Demography India (2016) ISSN: 0970-454X
Vol.45, Issue: 1&2, pp: 131-142

Research Article

Survival Pattern of AIDS Patients by Different Types of TB and Associated Prognostic Factors

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Abstract

This paper aims at studying the impact of Tuberculosis (TB) and Pulmonary Tuberculosis (PTB) on the survival time of AIDS patients and to identify impact of interactive effect of covariates with types of TB. The non-parametric approach of Kaplan-Meier product limit method is used to plot the survival function and estimate mean survival time and log rank test is used to compare it across covariates. Also, the semi-parametric Cox proportional hazard model is applied to determine the effect of various covariates on the survival time.

For a data collected from one of the largest Anti Retroviral Therapy (ART) centres across northern India, the significant covariates have been identified as type of TB, gender, age and stages. Also their interactive effects with the types of TB have been conclusively established. A comprehensive analysis reveals that AIDS patients suffering from PTB are exposed to the higher risks of death than other kind of TB. The hazard rate for TB patients is found to be 97.4% lower than that of PTB patients. Also it is found that survival time depends significantly on the interaction of type of TB with Age, Gender and WHO stages of the patient. This paper also incorporates the trend of survivability for the reported AIDS patients with respect to age, sex and stages across these 7 years.

Introduction

The global burden of Tuberculosis (TB) has risen dramatically in the past ten years due to the HIV epidemic. As per WHO Global TB Report, 2015, out of the estimated global annual incidence of 9.6 million TB cases, 2.2 million were estimated to have occurred in India. Further the incidence of HIV among the TB patients is 5%. (www.tbcindia.nic.in). On the other hand, TB is the leading infectious killer of people living with HIV, and accounts for an estimated 13% of AIDS deaths worldwide. HIV and TB are so closely connected that they are often referred to as co-epidemics or dual epidemics. These epidemics drive and reinforce one another. HIV activates dormant TB in a person, who then becomes infectious and able to spread the TB bacillus to others. The occurrence of TB, Human immunodeficiency virus (HIV) and Hepatitis infections in the same patient poses unique clinical and public health challenges because medication to treat TB and HIV are hepatotoxic (Sirinak,et al., 2008). According to World Health Organization (WHO) estimates, mortality from TB in India was 320,000 (210,000–470,000) in 2010. More than 80 percent of the burden of TB is due to premature death, as measured in terms of disability-adjusted life years (DALYs) lost. The DALYS is estimated to be around 63 and 46 lakhs of years of life lost in men and women respectively (YLL = 4.4%). The burden is likely to increase with HIV epidemic with an increase of cases with dual infection, increase in morbidity and mortality due to tuberculosis. Management of drug resistant tuberculosis is a major hurdle in tuberculosis control and is a major step in cutting the chain of transmission to those with HIV infection, AIDS and immunodeficiency. (http://www.searo.who.int, Prabhakar, 1996)

According to Sonnenberg et al. (2004) HIV infection increases the risk as well as incidence of tuberculosis. There was a direct increase in those who were HIV infected, but also a doubling in tuberculosis incidence in those remaining HIV negative, implying considerable ongoing

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Mycobacterium tuberculosis transmission. In fact, the risk of developing tuberculosis (TB) is estimated to be between 12-20 times greater in people living with HIV than among those without HIV infection (WHO, 2013).

Authors (Kwan and Ernst, 2011; Grover and Shivraj, 2004;Badri et al., 2001;Markowitzet al., 1997) have established associations between HIV infection and TB that go on to have a significant impact on the survival time of patients. Dheda et al., 2002 used univariate analysis, Kaplan-Meier curves and Cox proportional hazards model to compare the outcomes in patients starting TB treatment during the pre-HAART era (before 1996) with those in patients starting treatment during the HAART era (during or after 1996). Manosuthi et al., 2006 used Cox proportional hazard model to show that ART was associated with lower mortality rate; gastrointestinal TB and multidrug resistant TB were associated with higher mortality rate among HIV/TB co-infected patients. They concluded through their findings that initiation of ART within 6 months of TB diagnosis is associated with greater survival. Researchers (Shaweno et al., 2012; Maruzaet al., 2012) used Kaplan-Meier and Cox proportional method to estimate the probability of survival and associated risk factors for death in a cohort of persons living with HIV who had started TB treatment (Ackah et al., 1995) showed that among the patients with PTB, the overall mortality rate was significantly higher in HIV-positive than HIV-negative persons and increased with the severity of immune deficiency. They also showed that there is no significant difference in the median CD4 lymphocyte counts in those with extra pulmonary TB as compared to those with pulmonary TB. Elliott et al., 1990 established higher prevalence of HIV persons in patients suffering from PTB as compared to other diseases. Their findings conclude that high prevalence of HIV in patients with tuberculosis suggests an epidemic of reactivating tuberculosis is arising in those who are infected with HIV.

