SURVIVAL ANALYSIS AND RISK FACTORS FOR DEATH IN TUBERCULOSIS PATIENTS: EHU OF ORAN (MAY 2014 - JANUARY 2016), ALGERIA

DJOUAHRA Idris
Maitre Assistant au Centre Universitaire de Tipaza
Doctorant en Economie et Statistique Appliquée à l'Ecole Nationale Supérieure de Statistique et d'Economie Appliquée.
idris.djouahra@gmail.com

BENAMIROUCHE Rachid
Professeur à l'Ecole Nationale Supérieure de Statistique et d'Economie Appliquée.
rbena2002@hotmail.com

KADRI Wafa
Pneumologue au sein de l'Etablissement Hospitalier Universitaire d'Oran (EHU).
waf.kadri@gmail.com

ABSTRACT

The objective of this study is to identify risk factors susceptible to cause survival variations as well as death among tuberculosis patients during hospitalization period. It consists of a prospective cohort study for which tuberculosis patients registered for treatment at the Etablissement Hospitalier Universitaire (EHU) of Oran have been followed up to death. Survival comparison between treatment categories was done using Kaplan Meier analysis and Wilcoxon test. Cox proportional hazards model was used for multivariate analysis. There was a significant difference in survival among treatment categories (Wilcoxon statistic = 8.6, p-value = 0.013). The resulting significant risk factors of Cox model susceptible to cause death among tuberculosis patients and their corresponding hazard ratios (HR) are HIV infection (HR = 4.233), alcohol (HR = 4.872), smoking (HR = 4.349) and female gender (HR = 3.818).

Key words: Tuberculosis, survival, death, Cox

1. INTRODUCTION

Tuberculosis continues to be among the most important causes of death from infectious disease all over the world. Despite the recent advances in tuberculosis care and the reduced mortality rate (has dropped 47% since 1990), tuberculosis remains one of the world's biggest threats by killing 1.6 million people in 2015 (1). Like many developing countries, tuberculosis in Algeria constitutes one of the leading causes of morbidity. According to the National institute of public health (INSP [1]) report of 2015, more than 40,000 cases of tuberculosis have been registered in 2015 over all the national territory. Directly Observed Treatment Short-course (DOTS) strategy has considerably improved the quality of diagnosis and treatment results in Algeria by achieving an estimated cure rate of 75%. In spite of this, mortality rates among hospitalized tuberculosis patients are reaching 20% and remain a major concern that needs to be taken into consideration in order to reduce them (INSP, 2015). According to pneumo-phthisiology specialists of Algeria, the remarkable death rates are not caused by tuberculosis disease itself but rather by other suspected cofactors that would enhance the chances of death of patients. The hypothesis of our work suggests that variables from socio-demographic profile and other co-infections are the leading factors causing death among tuberculosis patients under therapy. In this paper, we are conducting survival analysis on tuberculosis patients and compare survival fluctuations among the different DOTS treatment categories in order to identify the principal factors susceptible to cause survival variations as well as death among tuberculosis patients during the hospitalization period.

2. Materials and Methods

Oran is situated in the north-west of Algeria (413 kilometers west of the capital; Algiers) with a population of about 2 million inhabitants. The DOTS strategy was initiated in Oran since 1982. Since that date, the infectious diseases surveillance

[1] Institut National de Santé Publique.

unit of Oran is registering increasing case detection rates, reaching 60 per 100,000 of the population of Oran in 2014 and a cure rate of 78% in the same year (INSP, 2015).

