Risk Factors Associated with Survival of Pulmonary Tuberculosis

Mehdi KAZEMPOUR DIZAJI 1, *Anoshirvan KAZEMNEJAD 1, Payam TABARSI 2,3, Farid ZAYERI 4

1. Dept. of Biostatistics, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran
2. Mycobacteriology Research Center, National Research Institute for Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran
3. Clinical Tuberculosis and Epidemiology Research Center, National Research Institute for Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran
4. Dept. of Biostatistics, Faculty of Paramedical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

*Corresponding Author: Email: kazem_an@modares.ac.ir

(Received 08 Feb 2017; accepted 23 Jun 2017)

Abstract
Background: We conducted this study among adults with pulmonary tuberculosis (TB) who received treatment, in order to determine the risk factors associated with survival of during treatments.

Methods: A retrospective cohort study was conducted from 2005-2015 with newly registered TB patients in the Hospital of Masih Daneshvari Doctor, Tehran, Iran. Overall, 5313 patients met our study's cohort definition, but the analysis was performed on 2299 patients (43.2%) who had a correct address and they could be traced-out by the Medical – registry. Time in days was used in survival model and patients who were still alive (until last follow-up date) considered as censored. To study the effect of risk factors on patients’ survival, the generalized gamma regression model was used.

Results: Based on the results of univariate analysis, gender (RR=2 (95% CI: 1.1−3.7), high school education (Relative Risk: RR=0.3 (95% CI: 0.2−0.7), higher education (RR=0.3 (95% CI: 0.1−0.9), smoker (RR=2.5 (95% CI: 1.4−4.2), drug user (RR=2.4 (95% CI: 1.4−4), TB contact (RR=0.5 (95% CI: 0.3−0.8) and HIV positive (RR=4 (95% CI: 1.7−9.2) affected patients’ survival. Moreover, the results of multivariate analysis showed that, gender (RR=5.5 (95% CI: 2.2−13.5), age (RR=1.1 (95% CI: 1−1.1), adverse drug effect (RR=2.5 (95% CI: 1.2−5.4), smoker (RR=3.3 (95% CI: 1.2−9.4), TB contact (RR=0.2 (95% CI: 0.1−0.5), diabetic mellitus (RR=3 (95% CI: 1−8.3), HIV positive (RR=26 (95% CI: 4.6−145.9) and comorbidities (RR=4.9 (95% CI: 2−11.6) were identified as factors affecting patients’ survival.

Conclusion: Our data indicated associated risk factors in TB mortality and could suggest way to progressing national tuberculosis program (NTP) for predicating and plan for effective interventional strategies.

Keywords: Tuberculosis, Generalized gamma regression model, Pulmonary TB

Introduction

Despite effective treatment strategies, tuberculosis (TB) still remains a major health problem. It infects millions of people and ranks as the second leading cause of death from infectious diseases, after human immunodeficiency virus (HIV). In 2013, there were an estimated 12 million TB cases, including 8.6 million new cases, and 1.5 million fatal cases (1).

Clinical trials in developed countries revealed that 6.6% of TB patients died during or after therapy,
whereas, in underdeveloped and developing countries the death rate was higher due to multidrug-resistant TB (MDR) and prevalence of HIV infection (2). The TB death rates globally are variable (7% to 35%) and reported to be different for each country (3, 4). Researches attributed TB mortality could consider to either TB or to unrelated diseases such as cardiovascular diseases, diabetes mellitus, HIV, cancers and drug toxicity (5).

Iran is a country with medium incidence of TB (21 per 100000 individuals) and low rate of TB mortality (4%) (6). Recently, few independent researchers showed a higher mortality rate (3.15% to 10%) for Iran cross-border provinces (7). At present we have no explanation for these discrepancies, but the proximity of Iran to the countries like Pakistan, Afghanistan, Iraq, and Azerbaijan might increase the risk of TB deaths in such area. Unfortunately, the lack of uniformity and accurate registration system, make the judgment more difficult in this area. Thus, the novelty and importance of the current study were to explore risks factors related to the increased mortality of TB especially pulmonary TB with time in population. Not much information available on this subject and we are the first groups for following up for 10 years.

