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EXPLORING TIME-DEPENDENT FACTORS IN THE SURVIVAL OF TUBERCULOSIS PATIENTS: A COX PROPORTIONAL HAZARDS ANALYSIS

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Abstract:

Background: This research paper is attempted to identify time dependent covariates effects of Tuberculosis patient's database using Cox proportional Hazard Model. The study of time-to-event data with censoring and variables has seen considerable application of the Cox proportional-hazards regression model. Over time, the covariates' values could fluctuate. At the 5% level of significance, the P value suggests that there is no difference between such Model 1 results and that the survival times are same in the male and female groups.

Methodology: The sources of data were collected from National Institute of Research in Tuberculosis (NIRT), Chennai (ICMR). 1237 tuberculosis patients were enrolled for the study, which consisted of a randomized clinical trial with three distinct treatment regimens and a control group. Each regimen was given a six-month course of treatment. Sputum conversion time (from positive to negative) during the course of treatment is the relevant event. The total number of events was 1062, of which 85.8% were cases that experienced the event of interest, which is defined as cases that became diseased throughout the treatment period (6 m), and the total number of censored observations was 175 (14.2%).

Result: In this research paper, initially 1236 samples of patients were considered with six month duration of study period. The patients are treated as the event of interest is smear sputum conversion time into positive to negative during the observation period. Hereafter the number of event occur 1062 patients and remaining patients has been censored. Model 2 results of gender not significant and sputum culture is statistically significant. Hazard ratio value is two groups; the values are 1.075 and 0.762 respectively. It's labelled as high positive and low positive sputum culture status. Model 3, the significant value at the 5% level of significant is P = 0.162, it represents the value from the product term's coefficient for the interaction between gender and sputum culture status.

Conclusion: The P value indicates that there is no significant interaction effect in gender and sputum culture, then remove this noisy model. In addition, point estimate coefficient of gender is proved the hazard ratio HR=1.091 it shows that there is no interaction effect of gender. Finally, the hazard ratio in the variable of sputum culture status HR= 0.847 and conclude the hazard for the high positive group is 0.86 times the hazard for the low positive status group. As a result, we discover that interaction has a minimal value, which making it a better model than crude and adjusted Estimate model.

Key Words: Survival time, Cox PH Model, Crude Model, Interaction model and TB

1.0 INTRODUCTION

1.1 Introduction of Tuberculosis

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The bacteria that cause TB, Mycobacterium tuberculosis, often has an impact on the lungs. Lung TB patients cough, sneeze, or spit, which allows the disease to spread through the air. To become unwell, just a small number of bacteria must be inhaled. Each year, ten million people get tuberculosis. TB is the largest infectious killer in the world, killing 1.5 million people each year (WHO), despite being a preventable and treated infection. HIV-positive people are most frequently killed by TB, and TB also contributes significantly to the rise in resistance to antibiotics. 9.9 million persons worldwide developed Tuberculosis in 2020.

Despite the fact that the illness is widespread, the majority of TB sufferers reside in low- and middle-income nations. Eight nations: India, China, Philippines, Indonesia, Nigeria, South Africa and Bangladesh are home to over half of the world's TB patients. One-fourth of the world's population is reportedly afflicted by the TB bacteria. Only 5 to 15 percent of such people will have active TB disease. While the remaining people are healthy and unable to spread the disease, they do have TB infection. Both TB infection and disease can be treated with antibiotics.

The spread of tuberculosis is a significant public health concern in India. According to estimations from the World Health Organization (WHO), India is home to the world's greatest tuberculosis pandemic. In 2020, 26% of incident TB cases worldwide originated in India. In India, there are 192 cases for per 100,000 people.

1.2 Introduction of Cox Model

The non-parametric test in survival analysis does not control the covariates, we find out only the median survival time is called as a Kaplan Meier curve. When we have the study incorporates many explanatory variables in these method multivariate approaches. So we are needs another technique in survival data with the censoring data. The semi parametric regression models are worn to examine the relation between survival time and one or many predictors variables, usually denoted as covariates in the survival analysis because the semi parametric model do not especially describe the baseline of hazard function.

2.1 Cox Proportional Hazard Model

The proportional hazard function was proposed by Cox in 1972. This survival model is a statistical method for examining the connection between a subject's survival and additional explanatory factors. For other explanatory factors, the cox model offered a treatment effect estimate. Then, based on the prognostic variable, calculate the risk or failure of a person. As a result, the hazard function for the distribution of survival time is constant across time.

