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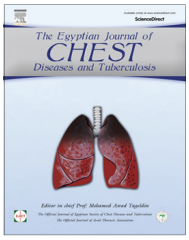

Determinants of delay in tuberculosis diagnosis in Hamadan province, 2006–2014

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Abstract *Introduction:* Identifying factors that delay diagnosis of tuberculosis (TB) are important for the health system when timely patient treatment and reducing TB transmission are desirable goals. Aim of this study was to investigate the prognostic factors that delay TB diagnosis.

Material and methods: This retrospective cohort study used National TB Program (NTP) data from 1056 TB patients during 2006–2014 in Hamadan province, western Iran. The Cox regression model was performed to determine associations between baseline explanatory variables and survival outcome with Hazard Ratio HRs (95% CIs).

Results: N (%) of delay in TB diagnosis more than 90 days was significantly higher in male patients, new case patients and pulmonary positive cases. After adjustment for covariates, HR (95% CI) in relapsed TB compared to new cases was 0.67 (0.53, 0.85) and these figures for positive pulmonary cases and extra pulmonary cases in compared to negative pulmonary cases were 0.80 (0.68, 0.94) and 0.84 (0.73, 0.98) respectively.

Conclusion: A high proportion of patients had delays in diagnosis exceeding three months. Our findings suggest that male gender, new cases, positive and extra pulmonary cases might increase the risk for delayeddiagnosis among TB patients.

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Introduction

Tuberculosis (TB) is known as a global public health problem accounting 9.4 million incident cases and 1.4 million deaths in 2012 [1]. Many factors including HIV epidemics, population growth, socio-economic changes and emergence of resistant new strains of *Mycobacterium Tuberculosis* (such as *W* and *Beijing*) lead to re-emerging of TB. In 1993, due to the steady increase in TB cases WHO declared a state of global emergency for TB and called it as a global enemy in addition to HIV and malaria [2].

The main goal of TB control programs is to arrest the transmission within the community. An effective TB control program requires early diagnosis and immediate initiation of treatment. Delay in diagnosis in individuals and community plays a crucial role in terms of disease prognosis and disease transmission respectively [3].

Delay in the diagnosis and treatment of pulmonary tuberculosis results in increasing severity, mortality, and transmission of TB. Most transmissions occurs when the appearance of cough in initiation of treatment. A published study reported that patients become more contagious as the delay progresses. In other words, the longest delays are associated with the highest bacillary numbers in sputum smears. On the other hand, patients with delay in TB diagnosis are more likely to develop pneumonia, other respiratory infections, and mortality in emergency departments [4].

A systematic review on delay in TB diagnosis is shown regardless of low or high endemic settings, a range of 60–90 days for total delay in TB diagnosis [5]. Eastern Mediterranean region of WHO (EMRO) also reported that the highest time between onset of symptoms and disease diagnosis in Iran was 127 days in 2006 [6]. Moreover, one other study argued that the main cause of delay in TB patients in Iran is healthcare system oriented. In other words, the main delay was the time taken by physicians to diagnose symptomatic patients [7]. It suggested that the reasons for delay in diagnosis embedded in cultural or educational deficiencies. However, postponed treatment initiation is rooted in the ability of the national program of TB control in establishment of technical and therapeutic facilities and providing the efficient control system in a given country [7].

Delay in the diagnosis and treatment of TB patients will result in spreading of infection in the community, increase in severity of the disease and also a higher risk of mortality. Therefore understanding the factors causing delay between TB symptoms and therapy initiation is crucial to combatting against the increasing TB epidemic, and to help healthcare system in designing and implementing TB control programs. Thus, aim of the present study is to determine the prognostic factors that delay TB diagnosis.

Material and methods

This retrospective cohort study was conducted involving 1056 TB patients in Hamadan province, western Iran, from 2006 to 2014. The cohort involved all registered TB patients with smear-positive, smear-negative or extra pulmonary. TB cases were defined according to WHO and Iran's national TB guidelines [8]. To reach a homogenous sample and generalize results to Iranian population, records of Afghan immigrants, patients with probable diagnosis of TB and non-native born citizens were excluded.