2.1 Study design

The planned study period starts on May 1st 2014 and ends on January 31th 2016. The present work consists of a prospective cohort study conducted on patients registered for treatment on DOTS from May 1st 2014 to April 30th 2015 at the Etablissement Hospitalier Universitaire (EHU) of Oran. The standard anti-tuberculosis therapy takes a period of 6 months. However, in some severe cases, anti-tuberculosis therapy may be extended to 9 months. Since some patients might be registered for treatment on April 30th 2015, we took into consideration the possibility that their cases might be severe and then they might be followed-up for 9 months, till January 31th 2016 (time of study period ends). The DOTS treatment categories are as following (2): Category 1 includes all new cases of pulmonary tuberculosis that are sputum smear positive, serious smear negative pulmonary tuberculosis and serious extra-pulmonary tuberculosis disease. Category 2 includes patients who had relapses, treatment failures or have had previous anti-tuberculosis treatment. Category 3 is prescribed to new patients with non-serious smear negative and extra-pulmonary tuberculosis. The anti-tuberculosis medicines (3) and their corresponding brand names set in brackets are: H: isoniazid (Rimifon); R: rifampicin (Rofact); Z: pyrazinamide (Pirilène); E: ethambutol (Etibi) and S: streptomycin (streptomycin). In Algeria, the standardized anti-tuberculosis regimens are set by the ministry of health, population and hospital reform based on circular number 919 of august 5th, 2002. These regimens which are the association of the previously mentioned medicines are given by: 2SRHZ/4RH for category 1; 2SRHZE/1RHZE/5RHE for category 2 and 2RHZ/4RH for Categories 3, where numbers that precede different medicines indicate the period, in months, of the use of those medicines. At initiation of treatment, patients were diagnosed whether they are co-infected with human immunodeficiency virus (HIV), hepatitis B virus

(HBV) or hepatitis C virus (HCV), since initial co-infection with one of these viruses or developing it during anti-tuberculosis therapy may constitute a leading risk factor having an impact on tuberculosis treatment outcomes (4-7). Also, Category of treatment and body weight at initiation of treatment were recorded for all patients. Using a questionnaire, patients were asked about socio-demographic profile variables including gender, age category, instruction level, smoking habits and drinking habits, as done in similar studies (8, 9). Patients were followed up from the initiation of treatment till the occurrence of the event of interest (death) or till censorship (success, default or failure), and survival times for all patients were recorded.

2.2 Statistical analysis

Data analysis was performed using "Survival" package of R software (version 3.3.1). Percentages were used to describe the general characteristics of tuberculosis patients. Kaplan Meier analysis and Wilcoxon test were used to draw survival plots corresponding to different treatment categories and to compare between them. For the identification of socio-demographic variables as well as co-infections susceptible to cause survival fluctuations as well as death among tuberculosis patients during anti-tuberculosis therapy, a multivariate analysis was conducted using Cox proportional hazards model. This latter is defined by the following formula (10):

$$h(t, X) = h_0(t) \times e^{(\sum_{i=1}^{p} \beta_i X_i)}$$

Where:

- $X_1, X_2, \ldots\ldots, X_P$: are the covariates included in the analysis;
- $h(t, X)$: is the hazard at time t with a given set of covariates.
- $h_0(t)$: is the baseline hazard.

Applications of Kaplan Meier analysis and Cox modeling are illustrated in numerous studies related to survival of tuberculosis, and they were the basis behind choosing those methods in our analysis (11-13).

Based on graphical method, cumulative hazard function was used to evaluate proportional hazards assumption.

3. Results

From May 1st 2014 to April 30th 2015, 268 tuberculosis patients have been registered for treatment on DOTS. We describe the general characteristics of patients under treatment in Table 1. Among the 268 followed up patients, 39.92% belonged to category 1, 13.43% belonged to category 2, and 46.64% belonged to category 3. The study sample revealed that 55.22% of patients were females. For age variable, it was the category of patients aged between 20 and 40 years old that dominated the sample with a percentage of 39.18%, whereas only 11.19% of patients exceed 60 years old. Social variables indicate that 89.55% of patients were literate, 40.67% were smokers and 23.13% were alcoholics. At initiation of treatment, 73.50% of patients weighed more than 35 kg. With a percentage of 7.46% of patients, HIV was found to be the most common co-infection among tuberculosis patients followed by HBV and HCV with percentages of 1.87% and 1.49% respectively. For our patients, success rate was 78.35% and death rate was 07.09%.

