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TANAFFOS

Evaluations of Factors Affecting of Short-and Long-Time of Occurrence of Disease Relapse in Patients with Tuberculosis Using Parametric Mixture Cure Model: A Cohort Study

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Background: The success of treatment strategies to control the disease relapse requires determining factors affecting the incident short-time and long-time of disease relapse. Therefore, this study was aimed to identify the factors affecting of short-and long-time of occurrence of disease relapse in patients with tuberculosis (TB) using a parametric mixture cure model.

Materials and Methods: In this historical cohort study; the data was collected from 4564 patients with TB who referred to the Tuberculosis and Lung Diseases Research Center of Dr. Masih Daneshvari Hospital from 2005 to 2015. In order to evaluate the factors affecting of short-and long-time of occurrence of disease relapse, a parametric mixture cure model was used.

Results: In this study, the estimation of the annual incidence of TB relapse showed that the probability of recurrence in the first year is 1% and in the third and tenth years after treatment is 3% and 5%, respectively. In addition, the results of this study showed that the variables of residence, exposure to cigarette smoke, adverse effects of drug use, incarceration, and pulmonary and extra- pulmonary tuberculosis were the factors affecting the short-time recurrence of TB. The variables of drug use, pulmonary and extra- pulmonary tuberculosis, and also incarceration affected the long-term recurrence of this disease.

Conclusion: Cure models by separating factors affecting the short-time occurrence from the long-time occurrence of disease relapse can provide more accurate information to researchers to control and reduce TB relapse.

Key words: Tuberculosis; Relapse; Risk factors; Parametric mixture cure model

INTRODUCTION

Despite advances in tuberculosis (TB) treatment and control, the disease remains a major health issue in developing countries. The prevalence of TB depends on poor social and economic conditions, malnutrition, population growth, and a low level of education. The World Health Organization (WHO) estimates that one-third of the world's population is currently infected with TB. Worldwide, every 4 seconds, a person is infected with TB, and every 10 seconds, one dies from this disease (1). Without treatment, 25% of patients die within 2 years, 50% within 5 years, and 25% recover spontaneously. With medication for each person, 8% of patients die during treatment, 90% recover, and only 2% have a positive

sputum smear at the end of treatment. Tuberculosis relapse is the onset of the disease in a person who is considered to have improved and strongly depends on the quality of treatment (2,3).

In the period before chemotherapy, the incidence of relapse was very high, so that the annual growth rate of relapse was 43.4% in the first five years and 1.6% in the next five years, and after chemotherapy, this figure will be very low (4). Identifying the factors affecting the disease relapse is one of the methods used to control and reduce the recurrence of the disease. The study of factors affecting the disease relapse in patients with TB has been indicated that for some patients, relapse occurs during the study, and for many patients, it will not give even despite long-term follow-up. In fact, there are two distinct categories of patients in these studies. The first group is patients who are at risk of relapse and will experience this event within a reasonable time after treatment (short-time relapse event) and the second group is patients who are not exposed to relapse until the end of the study. They will also not experience a disease relapse (long-time relapse), which in the clinical term of these patients is considered cured (5,6).

The idea of having a long-term event or the existence of cured people while there is a lot of censorship in the data is an interesting and very practical idea. In fact, this idea separates some patients from the censored patients during the study and provides the conditions for examining the factors affecting the long-time occurrence of the desired event in these patients. Focusing only on the short-time of the disease relapse and identifying the factors affecting it can lead to a misunderstanding of the disease process and the selection of inappropriate strategies to control and reduce the disease relapse (7,8). In addition, for a health policymaker, the influence of a variable on the short-time or long-time the disease relapse is very important to decide to control the variable. Because some variables only influence the occurrence of the short-time or the long-time of disease relapse and others affect both. In order to study the effect of effective factors on the disease relapse, it is necessary to consider a model that can distinguish the factors affecting the short-time and long-time disease relapse, separately.