The multiple regression method is a typical approach for inspecting the relationship between survival time and prognostic variables. Let we consider $x_1, x_2, \ldots, x_p$ be the P is the possible covariates or explanatory variables. The i^{th} patients and observed values of p variable are $x_{1i}, x_{2i}, \ldots, x_{pi}$. In this multiple regression model approach, the survival time of i^{th} patient andt_i, is the dependent variable. So we find out the relation of t_i and function of t_i.

Semi parametric model exposed, appropriate for the analysis of survival analysis with censoring data and without censoring data. The hazard function is dependent variable in this model. But when we have the survival times are continuously distributed and possibility of the failure or ties it can be ignored, the cox suggested using the model is given below

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$$g(x) = \exp(x\beta), \text{ where } x = (x_1, x_2, \ldots x_p) \text{ and}$$
$$\beta = (\beta_1, \beta_2, \ldots\ldots, \beta_p)^{t}.$$

Now the hazard function is

$$h(t|x) = h_o(t) \exp(\beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_p x_p)$$

Here, $h_o(t)$ is the failure rate of the survival function distribution when we have all the covariates are ignored and the $\beta's$ are regression coefficient. The hazard assumption in the semi parametric model is that study period or study group is proportional to that of the basic survival distribution $h_o(t)$. The baseline of hazard function contains only time t but does not involve the value of covariates.

2.2 Proportional Hazard Assumption

Lehmann (1953) proposed, the regression model exposed survival distribution is commonly containing the assumption of proportional hazard functions. A proportional hazards model possesses the property that different individuals have hazard functions that are proportional to one another, that is, $h(t|x_1)/\ h(t|x_2)$ the ratio of the hazard functions for two individuals with covariates. $x_1 = (x_{11}, x_{21}, \ldots, x_{p1})$ and $x_2 = (x_{12}, x_{22}, \ldots, x_{p2})$, does not vary with time t. This implies that the hazard function given a set of covariates x = $(x_1, x_2, \ldots, x_p)$ can be written as

$$h(t|x) = h_o(t)g(x)$$

where g(x) is a function of x which characterizes how the hazard function changes as a function of subject covariates and $h_o(t)$ can be considered as a baseline hazard function of an individual for whom g(x) = 1.

2.3 Partial Likelihood Ratio Test

The partial likelihood ratio test denoted as G. partial likelihood ratio test is calculated by two times the difference between the log partial likelihood but the model contains the covariates. The log partial likelihood this model not contains the covariates, so that the formula is given below,

$$G = 2\{L_p(\hat{\beta}) - L_p(0)\}, \text{ where } L_p(0) = -\sum_{i=1}^{m} \ln(n_i)$$

n_i Indicates the number subject in the risk set at observation survival time is called as $t_{(i)}$. The coefficient of covariates is equal to zero under the null hypothesis. This statistics will be follows the chi square distribution with one degree of freedom.in this distribution we can be used to obtained the probability value to test the significant of the coefficient. The level of significance for test id P $(\chi^2(1) \geq G) < 0.001$. when you get the result can you reject the null hypothesis and we conclude the covariates is significant associate to survival time.

2.4 Wald Statistic Test

We may compute the coefficient's significance by dividing the variable's estimated coefficient by the coefficient's estimated standard error. One of the ratio tests is frequently employed as a Wald statistic in this procedure. The Wald statistic, often known as Z, is based on the assumption that data will be distributed normally. same mathematical presumption that was necessary for the log partial likelihood ratio test was covered. Given by is the formula for the Wald statistic.

$$Z = \frac{\hat{\beta}}{\widehat{SE(\hat{\beta})}}$$

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$\hat{\beta}$ = The coefficient of the corresponding variable.

$\widehat{SE(\hat{\beta})}$ = Coefficient of standard Error.

3.0 Review of Literature

Farzaneh Amanpour, Erfan Ghasemi, Alireza Abadi, Parvin Yavari, Monireh Dehghani-Arani, Hamid Alavi-Majd, and Chris Bajdik (2014) 1. They are made aware of the four stages of breast cancer, which are stage I, stage II, stage III, and stage IV. Chemotherapy and radiotherapy were administered to the patients. The Cox proportional hazard model is used. Find out then how radiotherapy compared to chemotherapy for treating breast cancer in stages I and II.