There are various parametric models to assess the effects of risk factors on survival of pulmonary tuberculosis patients, including exponential, Weibull, log-normal, log-logistic, and generalized gamma regression models (8-12). The generalized gamma distribution showed better fit than the others, parametric models. Therefore, in this study to assess the risk factors for pulmonary tuberculosis, generalized gamma regression model has been used.

In the present study, we aimed to evaluate the causes of TB death during treatments of pulmonary TB who referred to National Referral TB Hospital in Tehran from all over the country. The information was not only collected through medical registry, but also by interviewing the family. For our knowledge, the current study is the first report of TB deaths in a longer period, i.e., 10 yr. The result of this study may help to identify the associated risk factors in TB mortality and could suggest to the national tuberculosis program (NTP) to predicate and plan for effective interventional strategies.

Materials and Methods

Study population
A retrospective cohort study was conducted from 2005-2015 with newly registered TB patients referred to the National Referral Center for Tuberculosis at Dr. Masih Daneshvari Hospital Tehran, Iran. In total, 5313 patients met our study's cohort definition, but the analysis was performed on 2299 patients (43.2%) who had a correct address and they could be traced-out by Medical registry. In this study, a newly diagnosed TB case was defined as bacteriologically (smear and culture positive report) or clinically confirmed TB patients. TB-specific deaths included TB patients in whom TB was cited as the cause of death and non-specific deaths included TB patients in whom TB was not cited as the cause of death. Comorbidities defined as patients hospitalized more than once or who visited outpatient service more than twice within a year before joining the TB registry. For all patients, dependent variable (time to TB-specific deaths) and the independent variables (sex, age, marital status, education, nationality, residency area, family size, TB type, Comorbidities) were investigated. The latest follow up (Jun 2015) for patients discharged with no death record were carried out by phone. The cause of death for those who expired check by medical –registry and by interviewing the close relatives.

This retrospective cohort study was approved by the Ethical Committee of Dr. Masih Daneshvari Hospital.

Statistical analyses
The effect of the independent variables such as sex, age, marital status, education, nationality, residency area, family size, TB type, Comorbidities on patients’ survival was evaluated. The distance between diagnosis of TB until death (time in days) was used as survival time and patients
who were still alive (until last follow-up date) considered as censored. Chi-square test was applied for testing distribution of characteristics among patients. To study the risk factors for pulmonary tuberculosis, generalized gamma regression model has been used. Moreover, to investigate the simultaneous effect of independent variables on patients’ survival all the variables in the univariate model was also entered into multivariate model. The only exception was age of start smoking variable, which had collinearity with smoking factor. In all analyses, \( \alpha=0.05 \) was considered as the significant level and Stata 11 software was used for all analyses.

**Results**

Table 1 & 2 summarize the baseline characteristics of the TB patients under study, of 2299 enrolled patients, 770 (33.4%) died and 134 (5.8%) returned as the relapses cases. The remaining had successful treatment (1395; 60.6%) with no sign of recurrence. Male to female ratio was almost similar, but the ratio of male patients in TB death cases was significantly higher than female cases. Majority of TB deaths was found in patients with higher age, between 50-69 and \( \geq 70 \) yr (Table 1). The death rate was higher in divorced and widow patients. Patient’s educational level showed that illiterate cases had the highest rate of death (Table 1).

Although the rate of death was higher in HIV positive people, this rate was lower in those who had diabetes mellitus or previous contact with other TB patients (Table 2). In other comorbidities i.e., cancer, liver disorders, etc, the TB deaths rate was high and significantly important (295/698; 42.3%).

**Table 1: Demographic characteristic of newly registered tuberculosis patients referred to the National Referral Center for Tuberculosis at Dr. Masih Daneshvari Hospital Tehran, Iran**