One of the methods that have been considered to differentiate the factors affecting short-time events from long-time events is the cure model (7,9,10). Cure models are divided into two general categories; mixture cure model and non-mixture cure model. In the mixture cure model, it is assumed that the community consists of two groups of heterogeneous patients, the first group is patients who are exposed to the event and will experience this event within a reasonable time, and the second group of patients may are not exposed to the intended event. Therefore, from the perspective of the cure model, a short-time event is considered for a percentage of patients and a long-time event for another percentage of patients. Of course, the fact that these patients are not exposed to the event does not mean that they do not experience the event until infinity. Rather, it is a statistical interpretation in the sense that they do not experience the event in question during the study. The word parametric mixture in these models is due to the fact that two statistical distributions are used to model the factors affecting the short-time and long-time occurrence of the desired event. Usually, to study the factors affecting the short-time occasion of the desired event, exponential parametric distributions, Weibull, Gamma, Log-normal, and Log-logistic, and to investigate the factors affecting the long-time occasion of the asked event, the Logistic link function is considered. Under appropriate conditions, this model is able to provide a more accurate interpretation of data to health researchers and policymakers in order to control and reduce the recurrence of TB. Therefore, the present study was aimed to evaluate the factors affecting of short-and long-time of occurrence of disease relapse in patients with TB referred to the Tuberculosis and Pulmonary Diseases Research Center of Dr. Masih Daneshvari Hospital using a parametric mixture cure model.

MATERIALS AND METHODS

In this study, the information of 4564 patients with TB who referred to the Tuberculosis and Lung Diseases Research Center of Dr. Masih Daneshvari Hospital from the beginning of 2005 to 2015 and was treated in the hospital archives based on a historical cohort study was examined. Study time in these patients after treatment and recovery, determination, and recurrence of the disease (based on sputum culture) were considered as the study event.

In order to follow the status of patients from the time to occurrence of disease relapse, data were collected through the patients' clinical records, and the last follow-up was performed by telephone for patients who had been discharged without a history of recurrence. Patients whose was alive until the end of the study without disease relapse and were not available after that, as well as patients whose information were complete and did not indicate any disease relapse until the end of the study, were also considered as cured people. For all patients, the effect of variables on gender, age, marital status, level of education, place of residence, nationality, family size, drug adverse effects, smoking, exposure to secondhand smoke (passive smoking), history of drug use, contact with a TB patient, imprisonment, pulmonary TB, extra-pulmonary TB, diabetes mellitus, HIV Positive, and comorbidities were evaluated for short-and long-time recurrence. A significance level of 5% was considered and data analysis was performed in STATA 14 software using the Kaplan-Meyer method and parametric mixture cure model (considering the Log-normal distribution for short-time recurrence and Logistic link function for long-time relapse).

RESULTS

This study was performed on 4564 patients with TB treated, in which 166 patients (3.64%) relapse occurred as the desired event after treatment and 4398 patients (96.36%) were considered as censored. Of these, about 94% of patients had a longer censorship time than the largest recurrence time, which is statistically defined as the cured patients (mean of cure time was 5±3/5 years). The results showed that 2282 patients (50.00%) were male, 20.04% single, 64.32% married, 13.29% widowed and 2.35% were divorced. The results of this study also indicated that 46.46% of patients were illiterate, 20.04% had primary education, 16.29% had middle school, 12.23% had high school education and 4.98% had a university education.

In the current study, 1282 patients (28.36%) were smokers and 433 patients (9.87%) were exposed to cigarette smoke (passives smoker). In addition, 938 patients (20.74%) had a history of drug use. 3623 patients (79.38%) had Iranian nationality and 3768 patients (82.67%) lived in urban areas. In this study, 247 patients (5.41%) were HIV Positive and 852 patients (18.67%) had diabetes mellitus. Also, 1305 patients (28.59%) had comorbidities such as cancer, liver disorders, etc. The results of this study indicated that 2323 patients (50.90%) had adverse drug effects and 352 patients (7.71%) were incarcerated. In addition, 745 patients (16.33%) had extra-pulmonary TB and 4135 patients (90.66%) had pulmonary TB, and 858 patients (18.80%) had TB. Further, in this study, the mean age and family size of patients were $51/78 \pm 21/47$ years and $3/81 \pm 2/10$ person, respectively (Table 1).