Kaplan Meier analysis (Table 2) showed that marginal death rates recorded in the three categories were 09.34% in category 1, 16.66% in category 2 and 2.4% in category 3. The analysis of Table 2 gives opportunity for patients of category 3 to have the highest survival and for those of category 2 to have the lowest one. Probabilities of survival at the end of the intensive phase of treatment were 0.943, 0.886 and 0.983 for categories 1, 2 and 3 respectively, and those at the end of the continuation phase and till all patients are censored were 0.902, 0.820 and 0.974 for the same categories respectively, too.

According to Figure 1, we notice a gap separating survival plots corresponding to the three treatment categories, indicating a significant difference in survival between those categories. At 5% degree of significance, this difference was

confirmed using the statistical test [Wilcoxon statistic = 8.6 on 2 degrees of freedom, P-value = 0.013].

Results concerning multivariate analysis are presented in Table 3. P-values and Z-statistics results of different variables showed that gender, smoking habits, alcoholic habits and HIV infection are the statistically significant variables having an impact on survival fluctuations and causing death among tuberculosis patients. Results corresponding to hazard rations (HR) indicate that HIV infected patients are 4.233 times more susceptible to death compared to patients who are not HIV infected. Alcoholics are 4.872 times more susceptible to death compared to non-alcoholics. Smokers are 4.349 times more susceptible to death compared to non-smokers and finally, females are 3.818 times more susceptible to death compared to males.

Evaluation of proportional hazards assumption revealed that hazards corresponding to each significant variable on Cox model appear to be proportional (see Figures 2, 3, 4 and 5).

4. Discussion

The small difference noticed between survival probability recorded at the end of the intensive phase of treatment and that recorded at the end of the continuation phase for each treatment category is due to the fact that the majority of deaths happened during the intensive phase of treatment (first 2 months). This latter was the most critical period for the survival of patients in the different categories since it counts for 63.15% of the total number of deaths. According to pneumo-phthisiology specialists of the Etablissement Hospitalier Universitaire of Oran, this may be explained by the fact that tuberculosis disease is very severe and serious during its earlier phases. The highest rate of death recorded in category 2 is caused by defaults, failures and relapses registered in that category. Taking treatment irregularly and incompletely represents a major risk factor for death in tuberculosis patients (14). Oran is one of the cities of the country where HIV virus is a growing pandemic with 353 cases of AIDS recorded in 2014 and an average of 5 to 8 new

cases of HIV per week registered by the AIDS screening center and sexually transmitted diseases of Oran. Studies investigating the impact of HIV infection on the outcome of treatment and survival of tuberculosis patients as well as those assessing the association between tuberculosis and HIV disease progression showed that mortality related to HIV is high during anti-tuberculosis therapy (15, 16). Because of the lower prices of alcohol from one side, and the easiness found in reaching it from another side, drinking habits are very prevalent among Oranian people (17). This gives opportunity to have a lot of number of drinkers among both people with and without tuberculosis. Alcohol and its excessive consumption have been well documented as strong risk factors increasing the incidence of tuberculosis (18). Smoking habits are also very common among the Oranian society, and all age categories are concerned even at the level of the primary school. According to a survey on smoking conducted by a medical team of the pulmonology department at the Etablissement Hospitalier Universitaire (EHU) of Oran (2014), nearly 88% of smokers of Oran are aged between 15 to 30 years old. Also, according to a study conducted by the service of the school health of the province between 2014 and 2015, around 9% of primary school students, 13% of middle school students and 21% of high school students in Oran are smokers. All this illustrates the large extent of smoking culture among Oranian people since the childhood. Smoking has been well documented to be associated with risk of dying of tuberculosis as well as the risk of development of more severe forms of the disease (19, 20). In contrast to our findings, another study revealed that smoking was only associated with radiographic manifestations of pulmonary tuberculosis but not with death among pulmonary tuberculosis patients (21).

Gender disparities in tuberculosis outcomes remain controversial worldwide (22-24). A bivariate analysis conducted in parallel revealed that two thirds of our HIV co-infected patients are females. Since HIV infection was found to be a risk factor for death among tuberculosis patients, the interaction effect between variables may play a big role in outbalancing the risk of death to females rather than to males.