Data were extracted from the National TB Program (NTP) as follow: background *characteristics* (gender, age, time of diagnosis, source of reporting, *place of residence* (urban and rural), and *type of TB*. Survival time was defined by symptom onset until diagnosis. Delay time was categorized into less than 30 days, 31–90 days, and more than 90 days (which was hypothesized as problem oriented delay).

The Log-rank test was used for comparison of survival curves. The Kaplan–Meier curves were tested under the null hypothesis that there is no significant difference between median of delay times. Null hypothesis is tested by Log-rank test. The Cox regression model was used to evaluation simultaneous effects of prognostic variables on survival outcome. Proportionality of hazards was tested using the *Schoenfield* test and graphical schemes. *P*-value $\leqslant 0.05$ was considered a significant level for all mentioned statistical tests. All analyses were conducted in Stata software version 11 ((StataCorp, College Station, TX, USA).

Results

Of the 1056 cases, N (%) of male and urban residence were 519 (49) and 649 (61) respectively. Table 1 shows the baseline characteristics of the patients. The results showed that male patients, relapse cases, and pulmonary positive patients compared to the references had a significantly higher percent of delay in diagnosis more than 90 days; but a significant difference was found between median delays for disease type (Table 2).

The results of Cox's proportional hazards model are demonstrated in Table 3. The adjusted hazard ratios (HRs) were statistically significant for treatment group, disease type, and year of diagnosis. Hazard Ratio HR (95% CI) of patients with pulmonary positive TB and extra pulmonary TB compared to negative pulmonary TB patients was 0.8 (0.68, 0.94) and 0.84 (0.73, 0.98) respectively. This figure for relapsed cases compared to new cases was 0.67 (0.53, 0.85).

Fig. 1 shows Kaplan–Meier curves for survival adjusted for gender, residency, disease type, and treatment group. Based on Fig. 1, there are satisfactory conditions to use the Cox Proportional models.

Discussion

Delay in TB case detection may worsen the disease and also increase TB transmission in the society. The results of this study showed that the median delay time in TB is higher in females, and negative smear cases, also relapse cases and pulmonary smear positive and extra pulmonary patients have lower hazard for delayed diagnosis compared to other groups. Results of other studies have shown that females [8–10], and negative sputum smear cases [11,12] have experienced increased diagnostic delay compared to males and other types of TB. Specifically, the given negative smear results might lead to a spurious confidence regarding not seeking further medical attention [13].

Consistent with the report from Ghana [14], further median delay in TB diagnosis in women in our study might be related to the seeking medical center differences between men and

Table 1 Main characteristics of TB patients in Hamadan province, 2006–2014.

Variable	No. (%)	Timely presentation (⩽30 days), $n = 153$	Moderate delay (31–90 days), $n = 258$	Problem oriented delay (>90 days), $n = 545$	*P* value
Gender					
Male	519(49)	90(17.34)	173(33.33)	256(49.33)	0.032
Female	537(51)	63(11.73)	185(34.45)	289(53.82)	
Residency					
Urban	649(61)	92(14.2)	211(32.5)	346(53.3)	0.36
Rural	407	61(15)	147(36.1)	199(48.9)	
Age groups (Year)					
<5	13 (1.5)	3(23.1)	4(30.77)	6(46.15)	0.38
5–14.9	16(1.5)	4(25)	4(25)	8(50)	
15–29.9	164(15)	24(14.63)	65(39.63)	75(45.73)	
30–44.9	201(19)	27(13.43)	75(37.31)	99(49.25)	
45–59.9	187(18)	30(16)	66(35.3)	91(48.66)	
60	475(45)	65(13.68)	144(30.32)	266(56)	
Treatment group					
New case	983	139(14.14)	345(35.1)	499(50.76)	0.01
Relapse case	73	14(19.2)	13(17.8)	46(63)	
Disease type					
Pulmonary (+)	510	85(16.67)	181(35.5)	244(47.8)	0.044
Pulmonary (−)	207	22(10.6)	61(29.5)	124(59.9)	
Extra pulmonary	339	46(13.57)	116(34.22)	177(52.21)	
Year of diagnosis					
2006–2009	561	62(11.05)	183(32.62)	316(56.33)	<0.001
2010–2014	495	91(18.38)	175(35.35)	229(46.26)	