The present study also showed the annual estimate of relapse occurrence in TB patients based on the Kaplan-Meyer method. According to the results, the cure rate was very high, about 94%, and for a small percentage of patients recurrence of the disease was happened as an event during the study. This study estimated the annual probability of the disease relapse; the probability of recurrence of the disease in the first year was 1% and in the third, fifth, and tenth years after treatment was 3, 4, and 5%, respectively, which indicated a low probability of TB recurrence after the treatment (Figure 1).

Before using the cure model, model assumptions should be investigated. One of these hypotheses is to examine the presence of a significant percentage of cured patients in the community. In fact, the question is whether a significant percentage of patients are cured or not? However, in some cases, using clinical experience and biological evidence, it is proven that there are cured

patients. This assumption is defined based on the percentage of people whose censorship time is greater than the largest recurrence time, which in this study was about 94%, and it can be ensured that there were an acceptable percentage of the cured patients. However, we examined this hypothesis based on the test presented by Maller and Zhou; in which there was a condition for using the cure model, statistically. In this study, Maller and Zhou test for the adequacy of cured patients showed that at a significance level of 5%, the hypothesis of a sufficient percentage of cured patients was confirmed.

Table 1. Demographic and clinical characteristic of TB patients

Factors	Category	N (%)	Mean(SD)
Gender	Female	2282(50.00)	
	Male	2282(50.00)	
Age	-	-	51.78(21.47)
Marital Status	Single	914(20.04)	
	Married	2933(64.32)	
	Widow	606(13.29)	
	Divorced	107(2.35)	
Education	Illiterate	2119(46.46)	
	Primary	914(20.04)	
	Middle	743(16.29)	
	High School	558(12.23)	
	University education	227(4.98)	
place of residence	Rural	790(17.33)	
	Urban	3768(82.67)	
Nationality	Iranian	3623(79.38)	
	Non-Iranian	941(20.62)	
Family size	-	-	3.81(2.10)
Adverse effect	No	2241(49.10)	
	Yes	2323(50.90)	
Smoker	No	3239(71.64)	
	Yes	1282(28.36)	
Passives smoker	No	3953(90.13)	
	Yes	433(9.87)	
Drug user	No	3585(79.26)	
	Yes	938(20.74)	
TB contact	No	3706(81.20)	
	Yes	858(18.80)	
Imprisoned	No	4212(92.29)	
	Yes	352(7.71)	
Pulmonary TB	No	426(9.34)	
	Yes	4135(90.66)	
Extra-Pulmonary	No	3816(83.67)	
	Yes	745(16.33)	
Diabetic Mellitus	No	3712(81.33)	
	Yes	852(18.67)	
HIV Positive	No	4317(94.59)	
	Yes	247(5.41)	
Co morbidities	No	3259(71.41)	
	Yes	1305(28.59)	

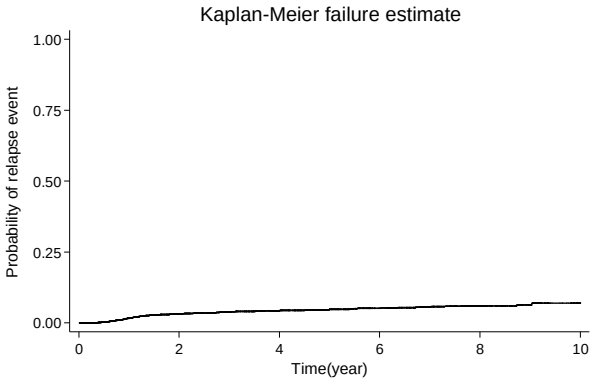

Figure 1. The Kaplan-Meier estimate of the probability of relapse event in TB patients

The second hypothesis is that the follow-up time is sufficient and the presence of cured patients is not due to the short follow-up time, which in this study with about 10 years of follow-up of patients with tuberculosis, this assumption was also established. However, the study of adequate follow-up time based on Maller and Zhou test also showed that at the significance level of 5%, the assumption of adequate follow-up time was also established. Therefore, statistically, there were two necessary presuppositions for the cure model.