Though many authors have assessed the impact of TB in HIV infected patients, not many studies have been conducted to identify the specific categories of TB that are likely to have more significant impact on such patients. To the best of our knowledge, no study has been done to identify the impact of various types of TB (i.e., PTB and other forms) on the survivability of HIV patients. Our study is restricted to AIDS patients who are diagnosed at ART center of Ram Manohar Lohia Hospital, New Delhi. A cohort of 162 AIDS cases in the year 2008 were considered and followed up for a period of 7years (i.e. up to 2014) with the variations noted according to age, sex and stages.

The aim of the present study is

(i) To observe the prognosis of AIDS over 7 years with respect to TB and PTB.
(ii) To estimate survival function of AIDS patient who were diagnosed at ART center with respect to TB and PTB.
(iii) Whether TB and PTB affect survivability with respect to risk factors age, gender and stages of AIDS patients.

For the reported AIDS patients, we have considered survival and censored time in a random manner. The estimation of survival functions for AIDS patients were done using both semi-parametric and nonparametric methods subcategorizing with respect to different variables of interest, like gender, age at the time of diagnosis and stage of AIDS (defined by WHO) (WHO, 2013).

Materials and Methods

In this article, we have considered two approaches to estimate the survival time (in days) of AIDS patients undergoing ART. The first approach is the Kaplan-Meier method which is a non-parametric approach and can be extended to include covariates. However, the covariates in this approach are not the predictors but, facilitate to identify the variations in survival time and establish correlations with variables. The second method is the Cox proportional hazards model which is a semi-parametric approach and utilizes the information provided by the covariates in estimating the hazard rate.

Kaplan-Meier Product Limit Method

The Kaplan-Meier survival curve is defined as the probability of surviving in a given length of time while considering time in many small intervals (Altman, 1992). There are three assumptions used in this analysis. *Firstly*, we assume that at any time patients who are censored have the same survival prospects as those who continue to be followed. *Secondly*, we assume that the survival probabilities are the same for subjects recruited early and late in the study. *Thirdly*, we assume that the event happens at the time specified. The Kaplan-Meier estimate is also called as "product limit estimate". It involves computing of probabilities of occurrence of event at a certain point of time. We multiply these successive probabilities by any earlier computed probabilities to get the final estimate. The survival probability at any particular time is calculated by the formula (1).

$$S(t) = \frac{\text{(No.of subjects living at the start) - (No.of subjects died)}}{\text{(No.of subjects living at the start)}} \qquad (1)$$

The Cumulative survival function of AIDS patients is obtained using Kaplan-Meier estimation method [Kaplan, E.L and Meier, P., 1958] shown in equation-(2)

$$\hat{S}(t) = \prod_{i=1}^{t} \left(\frac{n-i}{n-i+1} \right)^{c_i} \qquad (2)$$

where

$\hat{S}(t)$ = estimated survival function at time t

$\prod_{i=1}^{t}$ = denotes the multiplication of the survival times across all cases less than or equal to t.

t = time (in days)

n = total number of cases in the sample,

i = the number of cases surviving up to time t and

$$c_i = \begin{cases} 1, & \textit{uncensored case} \\ 0, & \textit{censored case} \end{cases}$$

Cox Proportional Hazard Method

Cox proportional hazard model is one of the most popular model used in survival analysis that can be used to assess the importance of various covariates in the survival times of individuals or objects through the hazard function. It has been extensively used for the prediction of significant prognostic factors related to survival time. The Cox proportional hazard model is usually written in terms of the hazard function shown in equation (3).

$$h(t, X) = h_0(t)\exp\left\{\sum_{i=1}^{p} \beta_i x_i\right\} \qquad (3)$$

where

$h_0(t)$ = baseline hazard function,

$X = (x_1, x_2, ..., x_p)$, i.e. explanatory / predictor variables.

