An Overview of Non Parametric Model in Tuberculosis Data

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Abstract

The objective of this paper to assess whether there is any difference in the sputum conversion with respect to the covariates age, types of regimen. The event of interest is the sputum conversion during the treatments periods, i.e sputum at the base line is positive, and then turns to negative during the treatment period. The covariates considered in the study areAge of the subject, Weight of the subject at baseline, Regimen, Pre-treatment drug susceptibility pattern.

Keywords - *Kaplan Meier Estimator, Kaplan Meier curve, Life table analysis*

I INTRODUCTION

Tuberculosis has probably been responsible for the greatest morbidity and mortality of all the infectious disease that have plagued man it has apparently plagued man ever since human beings emerged as a species on this planet. Tuberculosis is infectious disease caused by Bacillus called Mycobacterium tuberculosis most commonly affects the lungs but also can involve almost any organ of the body. The two types of TB are Pulmonary TB and Extra pulmonary TB. Pulmonary TB is the most frequent form of the disease occurring over 80% of cases. This is the form of TB, which may be infectious. Pulmonary TB mainly affects the lungs. Extra pulmonary TB is the TB affecting organs other than lungs, most frequently pleura lymph nodes, spine, joints and genitourinary tract, nervous system or abdomen. Tuberculosis may affect any parts of the body. Tubercular meningitis, tuberculoma of the brain, TB pleurisy etc., are the various types of extra pulmonary TB.

The term "survival analysis" pertains to a statistical approach designed to take into account the amount of time an experimental unit contributed to a study i.e., it is the study of time between entry into observation and a subsequent event. Survival times are data that measure follow-up time from a defined starting point to the occurrence of a given event, for example the time from the beginning to the end of a remission period or the time from the diagnosis of a disease to death. Standard statistical techniques cannot usually be applied because the underlying distribution is rarely Normal and the data are often 'censored'.

II METHODLOGY

The tools used to analysis the data are:

- Kaplan Meier Estimator
- Kaplan Meier curve
- Life table analysis

LIFE-TABLE ANALYSIS

The Life-table analysis is one of the oldest techniques for measuring mortality and describing the survival experience of a population. It has been used by actuaries, demographers, governmental agencies, and medical researchers in studies of survival, population growth, fertility, migration, length of the married life, length of working life, and so on. There are two kinds of population life tables; the cohort life table and current life table. The current life table is constructed by applying the age-specific mortality rates of a population in a given periods of time to a hypothetical cohort of 100,000 or 1,000,000 persons. The staring pint is birth at year 0. Two sources of data are required for constructing a population life table.

1.Census data on the number of living persons at each age for a given year at midyear and

2. Vital statistics on the number of deaths in the given year for each age. The population life table is often used to refer to the current life table.

The general notation of life table.

Column	Notation	Definition
1.	$(x, x+n)$	Age interval or time period of life between two exact ages stated in years.
2.	${}_nq_x$	Proportionof persons alive at the beginningof the age interval who dieduring the ageinterval.
3.	l_x	Starting number of new born in the life table.
4.	${}_nd_x$	The number of person in the cohort who die in the age interval $(x, x+n)$
5.	${}_nL_x$	Number of years of life lived by the cohort with in the indicated age interval $(x, x+n)$.
6.	T_x	Total persons years of life contributed by the cohort after attaining age x.
7.	$e^{o}{}_x$	Average number of years of life remaining for a person alive at the beginning of the age interval x.

KAPLAN MEIER SURVIVAL CURVE

The curve is defined as the probabilityof surviving is a given length of time whileconsidering time in small intervals. It is also called product limit estimate. Kaplan Meier probabilityof survival gives survival time and failure status informationin a sample of subjects.

III EXPERIMENTAL STUDY

In experimental studies, the effect of a specific intervention on the specific outcome id studied. They are done at various stages. The stages include pre-clinical trials and clinical trials may be undergone in different phases. Based on the design, the clinical trials may be randomized or non-randomized.

A clinical trial may be designed to

- Assess the safety and effectiveness of a new medication or device on a specific kind of patient.
- Assess the safety and effectiveness of a different dose of a medication than is commonly used.
- Assess the safety and effectiveness of an approved medication or device on a new kind of patient.
- Assess whether the new medication or device is more effective for the patient's condition than the already used standard medication or device.
- Compare the effectiveness in patients with a specified disease of two or more already approved interventions for that disease

RANDOMIZED CONTROLLED TRIAL (RCT)

It is a type of scientific experiment most commonly used in testing medicine or health technologies (such as pharmaceuticals or surgery). According to Lachine (1998), 'RCTs are considered the most reliable form of scientific evidence in healthcare because they eliminate spurious causality and bias. RCTs involve the random allocation of different intervention (or treatments) to subjects. This ensures that known and unknown confounding factors are evenly distributed between treatment groups.