Smokers have a greater risk than non-smokers, according to K. S. Joseph, Cande V. Ananth, , Michal Abrahamowicz , Justin Grondines, and Michael S. Kramer, Robert W. Platt (2004)8; however, the hazard ratio climbed from 1.09. The cumulative consequences of smoking on mortality are indicated by the rising negative effect of smoking with gestational age. The lung dataset was proposed by Zhongheng Zhang (2016)11 using the cox proportional hazard model. Investigated was the attributable fraction function for the age variable both adjusted and unadjusted. He learns from the data that, after adjusting for confounders, the age-attributable fraction is decreasing.

Mahdi Afshari, Jamshid Yazdani Charati, Siavosh Abedi, Mahmood Moosazadeh, and Asghar Nezammahalleh (2017)9, In this article, individuals with cancer and TB are found to be key determinants of TB treatment-related mortality. Kaplan & Meier, and Cox regression model usage, the applicable survival analysis was carried out. Finally, note that after adjusting for covariates, men with cancer and TB positive patients had considerably higher death rates.

Results from the application of cox and parametric models to cancer patient data were reported by Ebrahim Hajizadeh, , Azadeh Safaee, Alireza Abadi, and Mohammad Reza Zali1, Mohamad Amin Pourhoseingholi , Bijan Moghimi Dehkordi (2007)7. Patients who received their diagnoses after turning 45 had a higher risk of dying. There might not be one model that is perfect noticeably superior to others given how similar the cox exponential. The log normal regression is substantially supported by the data.

Wei Wang and Jeffrey M. Albert (2017) conducted the study in order to analyse the issue of how the social, behavioural, and health sciences partition and exposure effect among certain route effects and to gauge its importance. Mediation analysis is based on the potential outcomes estimate for or proportional hazard model. A formula approach with straightforward parametric models is used in conjunction with the baseline log communicative functions to carry out a sensitivity analysis to calculate the impact of meditation on several scales. This study II results in low bias of meditation effect Jackson heart study who conducted.

According to Jonathan E. Gellar, Elizabeth Colantuoni, Dale M. Needham, and Ciprian M. Crainiceanu (2015), the exposure is caused by two sampling functional processes and was measured using the Cox proportional hazards model at the baseline. Regression and the proportional hazard model must be combined. In order to better understand the association between time to death after discharge and daily measurements of illness severity gathered in the critical care unit, this analysis method was employed on patients with acute respiratory disease distress syndrome. Multiple functional predictors, time-varying coefficients, and missing spacing data were all added to the model.

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In David J. Hendry's (2014) paper, a technique for creating survival times that use Cox proportional hazards and a time-dependent covariant is developed. The researcher uses longitudinal biomedical data in this method, which is based on sample transformation of random variables generated according to truncated exponential distribution to produce for simulation experiments, where the results about the proposed procedure performed support the assumptions made with Cox proportional hazards.

4.0 Methodology

Retrospective cohort studies using TB patients provided the data. The data included in this application pertains to the 1237 tuberculosis patients who participated in a three-treatment, six-month trial at the Tuberculosis Research Centre of the Indian Council of Medical Research (ICMR), Chennai, India. The data have been analysed using STATA statistical software.

4.1 Database

In this study Split-drug regimens are an innovative method for treating patients with pulmonary tuberculosis that has been detected by sputum smear. Tropical Medicine and International Health, 9, pp. 551-458, 2004. Sputum conversion time (from positive to negative) during the course of treatment is the relevant event. The total number of events was 1062, of which 85.8% were cases that experienced the event of interest, which is defined as cases that became diseased throughout the treatment period (6 m), and the total number of censored observations was 175 (14.2%).

1. Age - The patients admitted in the age group between 9 to 68 years.
2. Sputum Culture (Status at End of Treatment (6m))

(i). Censored – (0) All Negative cases consistently

(ii). Event – (1)

3. Event - (i) Positive to negative sputum conversion – (1)

   (ii) Censored as code – (0)
4. Time(in Months)

The event is coded as 1, whereas censorship is labelled as 0. The data set is applied to comparison empirically the disparity in survival rates between two treatment groups under various model assumptions.