β_i = risk associated with covariates x_i, ($i = 1, 2, \ldots p$) .

This model gives an expression for the hazard at time t for an individual with a given specification of a set of explanatory variable denoted by the X, which represents a collection (vector) of predictor variables that is being modelled to predict an individual's hazard rate. The Cox model, a regression method for survival data, provides an estimate of the hazard ratio and its confidence interval. The hazard ratio is an estimate of the ratio of the hazard rate in any two groups. The hazard rate is the probability that if the event in question has not already occurred, it will occur in the next time interval, divided by the length of that interval. The time interval is made very short, so that in effect the hazard rate represents an instantaneous rate. An assumption of proportional hazards regression is that the hazard ratio is constant over time (Spruance et al.,2004). This assumption may be confirmed by graphically plotting the log minus log of the time against the survival time. The analysis is performed using Statistical Package for Social Sciences (SPSS) version 15.0 software. A p-value < 0.05 is considered statistically significant.

Data Source

We have collected data of AIDS cases reported in Anti-Retroviral Therapy (ART) centre at Ram Manohar Lohia Hospital, New Delhi, India. The patients who had a poor CD4 count (less than 200) or were at critical condition according WHO parameter, have been admitted to this centre and were being given therapy. The data comprises of all the AIDS patients who entered the ART centre in the year 2008 and were followed up till the end of year 2014. These patients have been followed till the period 31st December 2014 and included are the cases who were lost either because of death due to AIDS or lost to follow up against medical advice. The patients who were diagnosed with either TB or PTB during the course of their therapy were included in the study and those who were diagnosed of other or no opportunistic infections were excluded from the sample.

Calculations and Results

The descriptive summary of all the covariates of interest is given in Table 1. The data comprised of 56.17% TB patients while the rest (43.83%) are PTB. Majority of patients are males followed by Females and Eunuchs Patients are equally divided amongst the four WHO stages of AIDS. The youngest patient is of the age 7 years while the oldest one is 60 years. The mean age of patients is 32.49 ± 9.3 years. In addition, the data presented high percentage of deaths (31.48%).

Table 2 gives the Kaplan-Meier estimates of the survival time (in days) of AIDS patients on ART with respect to various covariates. The survival times between respective sub-categories of covariates are compared using Log-Rank test. The mean survival time for patients diagnosed of TB is 1199.10±104.324 days which is significantly higher than that of those which PTB i.e., 586.422±13.87 (p-value < 0.001). In the patients diagnosed of TB there are 21 deaths (23.08%) and for those diagnosed of PTB, there are 30 deaths (42.25%). Thus, the percentage of deaths in patients suffering PTB is significantly higher (chi-square p-value = 0.004) as compared to TB. Females have the highest survival time of 1033.64±127.40 days followed by males with 823.11±27.73 and Eunuch with 696.28±55.89 days respectively (p-value = 0.031). With respect to WHO staging of AIDS, the highest survival time of 1310.73±155.18 days is seen in patients who are in Stage 1. This is significantly higher than the survival times of patients in Stage 2 (810.54±32.83days) and Stage 3 (703.58±40.55days) while the lowest is for Stage 4 patients (655.64±79.38days). It is also observed that Age (in years) of AIDS patients on ART has a negative correlation (p-value = 0.029) with the survival time. For patients in the age group 0 - 14 years, the survival time is 1461.62±182.71 days while for 14- 30 and > 30 years age groups, the survival times are 798.56±54.77 and 773.22±25.49 days respectively. The patterns of survival with respect to various covariates is illustrated in Figure 1.

It is clear from the graph that the probability of survival of a PTB patient survives till 600 days is very high beyond which there is sudden fall in the survival curve. The maximum survival time of PTB patient in our data is recorded as 693 days. An overall estimate of the mean survival time for patients suffering from any kind of TB is 987.28±75.51 days i.e., 2.7 years. In order to identify the interactive effects of various covariates with the type of TB on survival time, Kaplan-Meier analysis is performed within each type of TB for each covariate level.