PHASES OF CLINICAL TRIAL

For pharmaceuticals, clinical trials are commonly classified into four phases. For new drugs, the drug development process will normally proceed through all four stages over many years. If the drug successfully passes through the phase I, II and III it will usually be approved for use in general population. Phase IV are 'post approval' studies. Before pharmaceutical companies start clinical trials on a drug. They conduct extensive pre-

clinical studies.Phase 0: This is a recent designation for exploratory, first in human trials conducted in accordance with US FDA 2006 guidance on exploratory investigational new drug studies.

Phase I:These are first stage of testing in human subjects. Normally a small (20-80) group of healthy volunteers will be selected. This phase includes trials designed to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of a medication.

Phase II*:*Once the initial safety of the study drug has been confirmed in phase I trials, phase II trials are performed on larger groups (200-300) and are designed to assess how well the drug works, as well as to continue phase I safety assessments in a larger group of volunteers and patients.

Phase III:These studies are randomized controlled trials on large patients groups (300-3000 or more depending upon the disease, medical condition studied) and are aimed at being the definitive assessment of how effective the drug is, in comparison with current 'gold standard' treatment. Once a drug has proven satisfactory after phase III trials, the trials results are usually combined into a large document containing a comprehensive description of the methods and results of human and animal studies, manufacturing procedures, formulation details and shelf life. This collection of information makes up the "regulatory submission" that is provided for review to various regulatory authorities in different countries so they can then grant the sponsor approval to market the drug.

Phase IV: It involves the post launch surveillance and on-going technical support of a drug. Post launch safety surveillance is designed to detect any rare or long-term adverse effects over a larger patient population and time scale than possible during the initial clinical trials. Such adverse effect detected by Phase IV trials. The data set contain 211 TB patients randomly allocated to controlled clinical data 5 treatment group (1, 2t, 2o, 3t, 3o) duration of 6 to 8 months. The event of interest is sputum culture conversion during treatment period. The covariates are given below:

Age (in years): The age patient is taken into consideration. It is the age observed the patient when they start the treatment.

Sex (Male-1, Female-0): This indicates the gender of the patient, Male or Female patient. Treatment: Each treatment has treated as a Regimen. This Regimen is a combination of certain drugs that are administered, based on the nature and the severity of the disease for an individual. Depending on the nature of the seriousness of the disease, the patients were treated with different Regimens.Regimen 1(1), Regimen 2(2t, 2o), Regimen 3(3t, 3o).Weight (base line weight in kg): The weight of patient is taken into consideration. It is the weight observed the patient when they start the treatment. Pre-treatment drug susceptibility: Conformation test for identifying sensitivity pattern.

Culture: A test to where there TB bacteria in our phlegm or other body fluids. This test can take 2 to 4 weeks in most laboratories.Directly observed therapy- A way of helping patients to take their medicine for TB. If you get DOT, you will meet with a health care worker every day or several times a week, you will meet at a place you both agree on. This can be the TB clinic, your home or work, any other convenient location. You will take the medicine while the health care worker watches. Negative- Usually refers to a test result. If you have a negative you probably do not have TB infection.Positive- Usually refers to a test result. If you have a positive, you probably do have TB infection.

Smear:A test to see whether there are TB bacteria in your phlegm. To do this test, lab workers smear the phlegm on a glass slide, stain the slide with a special stain, and look for any TB bacteria on the slide. This test usually takes 1 day to get the result.Sputum- Phlegm coughed up from deep inside the lungs. Sputum is examined for TB bacteria using a smear; part of the sputum can also be used to do a culture.

Time (in months):This Time indicates the month which the patient is cured of the disease. Many a times, the patients are cured, as soon as the treatment starts. In this case, the time is given as 0(which is the 0^{th}months). P12 this percentage intake of drugs in phase and phase.

Itu (Mantoux): It is < 10mm have more chances for conversion of sputum when compare to > 5mm. (The event code as 1 and censoring is 0)

LIFE TABLE ANALYSIS

Life table analysis is summarizing the mortality experience of a specific population for a Specific period of time. Life table method has been applied to patient with a given disease who has been followed for a period of time.

TABLE I LIFE TABLE ANALYSIS

INTERVAL	BEGINNING TOTAL	CONVERTED	CENSORED	SURVIVAL FUNCTION	S.E	95% CONFIDENCE INTERVAL
1-2	211	46	3	0.7804	0.0286	0.7180 0.8306
2-3	162	58	2	0.4993	0.0347	0.4294 0.5651
3-4	102	49	1	0.2582	0.0306	0.2005 0.3197
4-5	52	17	0	0.1738	0.0266	0.1254 0.2289
5-6	35	11	1	0.1184	0.0228	0.0784 0.1672
6-7	23	2	1	0.1079	0.0219	0.0698 0.1553
7-8	20	5	4	0.0779	0.0195	0.0454 0.1217
8-9	11	3	8	0.0445	0.0183	0.0177 0.0907