| Factor              | Category     | Alive N(%) | Dead N(%) | P-value |
|---------------------|--------------|------------|-----------|---------|
| Gender              | Female       | 835 (74.5) | 286 (25.5) | < 0.001 |
|                     | Male         | 694 (58.9) | 484 (41.1) |         |
| Age group (yr)      | Under 20     | 75 (83.3)  | 15 (16.7)  | < 0.001 |
|                     | 20-34        | 350 (76.6) | 107 (23.4) |         |
|                     | 35-49        | 244 (65.8) | 127 (34.2) |         |
|                     | 50-69        | 434 (68.0) | 204 (32.0) |         |
|                     | 70 and older | 426 (57.3) | 317 (42.7) |         |
| Marital status      | Single       | 279 (69.9) | 120 (30.1) | < 0.001 |
|                     | Married      | 1,054 (68.0)| 497 (32.0)|         |
|                     | Divorced     | 34 (47.9)  | 37 (52.1)  |         |
|                     | Widow        | 162 (58.3) | 116 (41.7) |         |
| Educational level   | Illiterate   | 650 (63.1) | 380 (36.9) | < 0.001 |
|                     | Primary school| 333 (66.2)| 170 (33.8) |         |
|                     | Secondary school| 252 (66.8)| 125 (33.2)|         |
|                     | High school  | 196 (73.7) | 70 (26.3)  |         |
|                     | Higher education| 98 (79.7)| 25 (20.3)  |         |
| Nationality         | Iranian      | 1,255 (64.8)| 681 (35.2)| < 0.001 |
|                     | Foreigners   | 274 (75.5) | 89 (24.5)  |         |
| Residency area      | Urban        | 1,225 (66.8)| 608 (33.2)| 0.553   |
|                     | Rural        | 304 (65.4) | 161 (34.6) |         |
| Family size         | Single       | 95 (49.0)  | 99 (51.0)  | < 0.001 |
|                     | 2            | 390 (62.9) | 230 (37.1) |         |
|                     | 3-5          | 806 (71.5) | 322 (28.5) |         |
|                     | More than 5  | 235 (67.0) | 116 (33.0) |         |
Table 2: Baseline characteristics of newly registered tuberculosis patients referred to the National Referral Center for Tuberculosis at Dr. Masih Daneshvari Hospital Tehran, Iran

| Factor                                | Category | Alive  | Dead  | P-value |
|---------------------------------------|----------|--------|-------|---------|
| Drug adverse effect                   | No       | 705 (68.7) | 321 (31.3) | < 0.001 |
|                                       | Yes      | 238 (59.8) | 160 (40.2) |         |
| Smoker                                | No       | 1,126 (72.3) | 432 (27.7) | < 0.001 |
|                                       | Yes      | 395 (54.3) | 333 (45.7) |         |
| Age of start smoking (for smokers)    | Under 20 | 142 (55.0) | 116 (45.0) | 0.352   |
|                                       | 20-24    | 105 (48.6) | 111 (51.4) |         |
|                                       | 25-29    | 44 (59.5) | 30 (40.5) |         |
|                                       | 30-34    | 24 (55.8) | 19 (44.2) |         |
|                                       | 35-49    | 34 (60.7) | 22 (39.3) |         |
|                                       | 50 and older | 13 (65.0) | 7 (35.0) |         |
| Passive smoker                        | No       | 1,399 (66.8) | 694 (33.2) | 0.426   |
|                                       | Yes      | 105 (70.0) | 45 (30.0) |         |
| Drug user                             | No       | 1,239 (70.6) | 515 (29.4) | < 0.001 |
|                                       | Yes      | 285 (53.6) | 247 (46.4) |         |
| Contact with other TB patients        | No       | 1,211 (65.1) | 650 (34.9) | < 0.001 |
|                                       | Yes      | 312 (73.9) | 110 (26.1) |         |
| Imprisoned                            | No       | 1,396 (70.0) | 598 (30.0) | < 0.001 |
|                                       | Yes      | 85 (43.4) | 111 (56.6) |         |
| Has Pulmonary TB                      | No       | 133 (71.5) | 53 (28.5) | < 0.001 |
|                                       | Yes      | 1,393 (66.1) | 716 (33.9) |         |
| Has extra-Pulmonary TB                | No       | 1,325 (66.4) | 669 (33.6) | 0.91    |
|                                       | Yes      | 201 (66.8) | 100 (33.2) |         |
| Diabetic Mellitus                     | No       | 1,241 (66.1) | 637 (33.9) | 0.36    |
|                                       | Yes      | 288 (68.4) | 133 (31.6) |         |
| HIV positive                          | No       | 1,472 (68.7) | 670 (31.3) | < 0.001 |
|                                       | Yes      | 57 (36.3) | 100 (63.7) |         |
| Comorbidities (other than HIV or Diabetes) | No    | 1,126 (70.4) | 473 (29.6) | < 0.001 |
|                                       | Yes      | 403 (57.7) | 295 (42.3) |         |