The results are given in Table 3. Even though the results exhibit same pattern as that of univariate findings, still it is noticed that the survival for PTB is significantly lower than that of TB patients. For PTB patients, the highest survival time of 606.07±21 is observed in Females and this value is lower than the lowest survival time of TB patients which is 784.833±34.78 for Eunuchs. With respect to WHO stages, the highest survival time of 623.3±27.89 is seen in stage 1 patients which is lower than the lowest value of 692.55±79.88 of stage 4 TB patients. Similarly, for PTB patients, >30 years age group have the lowest survival time of 579.77±21.64 while 0-14 years age group has the highest survival of 684±9 days. However, these values are much lower than the lowest survival time of TB patients which is 860.85±22.26 for the > 30 years age group.

These results seem to suggest that not only, the variables themselves have an effect on the survival time, but also their interactions with type of TB has a strong correlation with the survival time. This point is explored further by fitting the Cox proportional hazards model and the results are given in Table 4.

The validity of proportionality hazards assumption is verified with respect to each of the covariates and presented in Figure 2. The log minus log plots against the survival time are non-intersecting parallel curves with respect to all the covariates thereby justifying the assumption. The hazard rate for TB patients is 0.026 times that of PTB group i.e., the hazard rate for TB patients is 97.4% less than that of PTB patients which is highly significant (p-value < 0.001). The hazard rate for females is the lowest (p-value = 0.024) and this is 0.532 times or 46.8% less than that of males. Also, for Eunuchs the hazard rate is higher than that of males even though it is not significant. WHO stages 1 and 2 have no significant difference in the hazard rates while stage 3 and stage 4 have 200.2% (p-value 0.028) and 1535.7% (p-value < 0.001) higher hazard as compared to stage 1. With respect to age, the lowest hazard is for the 0-14 years patients while it is 229.2% higher for 14 - 30 years and 306.4% higher for > 30 years patients.

The estimated hazard for TB patients increases for females by a significant 4.558 times (p-value 0.047) as compared to males and for eunuchs it is 9.129 times (p-value = 0.025) as compared to males. For TB patients in WHO stage 2, the estimated hazard increases by 2.173 times and for stage 3, it is 2.656 times as compared to stage 1 patients. Also for TB patients in age group 14-30 years, the hazard is 2.393 times over the 0-14 age group and for > 30 years, the hazard is 6.828 times. The significance of the interaction terms comprising type of TB with gender, stage and age reemphasizes the severity of PTB over TB as an opportunistic infection. A female suffering from PTB has $\left(\frac{e^{-0.631}}{e^{-3.662-0.631+1.517}}\right)$ = 8.54 times higher hazard as compared to TB females. Also, for a Eunuch suffering from PTB, the hazard is 4.27 times higher than that of TB Eunuchs. A PTB female has 0.46 times hazard as compared to PTB eunuch and a TB female 0.23 times hazard as compared to TB eunuch. For a PTB patient in stage 2 (and 3), hazard is 29.46 (and 43.99) times higher than a TB patient in stage 2 (and 3). Also, for PTB infection, the hazard of patients in stage 2 is 0.55 times that of stage 3 and for TB infected patients, hazard of stage 2 is 0.45 times that of stage 3. In addition, for a PTB patient with age 14 - 30 (> 30) years, the hazard is 16.27 (5.70) times the TB patient in the same age group. Also for PTB patients, the hazard in age 14 - 30 years is 0.81 times that of > 30 years and for TB patients it is 0.28 times.