5.0 Result and Discussion

In this section used three Cox Proportional Hazard model and they are (1) Crude Model, (ii) Adjusted estimated model and (iii) interaction model. In crude model results are shown in table.1 and its shows that result in cox proportional hazard model, In this model is called as crude model because the model is consider for only one variable. Gender variable is very important of clinical trial randomized method. Gender consists into two groups in male and female.

Table.1 Crude Model - Cox Proportional Hazard Model

Variable	Coefficients (β)	Standard Error	Wald	P Values	Hazard Exp(β)	95% CI Exp(β)	
						LL	UL
Gender	-0.120	0.154	0.600	0.439	0.887	0.656	1.201
-2LL = 3053.86							

The P value is indicating there is no significance different so the survival times are same in the both groups. Wald test statistics is roughly equivalent to the ordinary normal or Z variable.

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However, the find out Z the coefficient of gender by divided the standard error.

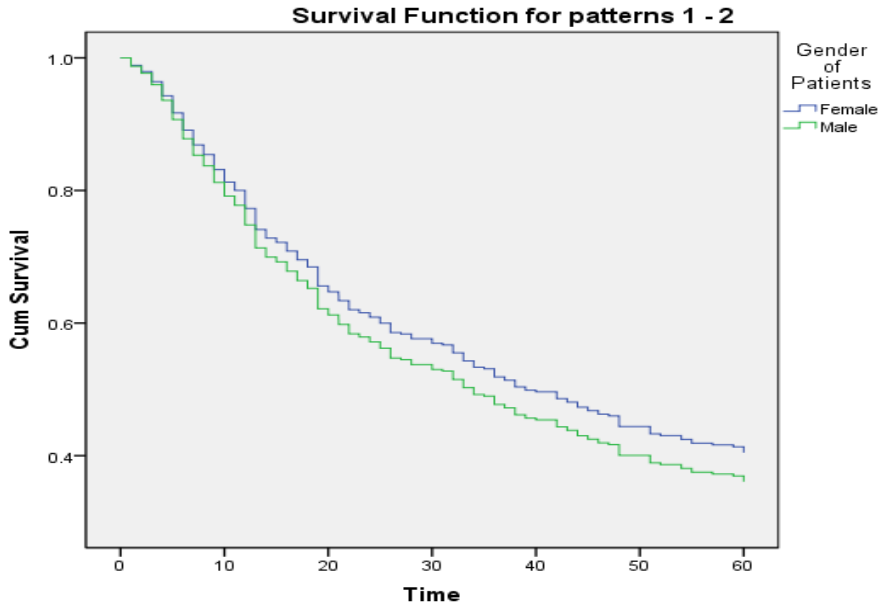

Figure.1 Survival Curve for Gender (Unadjusted)

Figure.1 shows that survival curves show that the unadjusted curve for the gender parameter and it is categorized as male and female. From the figure 1 give the information that the survival time compare the gender has male better than female survival time.

Table.2 Adjusted Estimate Model –Cox Proportional Hazard Model

Variables	Coefficients (β)	Standard Error	Wald	P Values	Hazard Exp(β)	95% CI Exp(β)	
						Lower	Upper
Gender	0.072	0.156	0.212	0.645	1.075	0.791	1.459
Culture Status	-0.272	0.138	3.885	0.049	0.762	0.581	0.998
-2LL = 3049.827							

Adjusted estimated model results shows in table.2 using two variables are gender and sputum culture status. This model to use and identify the effect of gender adjusted for sputum culture status. The probability value of gender variable (P = 0.645) and it is statistically not significant and there is no effect of adjusted estimate model. The other variable sputum culture value of P is 0.049 and it is significant. Hence there is significant difference between the adjusted sputum culture statuses. Hazard ratio value is two groups; the values are 1.075 and 0.762 respectively. It's labelled as high positive and low positive sputum culture status. The value of HR= 1.075 and its labelled high positive sputum culture states. The value of HR = 0.762 and it is labelled low positive sputum culture status.