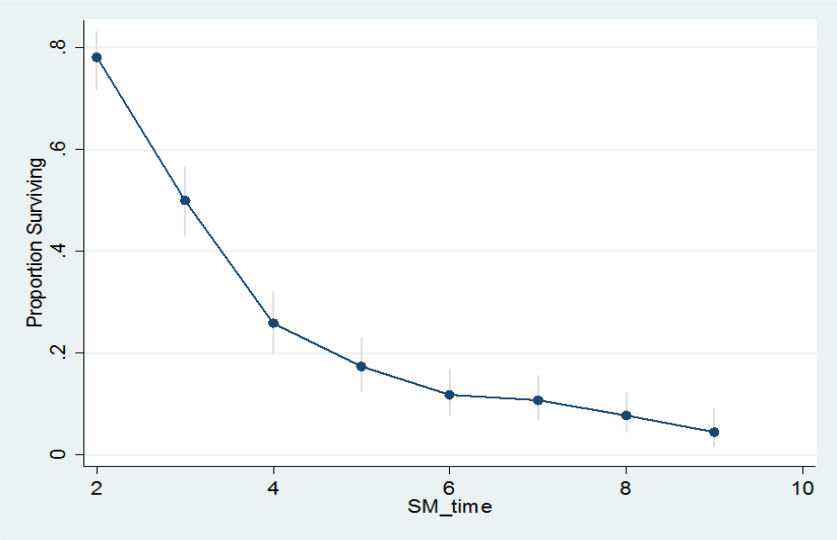

Fig. 1 LIFE TABLE ANALYSIS SURVIVAL TIME

Discussion

- The interval 1-2(<60days) beginning total is 360 after exclusive from converted 104
- Cases become from positive to negative converted (28.8%).
- The interval 2-3(60-90 days) beginning total is 256 among 167 cases convertedfrom positive to negative converted (46.3%) one not converted as negative during the period.
- Major converted period<3rdof month was 261 cases that is (72.5%) have converted within 3 months of Time.

COMPARISON OF THE EVENT OF INTEREST WITH RESPECT TO SEX:

Null hypothesis:

There is no significant difference among the male and female patientin the time of sputum conversion from positive to negative

Alternative hypothesis:

There is a significant difference among the male and femalePatients in the time of sputum conversion from positive to negative.

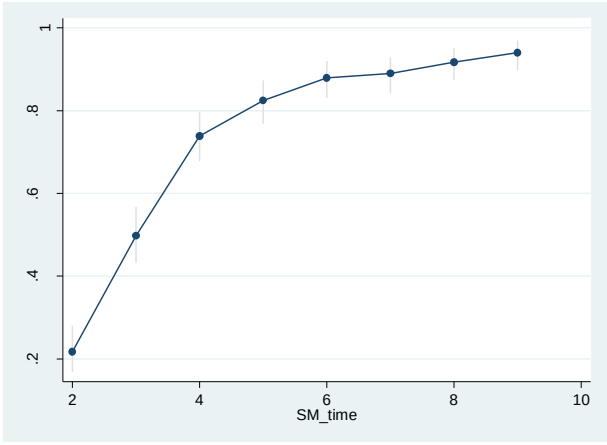

TABLE II SEX STATUS DISTRIBUTION

SEX	TOTAL NO	NO OF EVENTS	CENSORED NO	CENSORED PER
Female	37	34	3	8.1%
Male	174	157	17	9.8%
Overall	211	191	20	9.5%

Total number of subjects: 211Total number of events: 191Number of Males: 174
Number of events in males: 157Number of Females: 37 Number of events in females: 34

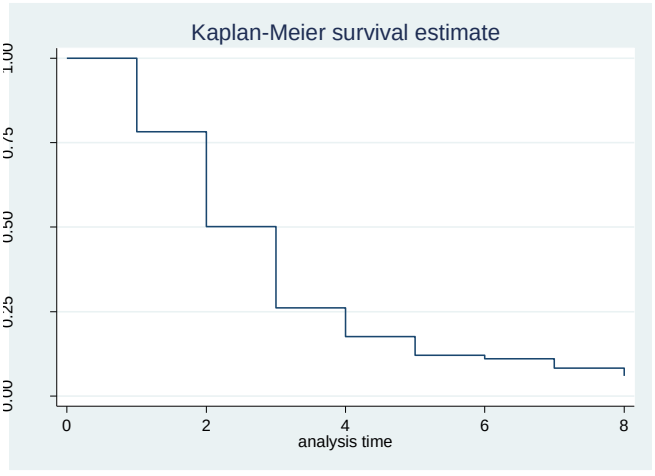

Fig. 3 KAPLAN – MEIER SURVIVALESTIMATE

CONCLUSION

The covariates such as age at baseline, 6 different regimen, weight at base line, pre Treatment drug susceptibility pattern for this analysis.

The Life table analysis from (Fig.1) the major converted period < 2rd of the month was 58 Cases that is (49.2%) have converted within 2 month of time.

The Kaplan – Meier Estimator from (Fig.3) there is a difference between the male a Female patients in the time of sputum conversion from positive to negative. The median time of Sputum conversion among the male and female patients is found to be 2 months.

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