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Estimation of Ten-Year Survival of Patients with Pulmonary Tuberculosis Based on the Competing Risks Model in Iran

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Background: Tuberculosis (TB) is a chronic bacterial disease, which despite the presence of effective drug strategies, still remains a serious health problem worldwide. Estimation of survival rate is an appropriate indicator for prognosis in patients with pulmonary TB. Therefore, this research was designed with the aim of accurate estimation of the survival of patients by taking both the death event and relapse into consideration.

Materials and Methods: Based on a retrospective cohort study, information of 2,299 patients with pulmonary TB that had been referred to and treated in Masih Daneshvari Hospital from 2005 to 2015 was reviewed. To estimate the survival of patients with pulmonary TB, the competing risks model, which considered death and relapse as competing events, was used. In addition, the effect of factors affecting the cumulative incidence function (CIF) of death event and relapse was also examined.

Results: The effect of risk factors on the CIF of death events and relapse showed that patients' age, marital status, contact with TB patients, adverse effect of drugs, imprisonment and HIV positivity were factors that affected the CIF of death. Meanwhile, sex, marital status, imprisonment and HIV positivity were factors affecting the CIF of relapse ($P < 0.05$). Considering death and relapse as competing events, survival estimation in pulmonary TB patients showed that survival in this group of patients in the first, third, fifth and tenth year after treatment was 39%, 14%, 7% and 0%, respectively.

Conclusion: The use of competing risks model in survival analysis of patients with pulmonary TB with consideration of competing events, enables more accurate estimation of survival.

Key words: Survival rate, Competing risks model, Incidence, Pulmonary tuberculosis

INTRODUCTION

Tuberculosis is a chronic bacterial disease caused by *Mycobacterium tuberculosis (M. tuberculosis,)* belonging to genus Mycobacteriaceae (1). For a long time, TB was proposed as one of the leading causes of morbidity and mortality. Nowadays, this disease is still one of the most serious health problems in the world, despite the discovery of the causative agent, vaccine and effective drug strategies. Now, according to the World Health Organization report, one-third of the world's population are infected with *M. tuberculosis* (2,3). Every four seconds, a person is infected with TB and every 10 seconds a person dies of TB in the world (3). Of about two billion people

infected with the bacilli every year, sixty million new cases are diagnosed yearly; half of which belong to infective type of disease. *Mycobacterium tuberculosis* infects about one third of the world's population, causing 8 million new cases of tuberculosis and about 2 million deaths per year (4,5). On global scale, TB has a devastating effect on developing countries. Without any therapeutic strategy, 25% of patients die in the first 2 years, 50% expire during 5 years, while only 25% recover from the disease. With therapeutic strategy based on antibiotics for each person, 8% expire during treatment and 90% recover, while only 2% have positive sputum smear at the end of treatment (1).

Association of TB with certain diseases such as diabetes mellitus and HIV increases the risk of progression of infection to active disease. Also, HIV infection greatly increases the risk of active TB, such that about one-third of HIV deaths globally are due to TB (6-12). Iran with a TB incidence of 21 persons/100,000 and mortality rate of 3 to 10%, is among countries with medium incidence and low mortality and morbidity rates of TB (13,14).

One of the most important indicators of prognosis after diagnosis and treatment of pulmonary TB patients is increase in the patients' survival rate, particularly 5-year survival rate. Various methods have been designed, which estimate the survival rate of patients with pulmonary TB. The most common models are standard survival models (methods such as Kaplan – Meier and survival regression models) (15-17). As these methods only evaluate the time until death event, the chance of being able to identify other factors (besides death) that can influence patients' survival is non-existent (18,19).

Another statistical model designed to solve such a problem is called competing risks model. Based on this model, the patients during the study experience various events such as death or relapse; the time for reaching any of these events and factors affecting it play essential role in patient survival (18,20). With the exception of death, events such as disease relapse (that are often called competing events) have led to the design of modern approaches in survival studies. In such cases, the natural course of the disease can be considered as a stochastic process, during which the patients may be exposed to different events (18,21,22). Competing risks models consider the occurrence of more events (except death) for patients during the study. Therefore, it offers a more accurate estimation of patients' survival in comparison to the standard models (23,24). These models are used whenever there is the possibility of occurrence of events besides death in patients during the study.