Also, the suggested interaction effect between female gender and HIV infection is due to the fact that the Etablissement Hospitalier Universitaire (EHU) of Oran is still receiving many cases of women who are sex workers. This gives opportunity to those women to have more chances of HIV infection, and consequently more risk of death from tuberculosis. In contrast to our findings, inconsistent reported results revealed that default from treatment as well as death from tuberculosis are more associated with males than females (25, 26). Also, other studies showed that there are no significant differences between males and females regarding treatment outcomes (27, 28).

The hypothesis suggesting that the remarkable death rates are not caused by tuberculosis disease itself among tuberculosis patients is now confirmed. HIV infection, smoking, alcohol and female gender are substantially the principal risk factors constituting the socio-demographic profile and co-infection causing death among tuberculosis patients.

5. CONCLUSION:

Our study's outcomes matched with the medical theory and reflected at somehow the characteristics of Oran regarding people's smoking and alcoholic habits. By ensuring regularity and completion of treatment, deaths, relapses and failures may considerably be lessened. It would be interesting to study connections between the different variables in the context of a systemic approach in order to well control the chain of interactions leading to death in tuberculosis patients.

6. ACKNOWLEDGEMENTS:

Our acknowledgements to all members of the pneumo-phthisiology service of the Etablissement Hospitalier Universitaire (EHU) of Oran for their great collaboration during the study period.

Table 1 : Characteristics of tuberculosis patients on DOTS [a] program

Variable		Number	Percentage (%)
Gender	Females	148	55.22
	Males	120	44.77
Age	< 20 yrs [e]	61	22.76
	[20 - 40[yrs	105	39.18
	[40 - 60[yrs	72	26.87
	> 60 yrs	30	11.19
Instruction level	literate	240	89.55
	Illiterate	28	10.45
Weight at initiation of treatment	> 35 Kg	197	73.5
	< 35 Kg	71	26.49
Smoking habits	Smoker	109	40.67
	Non-smoker	159	59.33
Drinking habits	Drinker	62	23.13
	Non-drinker	206	76.87
HIV [b]	Infected	20	07.46
	Non infected	248	92.54
HBV [c]	Infected	5	1.87
	Non infected	263	98.13
HCV [d]	Infected	4	1.49
	Non infected	264	98.51
Category of treatment	1	107	39.92
	2	36	13.43
	3	125	46.64
Treatment results	Success	210	78.35
	Death	19	07.09
	Default	23	08.58
	Failure	16	05.97

DOTS[a]: Directly observed treatment short course, HIV[b]: human immunodeficiency virus, HBV[c]: hepatitis B virus, HCV[d]: hepatitis C virus, yrs[e]: years.

Table 2 : Kaplan Meier analysis of tuberculosis patients corresponding to the three DOTS categories

Cat [a]. of treatment	Time (Months)	Nbr [b]. at risk	Nbr. of deaths	Pr [c]. of survival	Pr. of death
Cat 1	1	107	3	0.972	0.028
	2	100	3	0.943	0.057
	3	95	1	0.933	0.067
	4	92	2	0.913	0.087
	6	87	1	0.902	0.098
Cat 2	1	36	1	0.972	0.028
	2	34	3	0.886	0.114
	3	30	1	0.857	0.143
	8	23	1	0.820	0.180
Cat 3	1	125	0	1.000	0.000
	2	118	2	0.983	0.017
	5	109	1	0.974	0.026

Cat [a]: category, Nbr [b]: number, Pr [c]: probability.

