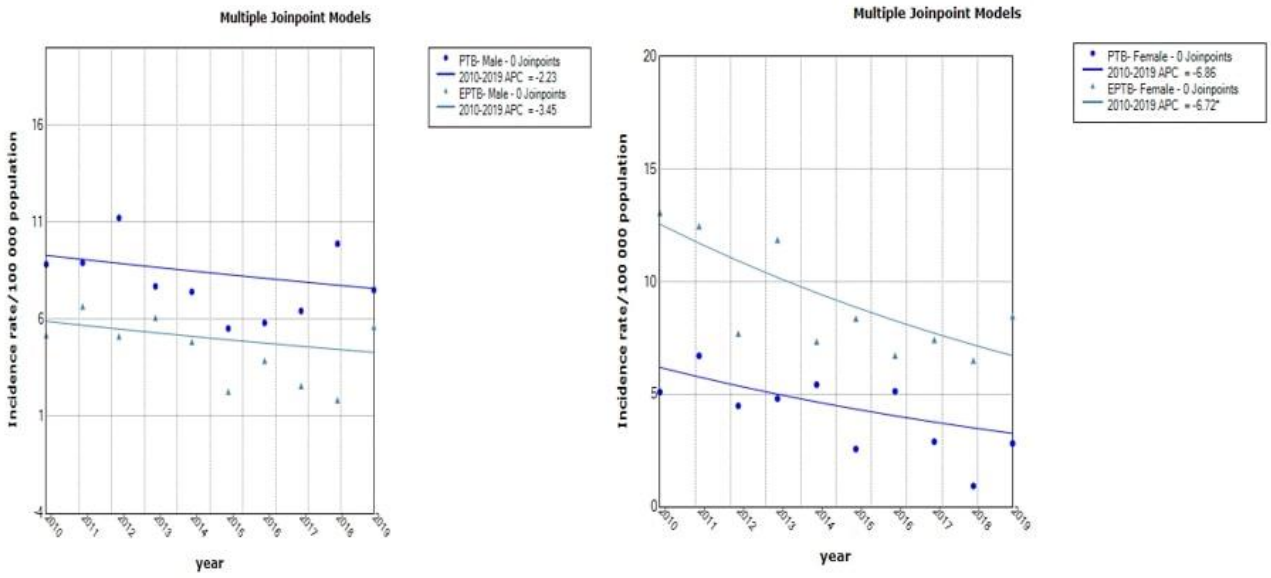

Fig 3: Joinpoint regression analysis of pulmonary tuberculosis (PTB) and extra-pulmonary tuberculosis (EPTB) incidence rates by gender between 2010 and 2019.