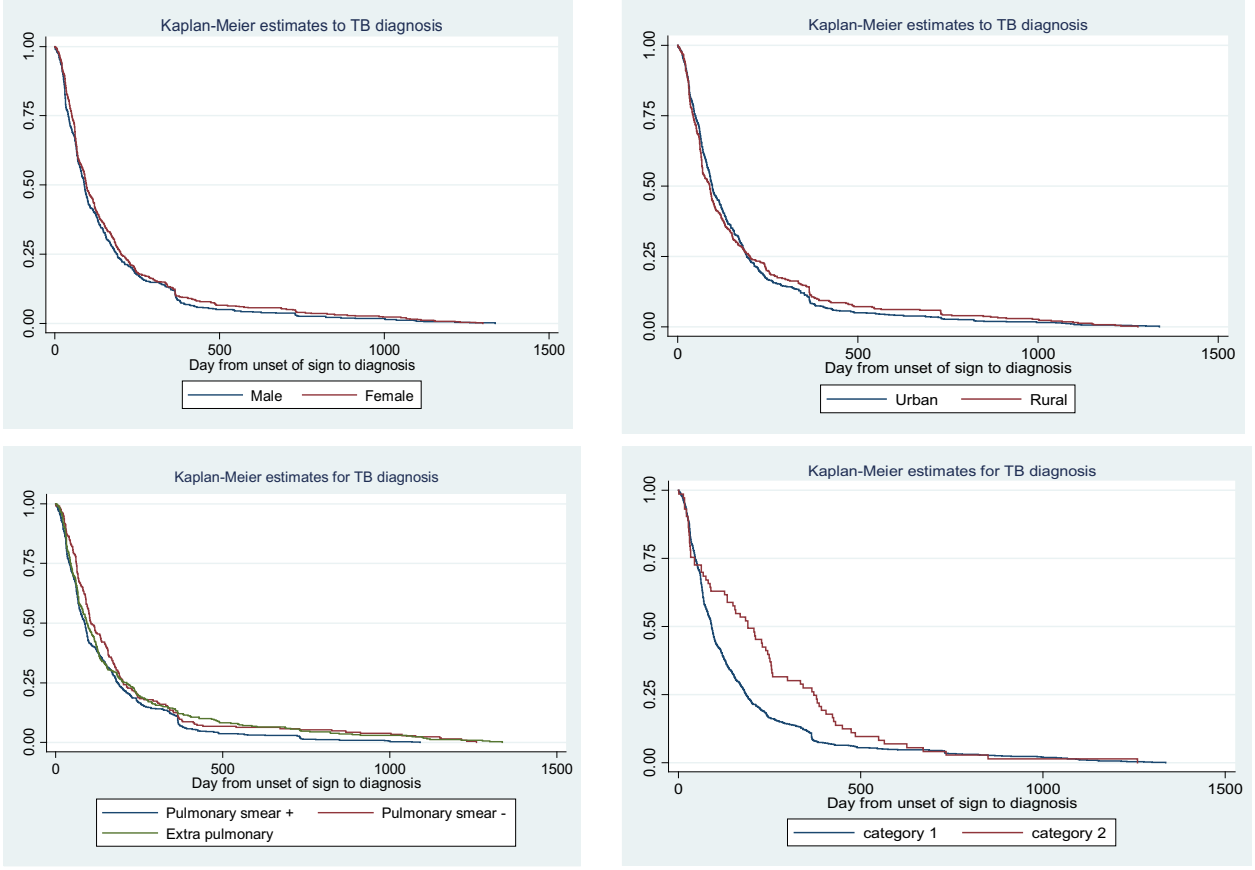

Figure 1 Kaplan–Meier survival curves adjusted for: (A) gender; (B) residency; (C) TB type; (D) treatment group.