Table 3 : Cox proportional hazards model of tuberculosis patients on DOTS

Variables	RC [g] ± SD	HR [h] [95% CI]	Z-stat	P-value
Cat [a] 1 vs. Cat 3	0.021 ± 0.875	1.021 [0.190-5.481]	0.001	0.980
Cat 2 vs. Cat 3	0.915 ± 0.859	2.497 [0.464-13.435]	1.136	0.287
Females vs. Males	1.340 ± 0.630	**3.818 [1.111-13.128]**	**4.521**	**0.033**
[20 - 40[yrs [b] vs. < 20 yrs	-1.375 ± 1.470	0.253 [0.015-4.738]	-0.940	0.349
[40 - 60[yrs vs. < 20 yrs	1.241 ± 1.124	3.462 [0.354-29.150]	1.100	0.269
> 60 yrs vs. < 20 yrs	1.231 ± 1.213	3.426 [0.318-35.452]	1.010	0.310
Illiterate vs. Literate	1.011 ± 0.652	2.749 [0.105-1.308]	1.550	0.120
< 35 kg vs. >= 35 kg weight	1.032 ± 0.631	2.806 [0.815-9.665]	2.674	0.102
Smoker vs. Non smoker	1.470 ± 0.715	**4.349 [1.009-16.174]**	**2.060**	**0.039**
Alcoholic vs. Non alcoholic	1.583 ± 0.556	**4.872 [1.457-12.577]**	**2.850**	**0.004**
HIV [c] inf [d] vs. Non HIV inf	1.443 ± 0.725	**4.233 [1.053-17.185]**	**1.990**	**0.046**
HBV [e] inf vs. Non HVB inf	1.400 ± 1.084	4.056 [0.030-1.922]	1.290	0.196
HCV [f] inf vs. Non HVC inf	0.349 ± 1.006	1.418 [0.106-5.446]	0.350	0.728

Cat [a]: category, yrs [b]: years, HIV [c]: human immunodeficiency virus, inf [d]: infection, HBV[e]: hepatitis B virus, HCV [f]: hepatitis C virus, RC [g]: regression coefficient, HR [h]: hazard ratio.
Values in bold are significant.