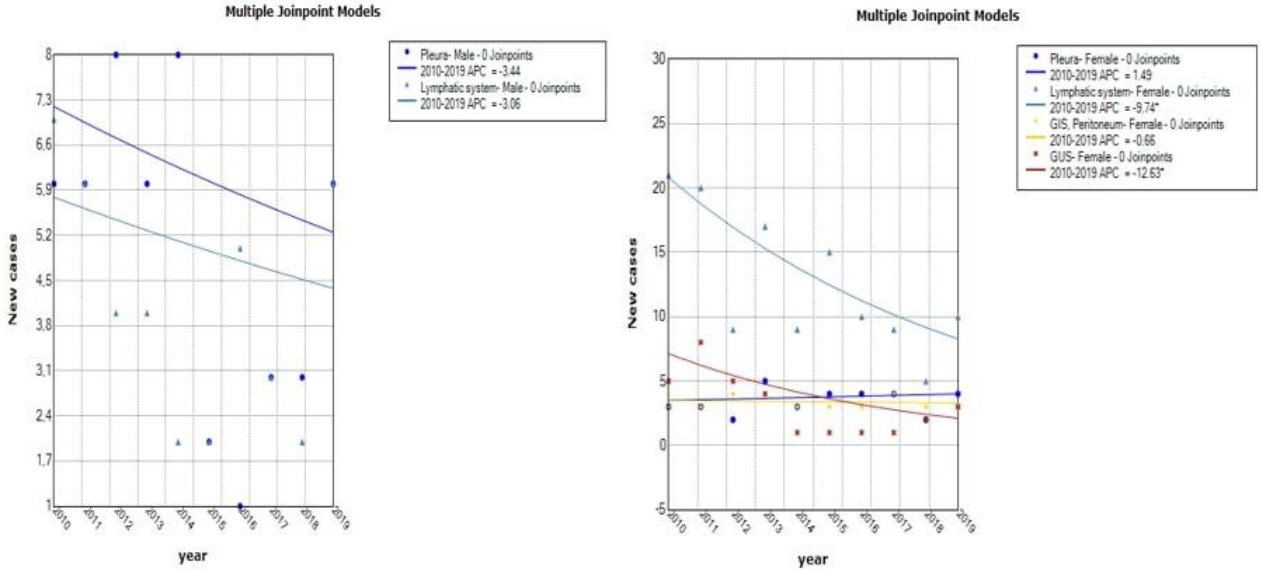

Fig 4: Joinpoint regression analysis of extra-pulmonary tuberculosis involvement annual numbers by gender between 2010 and 2019 (GIS: Gastrointestinal system, GUS: Genitourinary system).

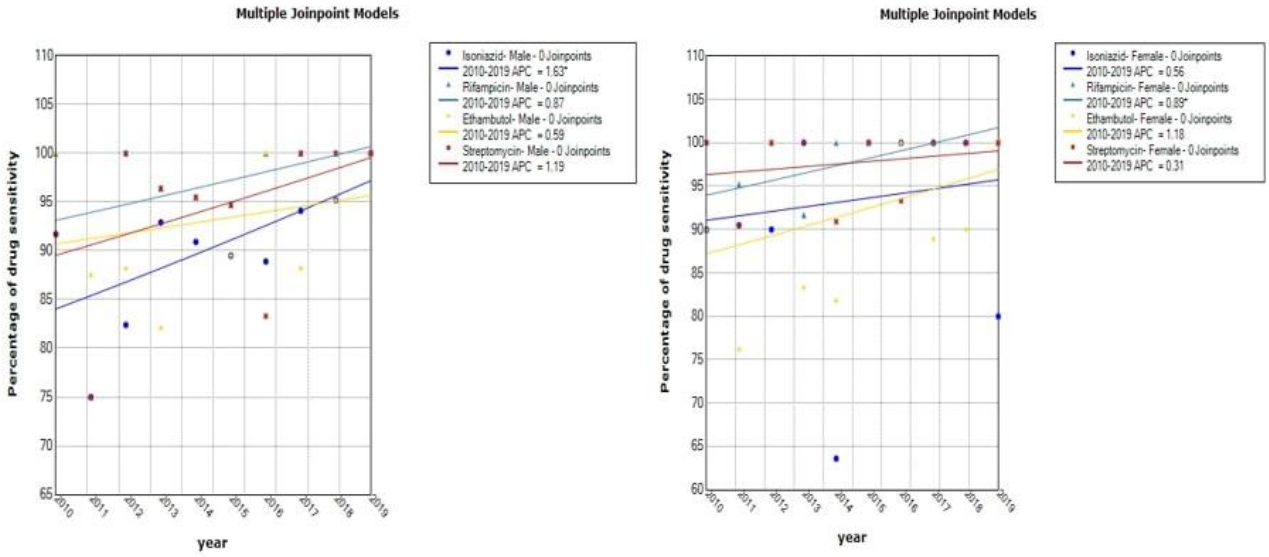

Fig 5: Joinpoint regression analysis of drug sensitivity percentages by gender between 2010 and 2019.

DISCUSSION

This retrospective epidemiological study was performed using 2010- 2019 patient records of Sivas Tuberculosis Dispensary which located in Turkey's Central Anatolia Region.

Similar to our study, TB patients diagnosed in 2017 in Turkey were determined as 92.2 % new cases [4] and in a trend study conducted in Iran 97.1 % of the cases were new, 1.45 % of the cases were relapsed, and 1.45 % of the cases were imported cases [13].