Very few studies have been performed on the survival of patients with pulmonary TB. Unfortunately most of the studies conducted were based on survival standard models focusing only on the death event (25-29). Evaluation of survival in patients with pulmonary TB shows that disease and relapse are competing events; meanwhile it is not possible to reach an accurate estimation of survival of patients with pulmonary TB irrespective of both disease relapse and death events. Therefore, in this study in order to achieve a more accurate estimation of survival in patients with pulmonary TB, competing risks model was used. In this method, CIF plays a major role; CIF is defined as the possibility of occurrence of death event in presence of other competing events such as disease relapse. Generally, this model considers circumstances such as death or disease relapse which compete with each other and any of which can occur in a patient. In other words, CIF estimates the probability of disease relapse or death events before competing event occurrence (death or disease relapse). Thus, with CIF determination of each competing event of death or disease relapse we will be able to accurately estimate patient survival.

Thus, the present study was designed with the aim of evaluating the survival rate during treatment of patients with pulmonary TB referring to the National Research Institute of Tuberculosis and Lung Diseases (NRITLD) at Masih Daneshvari Hospital, Iran using competing risks model.

MATERIALS AND METHODS

Based on a retrospective cohort study, information of 2,299 TB patients that had been referred to and treated at the NRITLD, Masih Daneshvari Hospital, from 2005 to 2015, was collected. The data were obtained from patient records present in hospital archives with address and phone number for later follow-up. "TB death" was specified for all those TB patients, in whom TB was mentioned as the cause of death in the medical records. Meanwhile "non TB related death" was allocated to any TB patient who had died as a result of non-TB related causes. For all patients, time-dependent variables of death and disease relapse and independent variables (sex, age, marital status, education, nationality, place of residence, family size, adverse effect of drugs, smoking, passive smoking, drug abuse, contact with TB patients, imprisonment, pulmonary TB, extra-pulmonary TB, diabetes mellitus and HIV comorbidities) were considered.

The last follow-up (June 2015) was done by phone contact for patients who were still alive. The causes of death of dead patients were found using medical records data and through interviews with patient's close relatives. In the follow-up of patients, time of occurrence of the first event and type of event (death/disease relapse) were obtained through medical records of patients and interviews with close relatives. Death (due to illness) and relapse of disease (based on sputum culture) were considered as competing events.

Censored cases included: 1) all those patients (whether alive or in relapse) whom until the end of the study (June 2015) were followed up and after that period there were no records on their status and 2) patients with complete information of 10 years without having any relapse or death.

For estimation of survival of patients with pulmonary TB, competing risks model was used with regard to death and disease relapse as competing events. In addition to the 10-year survival estimation for patients with pulmonary TB, factors affecting CIF of death event and disease relapse were also evaluated. Significance level was considered as 5% and all analyses were performed using the STATA 11 software.

RESULTS

This study was done on 2,299 patients with treated pulmonary TB; 770 patients (33.49%) expired and 134 patients (5.83%) had disease relapse as the first event after treatment. Also, 1,395 patients (60.68%) were considered as censored cases; 1,178 patients (51.24%) were males and 3.91% were under the age of 20 years, 19.88% between 20-34 years, 16.11% between 35-49 years, 27.75% between 50-69 years and 32.32% over 70 years. Meanwhile, 17.36% were single, 67.46% were married, 3.09% were divorced and 12.09% were widowed.

Also, the results of this study showed that 44.80% were illiterate, 21.88% had elementary school education, 16.40% had middle school education, 11.57% had high school education and 5.35% had university education. The surveys showed that 728 patients (31.85%) were smokers and 150 patients (6.69%) were passive smokers. Moreover, 532 patients (23.27%) were drug abusers; 1,936 patients (84.21%) were Iranian nationals and 1,833 patients (79.77%) lived in urban areas. In this study, 421 patients (18.31%) had diabetes mellitus and 157 patients (6.83%) had AIDS. Also, 698 patients (30.39%) had comorbidities such as cancer, liver disorders, etc.

Also, the results of this study showed that there were 398 patients (27.95%) with adverse drug effects and 196 patients (8.95%) were imprisoned. In addition, 301 patients (13.12%) had extra pulmonary TB and 422 patients (18.48%) had history of contact with TB patients. Further surveys also showed that the number of family members of pulmonary TB patients was as follows: 194 patients (8.46%)

had 1 family member, 620 patients (27.04%) had 2 family members, 1,128 patients (49.19%) had 3-5 family members and 351 patients (15.31%) had more than 5 family members.

Estimation of CIF of death event and disease relapse in Table 1 showed that with passage of time, the probability of death event in patients with pulmonary TB increased. The probability of death event in patients with pulmonary TB was 0.56 one year after treatment and 0.82 and 0.8 at 5 and 10 years after treatment, respectively. In other words, 5 and 10 years after treatment the probability of death event as the first event was 82% and 88%, respectively. This shows that the probability of death event in the first 5 years after treatment is more than that in the second 5 years after treatment (Figure 1).