From 770 TB deaths, 585 cases (75.9%) had documented "time of deaths" whereas no time was recorded, for 185 (24.02%). Majority of deaths occurred in the first year of treatment (369/585; 63.1%); while they were in hospital (250/369; 67.7%) or outside of hospital (119/369; 32.2%). The frequency was lowered from the second year (93/585; 15.90%) on words, reaches to 0.51% (3/585) in 10 yr of follow-up. Overall, the deaths rate was more in hospital (397/770; 51.5%) than outside of hospital (373/770; 48.4%), but the differences were not statistically significant. In this study, the TB –related deaths and other causes of deaths were 615 (79.8%) and 155 (20%), respectively.

The results of univariate generalized gamma regression model are presented in Table 3. The significant factors for TB deaths in univariate analysis were gender, high school education, higher education, smoker, drug user, TB contact and HIV positive (Table 3).

However, in multivariate analyses, gender, age, adverse drug effect, smoker, TB contact, diabetic mellitus, HIV positive and comorbidities were significant (Table 3). Overall, male gender, being smoker, facing drug adverse effect, drug use, having HIV positive, diabetic mellitus and comorbidities will significantly increase the risk of death and decrease the survival time.

Available at:  [http://ijph.tums.ac.ir](http://ijph.tums.ac.ir)
Table 3: Results of univariate generalized gamma regression model for assessing the effect different factors on patients’ survival

| Factor          | Category          | Generalized gamma regression model |
|-----------------|-------------------|-------------------------------------|
| Gender          | Male/Female       | 2* (1.1-3.7)                        |
| Age             |                   | 1 (1-1)                             |
| Marital Status  | Married/Single    | 0.9 (0.5-1.6)                       |
|                 | Widow/Single      | 1.5 (0.4-5.5)                       |
|                 | Divorced/Single   | 1.5 (0.7-3.2)                       |
| Education       | Primary/Illiterate| 1.1 (0.7-1.8)                       |
|                 | Secondary/Illiterate| 1.3 (0.7-2.3)                 |
|                 | High school/Illiterate| 0.3* (0.2-0.7)         |
|                 | Higher education/Illiterate| 0.3* (0.1-0.9)   |
| Nationality     | Iranian/Non-Iranian| 0.8 (0.4-1.3)                       |
| Residency area  | Rural/Urban       | 1.4 (0.9-2.3)                       |
| Family size     |                   | 1 (0.9-1.1)                         |
| Adverse effect  | Yes/No            | 1.1 (0.6-2)                         |
| Smoker          | Yes/No            | 2.5* (1.4-4.2)                      |
| Age of start smoking |               | 1 (1-1)                             |
| Passive smoker  | Yes/No            | 1 (0.4-2.2)                         |
| Drug user       | Yes/No            | 2.4* (1.4-4)                        |
| TB Contact      | Yes/No            | 0.5* (0.3-0.8)                      |
| Imprisoned      | Yes/No            | 2 (0.9-4.6)                         |
| Pulmonary TB    | Yes/No            | 0.9 (0.4-2)                         |
| Extra-Pulmonary TB | Yes/No     | 0.9 (0.5-1.6)                       |
| Diabetic Mellitus| Yes/No           | 1 (0.6-1.7)                         |
| HIV Positive    | Yes/No            | 4* (1.7-9.2)                        |
| Comorbidities   | Yes/No            | 1.4 (0.8-2.3)                       |