Contrary to the value found in our study, TB is more common in male than in female worldwide (1.75 male to female ratio) [3]. But as in our study, there are also studies that have found higher TB incidence in female compared to male [14,15]. On the other hand, when we consider age groups similar to our study, in the some studies the researchers found that female patients were more likely to be younger than male patients [12,16,17]. The reason we detected gender differences between age groups may be that social interactions and exposure to disease within the community can vary from country to country. The reason for the higher rate of infection in male in the older age group (20-59) in our study may be that older male are more exposed to the agent, especially through social contact in the community [18]. The increased prevalence of risk factors among male, such as smoking [9] and alcoholism, [19] which increase susceptibility to TB infection, may also explain the higher rate of infection in older male [12]. On the other hand, it has been shown in experimental conditions that estrogen has a protective effect against TB infection [20–22]. This may explain why the prevalence of TB in women was less in the 20-59 age group, while it was more common in younger (0- 19) and older (≥ 60) ages which we found in our study.

According to 2017 data in Turkey, EPTB rate was reported as 33.9 % and while the ratio of female and male in pleural TB was approximately equal, other EPTB was more common in female likely in the finding in our study [4]. In a study done in Malaysia, Khan et al. found that patients at the risk of EPTB were more likely to be females and pleural effusion and lymph node TB were the most frequent EPTB types [23]. Similar to our study, in the study conducted in southern Tunisia, the majority of the cases (59.5 %) were EPTB, among whom the main EPTB forms were lymph node in 45.7 % cases, followed by pleural TB in 14 % cases and urogenital TB in 11.4 % cases and the rate of EPTB was higher in female, as we found in our study ($p< 0.001$) [24]. On the other hand, similar to our study in a study done in India it was observed that lymph node TB, CNS TB and TB of bones and joints were more common in females than in males while pleural TB and abdominal TB were more common in males than in females [25]. The reason for the high rate of EPTB may be that TB drug resistance disrupts TB control and causes reactivation of Mycobacterium [24]. In a study conducted in Iran, Khazaei et al. [26] found that the incidence rates of PTB and EPTB were in a decreasing trend in the period 1995- 2012, similar to our study.

Similar to our study, in their study Safwat et al. [16] found that cases of treatment failure were found only in male, the rate of cure and deaths due to TB were higher in male than in female [16]. Feng et al.

[17] detected that female patients were significantly less likely to achieve cure than male patients, but the mortality rate for males was higher. Globally in 2019, 53 % of the HIV-negative people who died from TB were male, 31 % were female and 16 % were children (aged< 15 years) [3].

Global TB report [27] stated that in 2019, an estimated 3.3 % of new cases and 18 % of previously treated cases had MDR/ RR- TB (MDR: Multi drug resistance, RIF and INH, RR: RIF resistance). On the other hand, in 2019, an estimated 13.1 % of new cases and 17.4 % of previously treated cases had INH resistance [3]. In another study conducted in Turkey the researchers detected that single resistance to INH, EMB, SM, and RIF, were 3.5 %, 3 %, 1 %, and 0 %, respectively [28]. In their study Senoglu et al.[29] reported that the resistance rates were 27.8 % for INH, 14.7 % for EMB, 11.5 % for SM, and 3.2 % for RIF. Although the rates in the studies were different than the rates we found in our study, the drugs with the most resistance in these studies were INH and EMB. In studies conducted around the world, it was reported that the most common resistance was against INH [29]. On the other hand, in the studies in Turkey, INH and SM resistance was located in the first rows [30]. Resistance rates in some studies in Turkey were reported to be between 2.9 to 24.6 % for INH, between 2.1 to 19.2 % for SM, between 2.0 to 18.8 % for EMB, and between 0 to 15.8 % for RIF [29]. It is thought that this may be due to the fact that INH and SM are the most commonly used drugs in treatment and prophylaxis and that SM is also used for reasons other than TB [31]. On the other hand, it is thought-provoking that EMB resistance was in the first two places in the studies conducted in our country in recent years, as in our study. This situation should be reviewed with new studies.

The TB incidence rate varies between 5 and 500 per hundred thousand worldwide every year [3]. WHO has identified the low incidence of TB as < 10 cases per hundred thousand people per year and Turkey is not yet included in this group [3]. However, the TB incidence rates we found in our study showed our determination to be included in this group. In Turkey a total of 20,535 patients were registered in 2005 and the incidence was 29.4 per hundred thousand, while the incidence was 14.6 per hundred thousand in 2017 [4]. The fact that the rates in the last years, which we found in our study, were reported to be much lower than the rates in the country showed the determination of our country in implementing the TB control program. In a study conducted in Tunisia, the annual incidence rates for all TB forms, PTB and EPTB were found to be 13.91, 5.63 and 8.28 per hundred thousand, similar to our study [24]. In a study conducted in Iran, average annual incidence rates of all forms of TB, PTB and EPTB were reported as 8.34, 5.25 and 7.6 per hundred thousand, respectively [13]. In both studies, EPTB incidence rates were found to be higher than PTB as we found in our study. On the other hand, similar to our study, Ben Ayed et al. [24] found the annual incidence rate of EPTB higher in female, while the annual mortality rates of TB in all forms and PTB were higher in male. Considering age groups, annual TB incidence and mortality rates were found to be higher in the elderly, in other studies [13,24,32], similar to our study.