Based on the results of this study, the event of disease relapse occurred slower as compared to death and the probability of disease relapse increased during the 3 years after treatment in patients with pulmonary TB. In other words, the probability of disease relapse event is 0.05 in the first year after treatment and 0.10 in the third year after treatment; the probability of disease relapse event remains almost constant thereafter (Figure 1). In fact, as the first event, the probability of disease relapse event one year and three years after treatment is 5% and 10%, respectively.

While considering disease relapse and death as competing events, TB patients' survival estimation showed that the survival of these patients in the first, third, fifth and tenth year after treatment was 0.39, 0.14, 0.07 and 0.00, respectively. Thus, the probability that a patient with treated pulmonary TB does not relapse or die after 5 years is 7%; however, almost all patients showed disease relapse or expired after 10 years (Table 1).

Also, evaluating the effect of risk factors on CIF of death event and disease relapse revealed that patient's age, marital status, contact with TB patients, adverse effects of drugs, imprisonment and HIV positivity affect the CIF of death and variables of gender, marital status, imprisonment and HIV positivity are factors affecting CIF of disease relapse ($P < 0.05$).

More accurate surveys showed that variables of patient's age, marital status, adverse effect of drugs and HIV positivity increased the probability of death event and variables of TB contact and imprisonment reduced the probability of death event. The results also showed that variables of male gender, marital status and HIV positivity reduced the probability of relapse event and only imprisonment increased the probability of relapse event (Table 2).

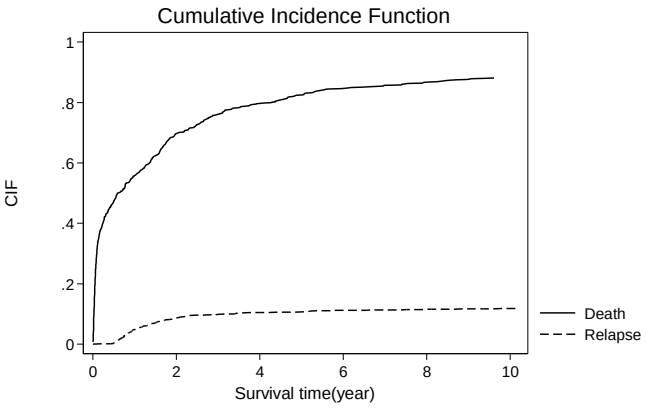

Figure 1. Cumulative incidence function (CIF) for death and relapse events

Table 1. Estimation of survival and cumulative incidence function (CIF) of death and relapse events (95% CI)

Time(years)	CIF $_{Death}$	CIF $_{Relapse}$	Survival
1	0.56(0.52,0.59)	0.05(0.03,0.06)	0.39
2	0.69(0.66,0.73)	0.09(0.07,0.11)	0.22
3	0.76(0.72,0.79)	0.10(0.08,0.12)	0.14
4	0.79(0.76,0.82)	0.10(0.08,0.12)	0.11
5	0.82(0.79,0.85)	0.11(0.08,0.13)	0.07
6	0.84(0.82,0.87)	0.11(0.09,0.13)	0.05
7	0.86(0.83,0.88)	0.11(0.09,0.14)	0.03
8	0.87(0.84,0.89)	0.11(0.09,0.14)	0.02
9	0.88(0.85,0.90)	0.11(0.09,0.14)	0.01
10	0.88(0.85,0.90)	0.12(0.09,0.14)	0.00

CI: Confidence interval.

Table 2. Effect of risk factors on cumulative incidence function (CIF) of death and relapse events