† 95% Confidence interval  RR= Relative Risk>P-value < 0.05

Table 4: Results of multivariate generalized gamma regression model for assessing the effect different factors on patients’ survival

| Factor          | Category          | Generalized Gamma regression model, RR (CI) |
|-----------------|-------------------|---------------------------------------------|
| Gender          | Male/Female       | 5.5* (2.2-13.5)                             |
| Age             |                   | 1.1* (1-1.1)                                |
| Marital Status  | Married/Single    | 0.3 (0.1-1.3)                               |
|                 | Widow/Single      | 1.9 (0.2-19.3)                              |
|                 | Divorced/Single   | 1.5 (0.3-9.3)                               |
| Education       | Primary/Illiterate| 0.8 (0.3-2.2)                               |
|                 | Secondary/Illiterate| 2 (0.6-6.5)                     |
|                 | High school/Illiterate| 0.8 (0.2-3)                  |
|                 | Higher education/Illiterate| 1 (0.1-7.2)               |
| Nationality     | Foreigners/Iranian| 1.8 (0.7-4.7)                              |
| Family size     |                   | 1 (0.8-1.3)                                 |
| Adverse effect  | Yes/No            | 2.5* (1.2-5.4)                              |
| Smoker          | Yes/No            | 3.3* (1.2-9.4)                              |
| passive smoker  | Yes/No            | 0.7 (0.1-3)                                 |
| Drug user       | Yes/No            | 2.1 (0.6-6.7)                               |
| TB contact      | Yes/No            | 0.2* (0.1-0.5)                              |
| Imprisoned      | Yes/No            | 0.4 (0.1-2.2)                               |
| Pulmonary TB    | Yes/No            | 1.4 (0.3-7.5)                               |
| Extra-Pulmonary TB | Yes/No    | 0.9 (0.2-3.3)                              |
| Diabetic Mellitus| Yes/No           | 3* (1.8-3)                                  |
| HIV Positive    | Yes/No            | 26* (4.6-145.9)                             |
| Comorbidities   | Yes/No            | 4.9* (2-11.6)                               |

† 95% Confidence interval  RR= Relative Risk>P-value < 0.05
Discussion

This is the first study that evaluates the TB deaths for a rather long follow-up period in Iran. The investigation on mortality rate was not only monitored through medical registry but also by interviewing the close by relatives. The overall mortality rate was 33.4% (770/2299), which is significantly higher than previous reports (13). In total, 79.8% of deaths were related to TB specific and 20% to non–TB specific deaths. Interestingly, majority of deaths occurred in the first year of treatment (63.1%), whether in Hospital (250/369; 67.7%) or outside of Hospital (119/369; 32.2%).

The study outlines the high mortality rate under complete treatment protocols. Therefore, a considerable amount of work must be performed to achieve the goal of a TB mortality rate less than 1.0 per 100000 individuals. In this study, the associated risk factors for TB deaths were identified. The current observation shows an increased risk of deaths in male patients (484/770; 62.8%). In previous studies male sex have been reported as an independent risk factor for TB deaths (14). They identified alcohol abuse, smoking behavior and utilization of health services as the main contribution to higher male deaths. In the present study, 65.7% of died male patients were smoker and 50.5% of them were drug user. While in died female patients the rate drops to 8.4% and 3.6%, respectively. Thereby a direct correlation between gender, smoking, drug user and TB deaths was observed. The advanced age has been reported by other investigators as risk factors in TB deaths. Likewise, both univariate and multivariate analyses showed significant importance. Although, the risk of TB death in old age (≥ 50) was more in female (77.2%) than male (62.7%). In overall, the old age was related to tuberculosis whether in alive (860/1529; 56.2%) or death cases (521/770; 67.6%). Generally, TB among the elderly is often caused by the recurrence of old infections (15). That is may account for the weakness of the immune system and/or socioeconomical problem (16).

In our study, 63.7% deaths were associated with HIV. Of all risk factors for TB deaths, HIV is by far the most potent factor. In this regards, a mortality rate up to 10 times higher in HIV positive patients compared to those without positive serology of HIV (16, 17).

Several factors, such as delays in diagnosis and advanced immunosuppression, intravenous drug users were explained this poor outcome. Recently, the importance of Albumin levels and weights were underlined as an unsuccessful outcome in TB-HIV co-infection (18). Our data show that, the mortality was high among those who presented to the Hospital within the first year of treatment. This could be attributed to delay in presentation and drug adverse effect. Mortality as a delay in presentation has been already reported by many investigators.

About 56% of deaths in Nigeria were associated with delay in diagnosis due to patient's factors (19). In Iran, about 57% of patients with TB are diagnosis, of which majority fall into late diagnosis categories (20). Delay in diagnosis is unacceptable as it may compromise the chance of a successful outcome and lead to increase transmission of TB both in household and in the community. In this study, pulmonary TB was the most common form of lesion associated with TB-deaths (716/770; 92.9%).