Discussion and Conclusion

Tuberculosis is the most common opportunistic infection and cause of death among HIV-infected patients in resource-limited settings (Grover et al., 2012;Cock et al., 1992). Patients with HIV infections are particularly vulnerable to primary disease following infection with tuberculosis, (Daley et al., 1992) and therefore are at high risk of illness and mortality when exposed to drug-resistant tuberculosis strains. Although ART has reduced the incidence of active tuberculosis, (Badri et al., 2002) HIV-infected patients on therapy still have a more than five-fold increased risk of developing tuberculosis compared with individuals without HIV infection. Though the combination of tuberculosis and ART can improve survivability in co-infected patients, (Jack et al., 2004;Dhedaet al.,2004)it is less likely to do so in patients with pulmonary tuberculosis and that too when supplemented by other significant cofactors. Similar to the findings of authors, (Gasnault et al., 1999; Cornet al,. 1996, DeSilvaet al., 2009; Johannessen et al., 2008) Kaplan-Meier analysis identify Age, Gender, WHO stage and type of TB as significant factors effecting the survival time of AIDS patients on ART though the results were contrary to a few others (Lempet al., 1992;DeSilvaet al., 2009;Ferradiniet al., 2006).Even though patients with higher age are expected to show better adherence to the ART and hence enhanced survival, our results show that patients with age greater than 30 years have the lowest survival time. The reason may be that the immune system of younger patients is better and supplements the efforts of ART while for older patients, the immune system doesn't respond too well despite better adherence.PTB is established as a serious health hazard for AIDS patients because of the reduced survival time of only 1.61 years as compared to 3.29 years for TB patients and that too when the patient is undergoing ART. Also, the analysis with respect to interactive effects of various covariates with type of TB bring out a very intriguing result. The survival time (in days) for PTB patients does not differ by much across various sub-categories for each covariate. However, for TB patients the survival time is significantly different across the same sub-categories. Also, the highest survival time for any sub-category of PTB patient is very much lower than the lowest sub-category of a TB patient. Thus, it appears that even though there exists correlation between the covariates and the survival time, the correlation is much stronger for the TB as compared to PTB patients. This reinstates the fact that PTB is indeed a serious hazard in AIDS patient and the improvement in survivability of such patients is modest even in the presence of ART.

Though the non-parametric Kaplan-Meier approach provides us with an estimate of mean survival time, it suffers certain limitations. One is that the methodology simply establishes a relation of variables with the survival time but doesn't allow the contribution of these variables as predictors of the survival time. Secondly, the behaviour of each variable in the presence or absence of other variables i.e., confounding effect on survival time cannot be incorporated in the Kaplan-Meier approach. Thirdly, interactive effects of various covariates on predicting the survival time cannot be found out. These limitations are overcome by using the Cox proportional hazards model though, the dependent variable here is the hazard at time t. However, this can be overcome by inducing certain mathematical calculations. The effect of the covariate values x_i on the survivor function is to raise it to a power given by the relative risk, $\exp\left\{\sum_{i=1}^{p} \beta_i x_i\right\}$.All the factors that were established significant in the non-parametric analysis have been corroborated by the Cox model findings. The results underscore PTB as a serious opportunistic infection as compared to other forms of TB and the findings agree with other research findings (Whalen et al., 2000).Patients with PTB had nearly 97.4 times higher risk of dying as compared to that of other TB infections. Females have a lower hazard as compared to Males and Eunuchs and hence a longer survival time. The hazard for patients in WHO stages 1 and 2 is similar but, as the stage worsens beyond these, the hazard rates significantly increase. Also, as the age increases, the survivability of AIDS patient on ART decreases. In this study, PTB was associated with reduced survival, but the effect varied according to the gender, stage of AIDS disease and age. While the survival time for PTB infected patients follows the conventional pattern with respect to gender, TB is found to be more serious hazard in females as compared to males. While deterioration of AIDS patients in terms of WHO stages is inversely correlated with survival time, PTB poses a more serious hazard as compared to TB in terms of rapid decline of survival time. In addition, the hazard in terms of age is more serious for PTB patients as compared to TB patients.

The results suggest that PTB is indeed a giant killer in AIDS patients undergoing ART as compared to any other form of TB. Also, it's effect on the survival time multiplies significantly with respect to interaction with various covariates. The analysis can be extended to include more variables like Body mass Index, CD4 cell count, number of follow-ups etc. to explore more diverse associations with the survival time. Such variables have been proven to be significant predictors of survival time and hence their associations with types of TB are bound to be significant. Also, it is worthwhile to explore the performance of the accelerated failure time models as a parametric alternative to the Cox model.

Acknowledgement

The authors are thankful to Director of ART center of Ram Manohar Lohia Hospital, Delhi for consulting the patients and providing the primary data for this research.