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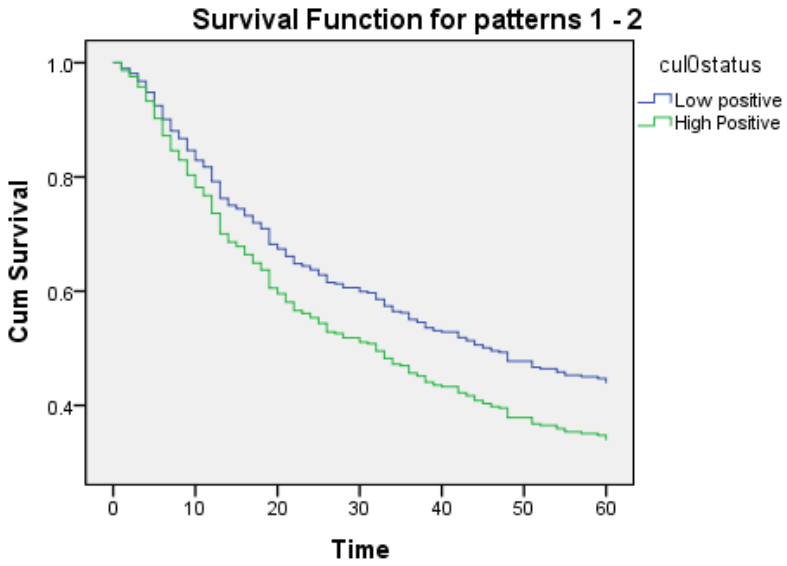

Figure-2 Survival Curve for Culture Status (Adjusted)

In the Figure.2 visualize that the adjusted survival curve is different significantly form the unadjusted survival curves. The variable was considered sputum culture status divided into two parts is high positive status and low positive status. Figure 2.shows that the survival time of sputum culture status is perform high positive better the survival time low positive status of sputum culture.

Table.3 Interaction Model – Cox Proportional Hazard Model

Variables	Coefficients (β)	Standard Error	Wald	P Values	Hazard Exp(β)	95% CI Exp(β)	
						Lower	Upper
Gender	0.087	0.187	0.219	0.640	1.091	0.757	1.573
Cul.Status	-0.166	0.154	1.163	0.281	0.847	0.626	1.146
Gender * Culture Status	-0.466	0.334	1.953	0.162	0.627	0.326	1.026
-2LL = 3047.824							

From the table 3 is show that the summary of Interaction affects between gender and culture status with the help of semi parametric model. It focuses the method of estimation in this model the coefficient of beta. The significant value at the 5% level of significant is P = 0.162, it's the value from obtained the interaction coefficient between gender and sputum culture status. There is no significant interaction impact, according to the P value in gender and sputum culture, then remove this noisy model. In addition, point estimate coefficient of gender is proved the hazard ratio HR=1.091 it shows that there is no interaction effect of gender. Finally, the hazard ratio in the variable of sputum culture status HR= 0.847 and conclude the hazard for the high positive group is 0.86 times the hazard for the low positive status group.

On the basis of the -2LL function, the third model is then contrasted with the first two models.

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The interaction model's -2 log likelihood value of 3047.824 was retrieved from STATA output. Compared to the crude model (-2LL = 3053.86) and the adjusted estimate model (-2LL = 3049.827), this model has a minimum value of log likelihood. As a result, we discover that interaction is a better model than other models because it has a minimal value.

6.0 Conclusion

In this research paper is to apply three Cox proportional hazard model. In these three models are achieved interesting results. In this study y is a time dependent covariates effect of Tuberculosis patient's database using Cox proportional Hazard Model. The secondary sources of data were collected from ICMR, Chennai. The patients admitted were based on randomized controlled clinical trial within three different types of treatment along with a control regimen. In this research paper, initially 1237 samples of patients were considered with six month duration of study period. The patients are treated as the event of interest is smear sputum conversion time into positive to negative during the observation period. Hereafter the number of event occur 1062 patients and remaining patients has been censored. Model 1 results are established the P value is indicating there is no significance different so the survival times are same in the male and female groups at 5% level of significance. Model 2 results of gender not significant and sputum culture is statistically significant. Hazard ratio value is two groups; the values are 1.075 and 0.762 respectively. It's labelled as high positive and low positive sputum culture status. Model 3, the significant value at the 5% level of significant is P = 0.162, it's the value from obtained the coefficient of product term for interaction of gender and sputum culture status. In addition, point estimate coefficient of gender is proved the hazard ratio HR=1.091 it shows that there is no interaction effect of gender. Finally, the hazard ratio in the variable of sputum culture status HR= 0.847 and conclude the hazard for the high positive group is 0.86 times the hazard for the low positive status group.

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