The other risk factors were residing in rural area, having a smoker in household, being imprisoned, and having comorbidities. Similar studies Asian countries showed association of male sex, anemia, dyspnea, chronic heart disease, malignancy, and ICU admission as a baseline prognostic factors for death during treatment of adult patients with pulmonary TB. In few studies, elderly age, Eastern residence, positive sputum bacteriology, abnormal chest X-ray and comorbidity with chronic kidney disease, stroke or chronic liver disease were most likely to be the cause of TB-specific deaths (21,22). We demonstrated that the comorbidities (other than HIV and diabetic) have significant effect (42.3%) on TB deaths. The three most frequently comorbidities diseases were identified as high blood pressure (43.3%) ischemic heart diseases (26.3%) and hepatitis C virus (11.8%). Indeed, correlation of TB deaths with comorbidities is various in different situations have been reported (23).
Recent studies documented comorbidity with chronic kidney disease, stroke, or chronic liver diseases was associated with TB specific deaths (4, 24), but in our study they were less likely to be implicated. The association of chronic kidney diseases (6.6%), stroke (2.9%) and cancer (2.0%) was not statistically significant. Usually, TB is curable diseases, and it is unlikely that a patient die from TB, until and unless there is severe or complicated chronic diseases. The high mortality rates (33.4%) highlight the urgent need for re-evaluation of the tuberculosis control program within the country. Although, as this study performed in a referral center of tuberculosis, we receive most complicated patients throughout the country. Thereby, the collected data may be a bit higher, but still we cannot ignore the high rate of mortality, especially when the study performed in large sample size and long duration of follow-up. Additionally, for the first time we not only take the information through medical registry, but also by interviewing the patients or their family members. To our astonished, considerable number of TB deaths cases (≥ 55) was identified when the family where interviewed. Therefore, gathering information by just reviewing the medical registry is not optional in Iran. This may explain the discrepancies between present and previous reports, and highlight the need for extensive investigation on accuracy of medical registry systems within the country. Using generalized gamma regression model showed that variables such as gender, high school education, higher education, smoker, drug user, TB contact and HIV positive in univariate model and variables of gender, age, adverse drug effect, smoker, TB contact, diabetic mellitus, HIV positive and comorbidities in multivariate model can described survival time of TB patients from starting their treatment to death. These results are consistent with the findings of most studies (11,12, 14, 23-26). Moreover, more detailed analyses based on generalized gamma regression model showed that variables of male gender, age, adverse effect, smoker, drug user, diabetic mellitus, HIV positive and comorbidities will increase death hazard and reduce survival time of patients. Conversely, variables of TB contact and education (high school and higher school education) reduce death hazard and will increase survival time of patients.

Conclusion

Despite implication of DOTS strategies over the past 15 yr, the mortality rate is high in Iran. Improvement of TB surveillance and rapid diagnosis strategies in Iran need to be emphasized. The associated risk factors for deaths are male gender, advanced age, smoking, facing drug adverse effect, drug use, having HIV positive, diabetic mellitus and comorbidities.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Acknowledgements

No financial support was received for this study.

Conflict of interest

The authors declare that there is no conflict of interests.

References

1. Glaziou P, Sismanidis C, Floyd K, Raviglione M (2014). Global epidemiology of tuberculosis. Cold Spring Harb Perspect Med, 5(2): a017798.
2. Miller TL, Wilson FA, Pang JW et al (2015). Mortality hazard and survival after tuberculosis treatment. Am J Public Health, 105(5):930-7.
3. Kwon YS, Kim YH, Song JU et al (2014). Risk factors for death during pulmonary tuberculosis treatment in Korea: a multicenter retrospective cohort study. J Korean Med Sci, 29(9):1226-31.
4. Wu YC, Lo HY, Yang SL et al (2015). Comparing the factors correlated with tuberculosis-specific and non-tuberculosis-specific deaths in different age groups among tuberculosis-related deaths in Taiwan. *PLoS One*, 10(3):e0118929.

5. Murray CJ, Ortblad KF, Guinovart C et al (2014). Global, regional, and national incidence and mortality for HIV, tuberculosis, and malaria during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*, 384(9947):1005-70.