Table 1: Descriptive summary of patients

Type of TB		**Gender**	
PTB	71 (43.83%)	Female	37 (22.84%)
TB	91 (56.17%)	Male	115 (70.99%)
		Eunuch	10 (6.17%)
WHO stage of AIDS		**Age (in years)**	
Stage 1	47 (29.01%)	0 - 14	10 (6.17%)
Stage 2	44 (27.16%)	14 - 30	60 (37.04%)
Stage 3	39 (24.07%)	> 30	92 (56.79%)
Stage 4	32 (19.75%)	*Mean ± SD*	32.49 ± 9.3

Table 2: Kaplan Meier estimates of Survival time (in days) with respect to various covariates

Covariate		**N**	**No of events**	**Mean**		**Median**		**p-value**
				estimate	**Std. error**	**estimate**	**std. error**	
Type of TB	PTB	71	30	586.422	13.864	593	18.155	< 0.001
	TB	91	21	1199.099	104.324	978	40.963	
Gender	Female	37	16	1033.636	127.397	615	114.598	0.031
	Male	115	26	823.108	27.729	930	109.227	
	Eunuch	10	9	696.275	55.89	759	149.049	
WHO stage of AIDS	Stage 1	47	7	1310.728	155.177	999	-	< 0.001
	Stage 2	44	24	810.535	32.827	827	49.565	
	Stage 3	39	16	703.577	40.547	630	35.049	
	Stage 4	32	4	655.634	79.381	787	-	
Age (in years)	0 - 14	10	3	1461.622	182.71	-	-	0.029
	14 - 30	60	17	798.559	54.773	652	36.407	
	> 30	92	31	773.223	25.491	794	31.06	
Overall Survival time		**162**	**51**	**987.283**	**75.517**	**794**	**77.989**	-

Table 3: Kaplan Meier estimates of Survival time (in days) with respect to interaction between Tuberculosis and various covariates

Covariates		B	Std. Error	p-value	Hazard Ratio	95.0% CI for Hazard Ratio	
						Lower	Upper
Type of TB	PTB	Ref.	-	-	-	-	-
	TB	-3.662	0.53	< 0.001	0.026	0.009	0.073
Gender	Male	Ref.	-	-	-	-	-
	Female	-0.631	0.279	0.024	0.532	0.252	0.825
	Eunuch	0.139	0.587	0.813	1.149	0.363	3.634
WHO stage of AIDS	Stage 1	Ref.	-	-	-	-	-
	Stage 2	0.497	0.512	0.331	1.644	0.603	4.483
	Stage 3	1.099	0.499	0.028	3.002	1.128	7.987
	Stage 4	2.795	0.766	< 0.001	16.357	3.643	73.441
Age (in years)	0 - 14	Ref.	-	-	-	-	-
	14 - 30	1.192	0.598	0.046	3.292	2.838	12.938
	> 30	1.402	0.697	0.044	4.064	1.037	15.929
Interaction terms							
Type of TB* Gender	Female	1.517	0.765	0.047	4.558	1.019	20.399
	Eunuch	2.211	0.988	0.025	9.129	1.316	63.322
Type of TB* Stage	Stage 2	0.776	0.269	0.004	2.173	1.325	14.511
	Stage 3	0.977	0.453	0.031	2.656	1.411	17.187
	Stage 4	-0.188	1.555	0.904	0.829	0.039	17.446
Type of TB* Age	14 - 30	0.873	0.404	0.031	2.393	1.153	37.525
	> 30	1.921	0.381	< 0.001	6.828	3.456	102.185

Table 4: Results of Cox-proportional hazards regression

Covariate		N	No of events	Mean		Median		p-value (adjusted for TB)
				estimate	Std. error	estimate	std. error	
Gender * Type of TB								
PTB	Female	16	12	606.069	21.006	652	58.805	0.004
	Male	51	15	580.083	8.774	584	18.187	
	Eunuch	4	3	528.125	82.796	535	161.916	
TB	Female	21	4	1433.299	176.51	-	-	
	Male	64	11	912.589	26.443	954	24.289	
	Eunuch	6	6	784.833	34.783	787	31.231	
WHO stage of AIDS*Type of TB								
PTB	Stage 1	32	4	623.3	27.892	658	70.032	< 0.001
	Stage 2	32	20	585.29	20.224	593	9.389	
	Stage 3	6	5	570	25.461	545	10.954	
	Stage 4	1	1	323	0	323	-	
TB	Stage 1	15	3	1491.35	166.917	-	-	
	Stage 2	12	4	938.167	68.429	954	119.555	
	Stage 3	33	11	854.927	31.944	933	89.321	