In this study, using the parametric mixture cure model, considering the Log-normal distribution for short-time relapse and the Logistic link function for long-time relapse, the results of factors affecting short-time and long-time relapse were investigated. The results of this analysis showed that the variables of residence, exposure to cigarette smoke, drug use, adverse effects, imprisonment, and having pulmonary and extra-pulmonary TB were the factors affecting the short-time relapse. So that the variables of residence (urban), exposure to cigarette smoke, adverse effects, drug use, and imprisonment increased the risk of short-time relapse, and variables of pulmonary and extra-pulmonary TB reduced the risk of short-time recurrence.

Also, the evaluation of the factors affecting the long-time recurrence of the disease showed that the variables of drug use, pulmonary and extra-pulmonary TB, and the variables of imprisonment were effective on the long-time

recurrence of the disease. The study analysis showed that the variables of drug use, pulmonary TB, and extra-pulmonary TB reduced the risk of long-time recurrence of the disease and increased the chances of patients recovering, and conversely, the variable of incarceration of long-time recurrence increased the disease and decreased the chances of patients recovering (Table 2).

DISCUSSION

Evaluation of the factors affecting rare events such as disease relapse is not possible without considering the high percentage of cured patients who do not experience a relapse during the study and often leads to an ambiguous understanding of the mechanism of disease relapse. Despite the extensive studies that have been done on TB so far, researchers do not have comprehensive information on the factors that affect the relapse of the disease (11-15).

Due to attention to the occurrence of death and also because of the low incidence of disease relapse, it is less important (11-18). Based on the results of this study, the annual incidence of TB relapse was very low and was estimated at 5% for 10 years after treatment, which indicates that the recurrence of the disease in patients with tuberculosis is rare. Other studies have estimated the recurrence rate of TB at about 7% for Iran in the ten years after treatment (4).

Table 2. The effect of risk factors on short-time and long- time disease relapse event based on parametric mixture cure model.

Factor	Category	Parametric mixture cure Model	
		Short-time disease relapse event	Long-time disease relapse event
		β(SE)	β(SE)
Gender	Male/Female	-0.47(0.40)	-0.44(0.36)
Age	-	0.01(0.01)	0.01(0.01)
Marital Status	Married/Single	0.42(0.45)	0.11(0.51)
	Widow/Single	0.85(0.78)	0.09(0.81)
	Divorced/Single	-0.75(0.49)	0.07(0.73)
Education	Primary/Illiterate	-0.76(0.42)	-0.43(0.39)
	Middle/Illiterate	-0.31(0.44)	0.04(0.44)
	High School/Illiterate	-0.18(0.56)	-0.31(0.55)
	University education/ Illiterate	0.51(0.89)	0.09(0.87)
Residence	Urban /Rural	0.89(0.43)*	-0.67(0.45)
Nationality	Non-Iranian /Iranian	0.06(0.49)	0.46(0.52)
Family size	-	0.09(0.08)	0.12(0.10)
Adverse effect	Yes/No	0.85(0.42)*	-0.17(0.43)
Smoker	Yes/No	-0.16(0.44)	0.39(0.38)
Passives smoker	Yes/No	3.05(0.67)†	3.16(2.15)
Drug user	Yes/No	1.42(0.52)*	-0.17(0.43)*
TB contact	Yes/No	0.40(0.33)	0.34(0.35)
Imprisoned	Yes/No	2.27(0.48)†	4.14(1.38)†
Pulmonary TB	Yes/No	-2.80(0.75)†	-3.07(0.74)†
Extra-Pulmonary	Yes/No	-2.03(0.67)†	-3.18(0.78)†
Diabetic Mellitus	Yes/No	0.23(0.41)	0.19(0.43)
HIV Positive	Yes/No	-0.09(0.42)	-0.42(0.79)
Co morbidities	Yes/No	-0.32(0.36)	-0.17(0.34)

*P-value< 0.05 †P-value< 0.005 Cure fraction estimation=0.94

The low incidence of relapse may be attributed to the success of treatments of TB patients because clinical studies also show that disease relapse is highly dependent on the quality of treatment and strategies that specialists consider for patients (4,15).