6. Alavi-Naini R, Moghtaderi A, Metanat M et al (2013). Factors associated with mortality in tuberculosis patients. *J Res Med Sci*, 18(1):52-5.

7. Torkaman MR, Nasiri MJ, Farnia P et al (2014). Estimation of Recent Transmission of Mycobacterium Tuberculosis Strains among Iranian and Afghan Immigrants: A Cluster-Based Study. *J Clin Diag Res*, 8(9):DC05-8.

8. Klein JP, Moeschberger ML (2005). *Survival analysis: techniques for censored and truncated data* 2 ed. Springer Science & Business Media.

9. Kleinbaum D, Klein M (2011). *Survival Analysis: A self-learning text* 2nd ed. New York.

10. Kalbfleisch JD, Prentice RL (2011). *The statistical analysis of failure time data* 2ed. John Wiley & Sons.

11. Albuquerque MdFPM, Batista J.d.A.L., Ximenes R.A.dA et al (2009). Risk factors associated with death in patients who initiate treatment for tuberculosis after two different follow-up periods. *Rev Bras Epidemiol*, 12(4):513-522.

12. Akessa, G. M., Tadesse, M., & Abebe, G. (2015). Survival Analysis of Loss to Follow-Up Treatment among Tuberculosis Patients at Jimma University Specialized Hospital, Jimma, Southwest Ethiopia. *International Journal of Statistical Mechanics*, 2015;9:23025.

13. Forrellad MA, Klepp JJ, Gioffré A et al (2013). Virulence factors of the Mycobacterium tuberculosis complex. *Vindulence*, 4(1):3-66.

14. Fiske CT, Yan FX, Hirsch-Moverman Y et al (2014). Risk factors for treatment default in close contacts with latent tuberculous infection. *Int J Tuberc Lung Dis*, 18(4):421-7.

15. Guerra-Laso JM, González-García S, González-Cortés C et al (2013). Macrophages from elders are more permissive to intracellular multiplication of Mycobacterium tuberculosis. *Age (Dordr)*, 35(4):1235-50.

16. Girardi E, Antonucci G, Vanacore P et al (2004). Tuberculosis in HIV-infected persons in the context of wide availability of highly active antiretroviral therapy. *Eur Respir J*, 24(1):11-7.

17. Millet JP, Orcau A, Rius C et al (2011). Predictors of death among patients who completed tuberculosis treatment: a population-based cohort study. *PLoS One*, 6(9):e25315.

18. Tabarsi P, Chitsaz E, Moradi A et al (2012). Treatment outcome, mortality and their predictors among HIV-associated tuberculosis patients. *Int J STD AIDS*, 23(9):e1-e4.

19. Erhabor GE, Adevole OO, Ogunlade O (2006). A five-year review of tuberculosis mortality amongst hospitalised patients in Ilé-Ife. *Indian J Chest Dis Allied Sci*, 48(4):253-6.

20. Bahamahmoodi F, Alikhani A, Yazdani Charati J et al (2015). Clinical epidemiology and paraclinical findings in tuberculosis patients in north of Iran. *Biomed Res Int*, 2015:381572.

21. Lin CH, Lin CJ, Kuo YW et al (2014). Tuberculosis mortality: patient characteristics and causes. *BMC Infect Dis*, 14:5.

22. Pachi A, Bratis D, Moussas G, Tselebis A (2013). Psychiatric morbidity and other factors affecting treatment adherence in pulmonary tuberculosis patients. *Tuberc Res Treat*, 2013:489865.

23. Wu YC, Lo HY, Yang SL, Chou P (2014). Factors correlated with tuberculosis reported after death. *Int J Tuberc Lung Dis*, 18(12):1485-90.

24. Oakes D (1983). Comparison of models for survival data. *Stat Med*, 2(2):305-11.

25. Vasantha M, Gopi P, Subramani R (2008). Survival of tuberculosis patients treated under DOTS in a rural Tuberculosis Unit (TU), south India. *Indian J Tuberc*, 55(2):64-9.

26. Oursler KK, Moore RD, Bishai WR et al (2002). Survival of patients with pulmonary tuberculosis: clinical and molecular epidemiologic factors. *Clin Infect Dis*, 34(6):752-759.