	Stage 4	31	3	692.554	79.884	787	0	
Age (in years)*Type of TB								
PTB	0 - 14	2	2	684	9	675	-	0.005
	14 - 30	28	13	582.462	16.027	584	37.147	
	> 30	41	15	579.772	21.638	591	17.522	
TB	0 - 14	8	1	1683.8	153.126	-	-	
	14 - 30	32	4	995.926	65.365	-	-	
	> 30	51	16	860.847	22.265	890	68.242	

Figure 1: Survival plots with respect to various covariates using Kaplan Meier estimates

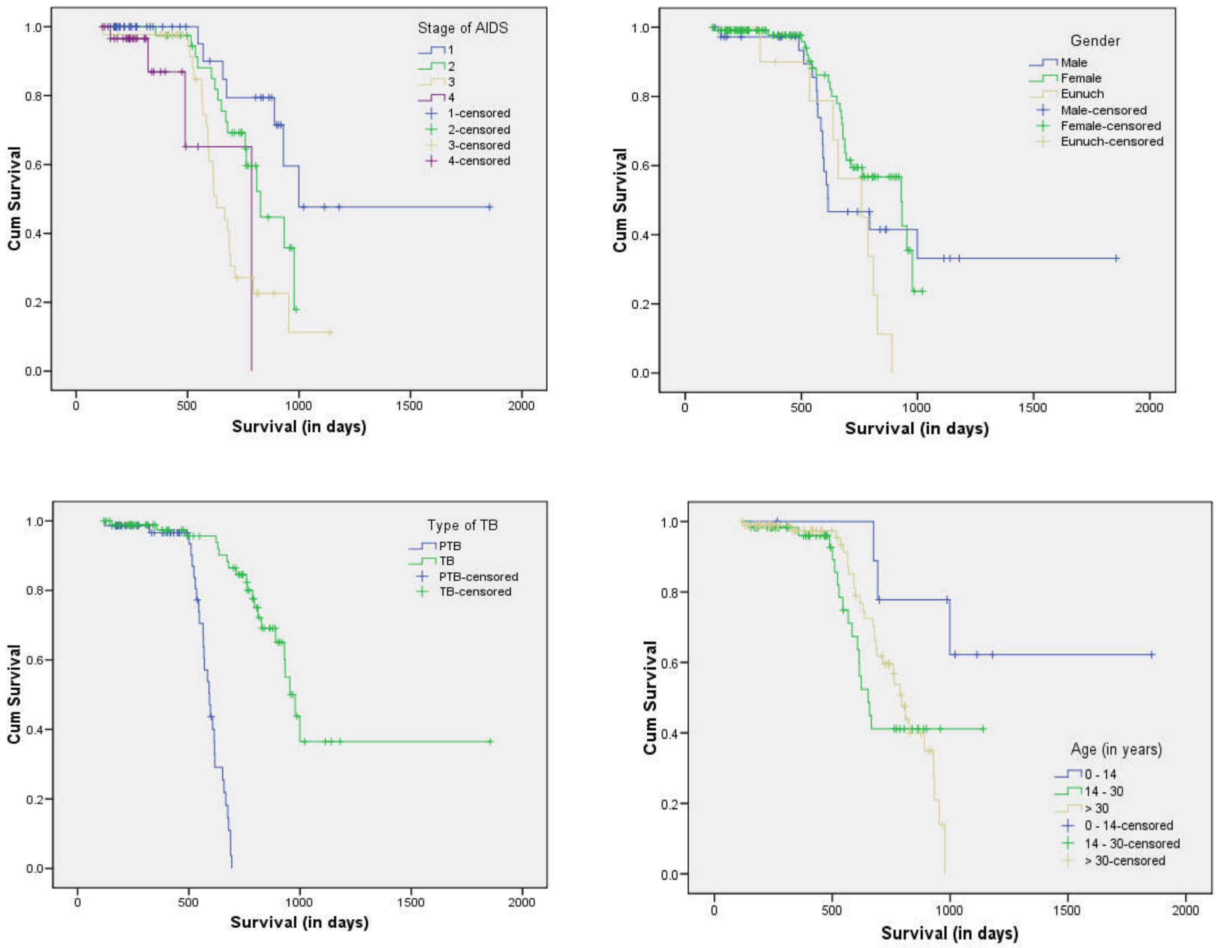
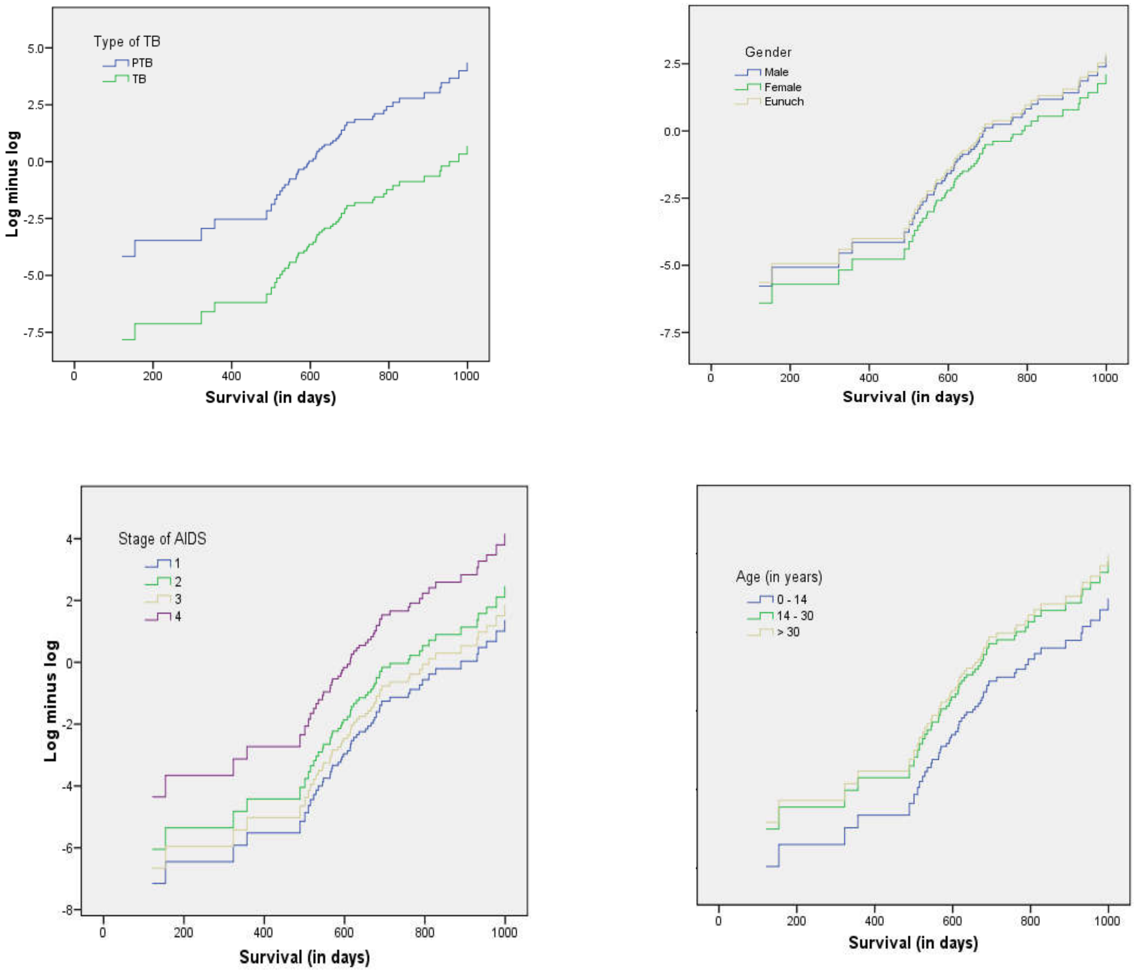


Figure 2: log minus log plots with respect to various covariates



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