Factor	Category	CIF_{Death}		$CIF_{Relapse}$	
		β (SE)	P-value	β (SE)	P-value
Gender	Male/Female	0.29(0.17)	0.08	-0.80(0.36)	0.03
Age	-	0.01(0.01)	0.03	-0.02(0.01)	0.08
Marital Status	Married/Single	0.10(0.23)	0.67	0.23(0.55)	0.68
	Widow/Single	0.01(0.32)	0.00	-23.77(0.56)	0.00
	Divorced/Single	0.20(0.29)	0.48	-0.94(0.82)	0.25
Education	Primary/Illiterate	0.27(0.15)	0.06	-0.86(0.50)	0.09
	Secondary/Illiterate	0.38(0.23)	0.10	-0.55(0.51)	0.28
	High School/Illiterate	0.08(0.25)	0.75	-0.47(0.56)	0.40
	Higher education/ Illiterate	-0.68(0.49)	0.17	0.89(0.54)	0.10
Place of residence	Rural/Urban	0.07(0.16)	0.66	-0.08(0.42)	0.84
Nationality	Foreigners/Iranian	0.14(0.26)	0.59	0.18(0.47)	0.71
Family size	-	0.00(0.04)	0.88	0.07(0.07)	0.34
Drug Adverse effect	Yes/No	0.28(0.13)	0.04	-0.48(0.33)	0.14
Smoking	Yes/No	-0.02(0.18)	0.91	0.33(0.40)	0.41
Passive smoking	Yes/No	0.15(0.20)	0.44	-1.32(0.99)	0.19
Drug use	Yes/No	0.01(0.17)	0.93	-0.13(0.42)	0.76
Contact with TB patients	Yes/No	-0.43(0.19)	0.02	0.52(0.36)	0.15
Imprisonment	Yes/No	-0.62(0.27)	0.02	1.61(0.60)	0.01
Pulmonary TB	Yes/No	0.15(0.24)	0.53	-0.31(0.53)	0.56
Extra-pulmonary TB	Yes/No	0.01(0.17)	0.97	0.08(0.39)	0.83
Diabetes Mellitus	Yes/No	0.09(017)	0.58	-0.32(0.51)	0.54
HIV Positivity	Yes/No	0.71(0.28)	0.01	-1.65(0.62)	0.00
Comorbidities	Yes/No	0.09(0.14)	0.52	-0.02(0.34)	0.96

DISCUSSION

In this study, using competing risks method and taking into account the competing events of death and relapse, 10-year survival of patients with pulmonary TB during treatment was surveyed. Based on the results of this study, survival estimation of one, three and five-years in these patients during treatment was 39%, 14% and 7%, respectively. These values were less as compared with survival estimation in the first five-years in many studies conducted in other countries (25-29).

The present study is the first study on 10-year survival estimation of patients with TB based on the competing risks model in Iran and the world. Most of the conducted studies have been designed only considering death event and estimating patients' survival in the first few years after treatment, especially in the first five years (25-29).

Precise survival estimation in these patients during treatment requires recognition of several factors including demographic, clinical, diagnostic and therapeutic factors. Several statistical methods are available for estimation and evaluation of the effect of various factors on the survival of these patients; most of the researches have been conducted by survival standard models regardless of competing events (15-17). Generally, these models focused on death event only. But in many cases, certain events such as disease relapse occurred during the survey that affected the final results. Lack of attention to these competitive events and the time of their occurrence could overshadow the survey result and lead to bias in data analysis (18,19, 22).

Perhaps at first glance, use of competing risks model seems complex; however, this method has several

advantages over the standard methods. One of the advantages of the competing risks model is taking into account the competitive events such as disease relapse in study of survival of patients with pulmonary TB, which shows the effect of different variables on survival of patients. In other words, some variables can affect the death event only, some others only affect the disease relapse, while some affect both the death and disease relapse competing events. In fact, many factors affecting the survival of patients directly affect death event. But for other groups of variables, indirect effect on competitive events such as disease relapse, will affect the survival of patients. Certainly in this condition, analysis of results based on competing risks model is more accurate.

In the present study, the effect of different variables on the CIF of competing events of death and disease relapse based on competing risks model was evaluated. The results showed that patient's age, marital status, contact with TB patients, adverse effects of drugs, imprisonment and HIV positivity are factors affecting CIF of death and variables of gender, marital status, imprisonment and HIV positivity are factors affecting CIF of disease relapse. Variables of marital status, imprisonment and HIV positivity are effective on both competing events of death and disease relapse; in other words, they have both direct and indirect effects on survival of patients. Variables of patient's age, contact with TB patient and adverse effects of drugs are effective only on death event; thus, these variables have a direct impact on patient survival. These results are consonant with those of most studies done by standard models of survival; the reason being the direct impact of these variables on the survival of patients (25,27,29). Gender variable, however, is effective only on disease relapse event and has indirect impact on survival of patients. For the same reason in many conducted studies on patients' survival using standard models, the significance of gender effect on patient survival has not been mentioned (25-29).

Another advantage of competing risks model is that it shows interesting results in comparison to standard analysis. This model studies the effect of various variables on different events that patients might experience during the study and allows more accurate understanding of their effect on survival of patients. Accordingly, most studies have shown that marital status, imprisonment and HIV positivity are factors that affect death event and reduce the chance of patient survival (25,28). However, more detailed analyses based on the CIF in this study showed that variables of marital status, imprisonment and HIV positivity increased the probability of death event and reduced the probability of disease relapse event.

The use of competing risks model instead of the standard models of survival in study of patients with pulmonary TB leads to a better understanding of the natural course of disease; with the evaluation of factors that affect the probability of competing events such as death and disease relapse, more accurate estimation of survival in these patient is possible allowing selection of appropriate therapeutic strategies.

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