Table 2 Comparison of median delay time in TB patients.

Variable		Median delay ± 95% CI (day)	*P* value (Log-rank)
Gender	Male	90(80–96.3)	0.17
	Female	96(89–109)	
Residency	Urban	96(89–105.9)	0.76
	Rural	89(62.9–95)	
Disease type	Pulmonary (+)	86(75–93.6)	0.01
	Pulmonary (−)	105(94.9–136)	
	Extra pulmonary	93(80.9–110.1)	

women. Women in rural areas are dependent on their husbands to take them to health services. In general, women experienced greater barriers such as financial, physical and stigma than men [15].

We have found also that urban residents had a non-significant higher median delayed time; this finding could be challenged by the previous studies that showed due to poorer access to medical facilities and socio-economic disadvantages, rural residents have experienced a higher delayed diagnosis [9,16–18]. This could be due to the establishment of health houses in rural areas in Iran. In contrast to our results, in one study in Bangladesh, delay in diagnosis in rural areas was higher and it was due to the low level of knowledge and awareness of the disease and income in rural areas [19].

Our finding showed pulmonary smear positive and extra pulmonary cases have 20%, and 16% lower hazard for delayed diagnosis compared to pulmonary negative cases. This finding is in conflict with prior reports showing that extra pulmonary cases have a higher chance of delayed diagnosis [20–23]. One reason for this inconsistency could be due to long process for detecting of smear negative pulmonary TB patients such as sputum culture.

One of the important causes of delayed diagnosis of a TB patient is attributed to the beliefs and attitudes that exist in the community. It has been shown that lack of knowledge about the TB, internalized stigma, shame of being a TB patient, self-treatment, and seeking unqualified or traditional practitioners plays a significant role as a barrier to timely and proper diagnosis of TB [1,24–27].

We have also found that patients diagnosed in 2006–2014 had a higher risk for delayed treatment compared to the previous time period. This is questionable regarding to the anticipation of improvement in diagnostic tools in health care settings. One explanation for observed paradox might be as a result of the fact that most patients suffering from TB belonged to deprived socio-economic classes where the ability of healthcare settings to properly diagnose is not comparable with those in larger cities in Iran.

Our study has some limitations. We used a registry based data for analysis. Actually, we could not directly investigate the effect of some variables such as household income, education, and socio-economic status of patients on delayed treatment; moreover the distinction between patient delay and health care system was impossible. Delay time was based on self-reporting of patients, therefore is prone to information bias.

Conclusion

We found that females, urban residents, new cases and cases with negative smear results, and the second half of the study period had a higher risk for delayed TB diagnosis. Further evaluation of these subgroups along with educational and screening programs focusing on them would be beneficial for the patients and the population as a whole. Improving health staff education regarding TB symptoms and also implementing active case finding in the populations may reduce delays.

Table 3 Hazard ratio and 95% confidence intervals of survival adjusted for covariates.

Variables	Unadjusted		Adjusted*	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Gender				
Male	Reference	0.17	Reference	0.16
Female	0.92(0.81, 1.04)		0.91(0.8, 1.03)	
Residency				
Urban	Reference	0.77	Reference	0.74
Rural	0.98(0.87, 1.1)		0.98(0.86, 1.1)	
Treatment group				
New case	Reference	0.002	Reference	0.001
Relapse case	0.69(0.54, 087)		0.67(0.53, 0.85)	
Disease type				
Pulmonary (−)	Reference		Reference	
Pulmonary (+)	0.8(0.68, 0.94)	0.009	0.8(0.68, 0.94)	0.009
Extra pulmonary	0.85(0.74, 0.98)	0.028	0.84(0.73, 0.98)	0.024
Year of diagnosis				
2006–2009	Reference	0.001	Reference	0.001
2010–2014	1.22(1.08, 1.38)		1.23(1.09, 1.38)	

* Adjusted for age, gender, residency.

Conflict of interest

The authors claim no conflict of interest.

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