Figure 1: Kaplan Meier survival plots

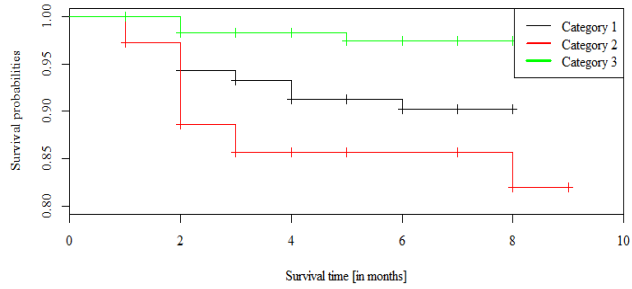


Figure 2: Log of Cumulative Hazard Function for HIV

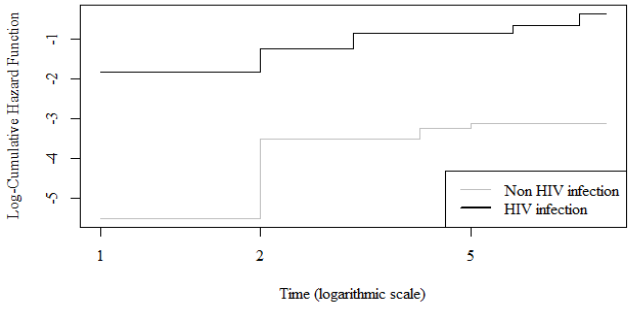


Figure 3: Log of Cumulative Hazard Function for Drinking

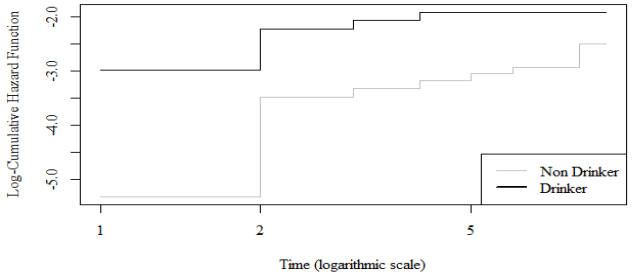


Figure 4: Log of Cumulative Hazard Function for Smoking

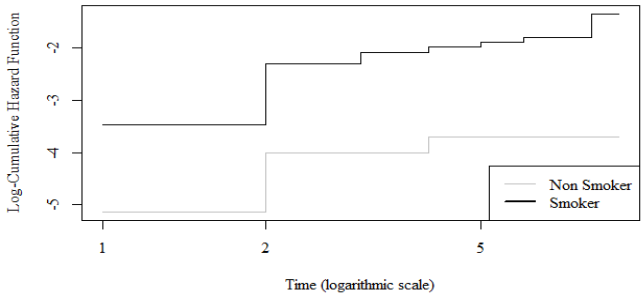
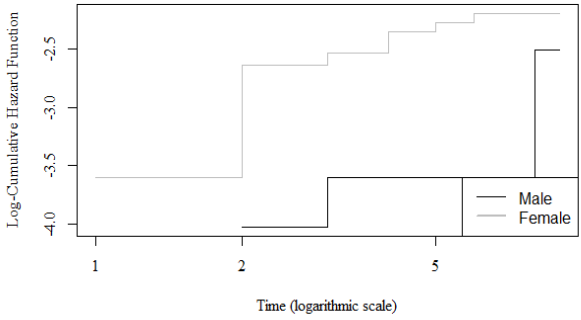


Figure 5: Log of Cumulative Hazard Function for Gender



REFERENCES:

1. Tuberculosis, World Health Organization, Fact sheet N°104, 2016.
2. A Handbook for National Tuberculosis Control Programmes, World Health Organization; 2008, P 51.
3. A Handbook for National Tuberculosis Control Programmes, World Health Organization; 2008, P 25.
4. Chien (JY), Huang (RM), Wang (JY), Ruan (SY), Yu (CJ), Yang (PC). *Hepatitis C virus infection increases hepatitis risk during anti-tuberculosis treatment*. Int J Tuberc Lung Dis 2002; 14(5): 616–621.
5. Rodríguez (M), Antela (A), Prieto (A), Otero (E), Molina (E), Varo (E). *Tuberculous hepatic abscess appearing after liver transplantation in a patient*

with human immunodeficiency virus and hepatitis B and C virus co-infection. Transpl Infect Dis 2001; 13(5): 515-519.

6. El-Sony (AL), Khamis (AH), Enarson (DA), Baraka (O), Mustafa (SA), Bjune (G). *Treatment results of DOTS in 1797 Sudanese tuberculosis patients with or without HIV co-infection*. Int J Tuberc Lung Dis 2002; 6(12):1058–1066.
7. Madhi (SA), Huebner (RE), Doedens (L), Aduc (T), Wesley (D), Cooper (PA). *HIV-1 co-infection in children hospitalised with tuberculosis in South Africa.* Int J Tuberc Lung Dis 2000; 4(5): 448–454.
8. de Fátima Pessoa Militão de Albuquerque (M), Batista (JAL), de Alencar Ximenes (RA), Carvalho (MS), Diniz (GT), Rodrigues (LC). *Risk factors associated with death in patients who initiate treatment for tuberculosis after two different follow-up periods*. Rev Bras Epidemio 2009; 12(4): 513-522.
9. Pardeshi (G). *Survival analysis and risk factors for death in tuberculosis patients on directly observed treatment-short course.* Indian J Med Sci 2009; 63(5):180-186.
10. Cox (DR). *Regression model and life tables.* J Royal Stat Soc 1972; 34(B): 187-220.
11. Balabanova (Y), Radiulyte (B), Davidaviciene (E), Ooper ®, Ignatyeva (O), Nikolayevskyy (V), Drobniewski (FA). *Survival of drug resistant tuberculosis patients in Lithuania: retrospective national cohort study*. BMJopen 2011: 000351.
12. Oursler (KK), Moore (RD), Bishai (WR), Harrington (SM), Pope (DS), Chaisson (RE). *Survival of Patients with Pulmonary Tuberculosis: Clinical and Molecular Epidemiologic Factors*. CID 2002 ; 34 : 752-759.
13. Ajagbe (OB), Kabair (Z), O'Connor (T). *Survival Analysis of Adult Tuberculosis Disease.* PLOS ONE 2014; 9(11) e112838: 1-10.
14. Kolappan (C), Subramani (R), Kumaraswami (V), Santha (T), Narayanan (PR). *Excess mortality and risk factors for mortality among a cohort of TB patients from rural south India*. Int J Tuberc Lung Dis 2008;12: 81-86.