In studying the factors affecting the occurrence of rare events such as disease relapse of TB patients, researchers often encounter two groups of patients susceptible and non-susceptible to the recurrence of the disease during the study. The first group of patients who experience a recurrence of the disease during the study and have a short-time recurrence of the disease, and the second group of patients who are not exposed to the relapse and do not experience a recurrence until the end of the study. In statistical terms, these patients have a long-time recurrence of the disease and are considered clinically cured (5,6). Focusing only on the short-time occurrence of events such as relapse not only deprives the researcher of the opportunity to study the factors influencing the long-time occurrence but also leads to incorrect inferences about the disease relapse and consequently the failure of treatment strategies to control relapse.

Various statistical methods have been designed to study the factors affecting events such as death and recurrence of the disease in TB patients, the most common of which is the Cox regression model (11,15,16). In studies where numerous patients do not experience the desired event at the end of the study, there are no conditions for using common methods to investigate the factors affecting the event (7,9). In these circumstances, a model is needed that is able to distinguish the factors affecting the short-time and long-time recurrence of the disease. The model designed for this purpose is cure models. These models are used by many researchers in various fields of medicine (8,19). The use of cure models has advantages in studying the factors affecting events such as disease recurrence in patients with TB. One of the advantages of the cure model is to consider long-time events for patients who are not exposed to recurrence during the study, which makes a difference in the impact of factors affecting the short-and long-time of occurrence of disease relapse. So that some variables can affect both short-time and long-time recurrence of the disease and others only influence on the long-time or short-time disease relapse. In fact, another advantage of this model in distinguishing the effect of factors affecting the short-time and long-time recurrence of the disease is related to the health policy and control of risk factors in the community.

In this study, considering the distribution of Log-normal for short-time recurrence and Logistic link function for long-time recurrence, the factors affecting short-and long-time recurrence were investigated using a parametric mixture cure model. The results of this study showed that the variables of drug use, pulmonary and extra-pulmonary TB, and imprisonment were effective on both short-and long-time recurrence of the disease. The variables of pulmonary and extra-pulmonary TB reduced the risk of short-and long-time recurrence of the disease and the variable of incarceration increased the risk of short-and long-time recurrence of the disease. The variable of drug use also increased the risk of short-time relapse of the disease and reduced the risk of long-time relapse of the disease. The results of this study also showed that the variables of residence (urban), having adverse effects, and exposure to cigarette smoke were effective only on the short-time relapse of the disease and all increased the risk of short-time relapse of the disease.

Some studies have suggested other factors such as incomplete treatment of the disease, misdiagnosis, voluntary discharge, nosocomial infection, temporary discharge, and complications of the disease were known as the reasons for disease recurrence and failure of treatment strategies (5,6,20). However, the effect of these factors has only been evaluated on the short-time occurrence, and it is not clear that these factors affect the long-time occurrence of disease relapse and healing of patients. By improving

treatment methods and improving the level of health and quality of life of patients with TB, the likelihood of events such as relapse, death, and refractory TB is reduced in these patients; hence the use of a cure model is appropriate in data analysis for patients with TB.

CONCLUSION

Cure models have the ability to be used in appropriate conditions to analyze the factors affecting the occurrence of events such as relapse in patients with TB and to distinguish the factors affecting short-and long-time events. This statistical model is also able to provide a more accurate interpretation of data to health researchers and policymakers to control and reduce the recurrence of TB.

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