In the worldwide the mean rate of decline in the TB incidence rate was 1.7 % per year in the period 2000- 2019, and 2.3 % per year in 2018-2019 [3]. In our country, an average annual decrease of 5% was observed in the incidence of registered TB between 2005 and 2017, similar to our study [4]. In the study conducted by Marvi et al[13] in Iran, between 2005- 2015 a decrease was found in the TB incidence trend in female, but a significant increase was observed in male. In our study, also, the downward trend in TB incidence was found to be lower in male than in female. As a matter of fact, when we consider age groups, we observed an increase in the incidence of TB since 2016, only at the age of 60 and above in male. The reason for this may be that elderly male cannot do self-care, unlike female, due to being alone. These results showed us the importance of evaluating age and gender together when commenting on TB incidence.

TB is one of the leading fatal infectious diseases in the world and one of the top 10 causes of death [33]. The number of TB deaths per year is in a downward trend globally, with a cumulative reduction of 14 % between 2015 and 2019 [3]. In a study evaluating the trend of TB data in Iran the researchers found that the estimated mortality rate of all forms of TB except HIV cases had decreased to during 1994- 2009, but after that period this trend has become upward likely in our study [34]. However, no other study evaluating the TB mortality trend by gender was found in the literature. The rapid increase in the mortality rate trend in female is a situation that should be taken into account and it. The reason for this may be that the EPTB rate was found to be higher in female.

According to global TB report [3] it was stated that the burden of MDR/RR- TB relative to the number of new and previously treated cases

remains stable and at the national level, the proportion of TB cases with MDR/ RR- TB should be interpreted within the overall context of the country's TB epidemic. As a matter of fact, it was observed in our study that TB drug sensitivity percentages tend to increase in both genders. In the study conducted in China Wu et al. [35] reported that MDR- TB showed a decreasing trend while resistance to any first-line drugs showed an increasing trend from 1999 to 2013. Also they reported that there were no statistically significant demographic differences between non- MDR- TB and MDR- TB patients [35]. In another study stated that the prevalence of MDR-TB decreased from 8.6 % in 1999 to 6.0 % in 2008 [36].

The present study is the first in Turkey to evaluate the trend of 10- year TB data in terms of gender differences using joinpoint regression analysis. The strengths of the present study are that the presentation of some characteristics of TB trend change over a period of 10 years by especially gender and then age groups, using accurate and comprehensive data. The limitations of our study are that some data records were not considered due to missing (drug resistance, HIV positive patients), the patients were not included in the evaluation due to the lack of multidrug resistance records.

CONCLUSION

As a result, in our study, the total number of female new patients was 51.4 % and the female to male ratio was 1.05. Female was in the majority in cases in the 0-19 and ≥ 60 age group, while male was in the 20- 59 age group. The gender difference in rates was highest in the 0- 19 age group. 49.9 % of the cases were EPTB and EPTB rate in female was significantly higher than in male. The most common extra-pulmonary involvement was the lymphatic system. Complete the disease as a cure, treatment failure and deaths due to TB were significantly higher in male. The drug resistance was 9 % for EMB, 8.6 % for INH, 4.5 % for SM and 2.8 % for RIF and there was no significant difference by gender. The annual TB incidence and annual TB mortality were higher in those aged 60 and over. The incidences of all TB forms, PTB and EPTB showed a decreasing trend in both genders. TB mortality rate and drug sensitivity percentages were in an increasing trend in both genders. In female, a significant decrease was observed in the number of cases for lymphatic system and GUS involvement. In conclusion, significant changes were found in some clinical features of TB according to gender. It is thought that situations arising from gender changes in TB control programs should be considered.

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