15. Van den Broek (J), Mfinanga (S), Moshiro (C), O'Brien (R), Mugomela (A), Lefi (M). *Impact of human immunodeficiency virus infection on the outcome of treatment and survival of tuberculosis patients in Mwanza, Tanzania*. Int J Tuberc Lung Dis 1998; 2(7): 547–552.
16. Badri (M), Ehrlich (R), Wood (R), Pulerwitz (T), Maartens (G). *Association between tuberculosis and HIV disease progression in a high tuberculosis prevalence area.* Int J Tuberc Lung Dis 2001; 5(3): 225–232.
17. Riad (A). *Consommation d'alcool en Algérie entre tabou et hypocrisie ? : A Oran, les bars sont toujours ouverts*. Réflexion. November 3ed 2013. P5.
18. Kuznetsov (VN), Shelygin (KV), Grjibovski (AM), Mariandyshev (AO), Johansson (E), and Bjune (GA). *Incidence of Tuberculosis and Associations with Indicators of Alcohol Consumption in Three Regions of Northwest Russia in 1975–2009: A Time-Series Analysis*. Journal of Environmental and Public Health 2013.
19. Gyawali (N), Gurung (R), Poudyal (N), Amatya (R), Shrestha (R), Khanal (LK), Timilsina (S), Bhattacharya (SK). *Tobacco and alcohol: The relation to pulmonary tuberculosis in household contacts*. Nepal Med Coll J 2012; 15(2): 125-128.
20. Hassmiller (KM). *The association between smoking and tuberculosis.* Salud Publica Mex 2006;48 :S201-S216.
21. Wang (JY), Hsueh (PR), Jan (IS), Lee (LN), Liaw (YS), Yang (PC), Luh (KT). *The effect of smoking on tuberculosis: different patterns and poorer outcomes.* Int J Tuberc Lung Dis 2007; 11(2): 143–149.
22. Yamasaki-Nakagawa (M), Ozasa (K), Yamada (N), Osuga (K), Shimouchi (A), Ishikawa (N), Bam (DS), Mori (T). *Gender difference in delays to diagnosis and health care seeking behaviour in a rural area of Nepal*. Int J Tuberc Lung Dis 2001; 5: 24–31.

23. Weiss (M), Somma (D), Abouihia (A). *Gender and tuberculosis: cross-site analysis and implications of a multi-country study in Bangladesh, India, Malawi and Columbia*. WHO 2006; ref: TDR/SDR/SEB/RP/061.
24. Karim (F), Ahmed (F), Begum (I), Johansson (E), Diwan (VK). *Female-male differences at various clinical steps of tuberculosis management in rural Bangladesh*. Int J Tuberc Lung Dis 2008; 12: 1336–1339.
25. Faustini (A), Hall (AJ), Mantovani (J), Sangalli (M), Perucci (CA). *Treatment outcomes and relapses of pulmonary tuberculosis in lazio, Italy, 1999–2001: a six-year follow-up study*. Int J Infect Dis 2008; 12: 611– 621.
26. Jiménez-Corona (ME), García-García (L), DeRiemer (K), Ferreyra-Reyes (L), Bobadilla-del-Valle (M), Cano-Arellano (B), Canizales-Quintero (S), Martínez-Gamboa (A), Small (PM), Sifuentes-Osornio (J), Ponce-de-León (A). *Gender differentials of pulmonary tuberculosis transmission and reactivation in an endemic area*. BMJ 2006; 61: 348–353.
27. Belo (MT), Luiz (RR), Hanson (C), Selig (L), Teixeira (EG), Chalfoun (T), Trajman (A). *Tuberculosis and gender in a priority city in the state of Rio de Janeiro, Brazil*. J Bras Pneumol 2010; 36: 621–625.
28. Kamel (MI), Rashed (S), Foda (N), Mohie (A), Loutfy (M). *Gender differences in health care utilization and outcome of respiratory tuberculosis in Alexandria.* East Mediterr Health J 2003; 9: 741–756.