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Dose Escalation using Kaplan-Meier (Product-Limit) Model

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Abstract:- This paper majorly deals with the different statistical techniques that can be applied to the dose escalation data of phase-I clinical trials in oncology. The paper proposes the use of Kaplan-Meier estimation of a non-parametric model which is further extended to the Ph (Proportional Hazard Model) with the help of the Cox-Regression. It is focused on the DLE (Dose Limiting Event) along with the covariates like Anti-Factor rendered, doses given subjected to the cohorts .The maximum level of dose toleration is considered as the estimate of the maximum likelihood estimation of the density function derived. The paper proposes these new statistical methods for the data to improvise the efficacy of cytostatic drugs by validation using the R-software to generate these results.

Keywords:- *Dose-Escalation,Kaplan-MeierEstimate,PH model,Cox Regression Model.*

I. INTRODUCTION

Cancer is the world's leading ailment that has caused myriad deaths to near and dear ones globally. According to the estimate in the United States there has been as many as 606880 deaths in 2019.Cancer has always been subjected to treatment in the form of doses of drugs or radiation therapy. The main objective of this research paper is to deal with the issue of what should be the maximum therapeutic dosage delivered which would minimize the damage to the healthy cells by proposing new statistical inference to the phase-I clinical trials. In this paper the evaluation of the dose toxicity has been taken into consideration for finding the target dose necessary for intake in phase-I clinical trials related to oncology.

II. LITERATURE SURVEY

The last twenty-five years have seen significant development in the use of Bayesian techniques in the design and analysis of clinical trials (Ashby (2006), Grieve (2007)). When more than one dose of the same drug was tested, some dose-response curve may be assumed and if the Bayesian principle is used to make inference, it is necessary to give the joint prior distribution of the parameters of the dose response curve. Prior distributions for generalized linear models' parameters were proposed by Bedrick et al. (1996). The form of prior distribution for generalized linear models' parameters proposed by Bedrick et al. (1996) generalizes the prior distribution proposed by Tsutakawa (1975). This form of prior distributions is used in one of the phase II design that is reviewed and will also be adopted in the dose selection procedure. The models were demonstrated by Bedrick et al. (1996), which we are interested in. Whitehead (2006) has reviewed this form of prior distribution in his paper wherein he has made use of binary DLE (Dose Limiting Event) and continuous Desirable Outcome (DO). Stallard (1998) points out that the outcome of a phase II study is a decision of whether to continue with further evaluation or to abandon the therapy due to lack of efficacy or high toxicity or cost and hence argues for Bayesian decision techniques. Decision theory involves defining gain functions for different actions (or decisions) that can be taken and comparing the expected gain from each action. The best decision is the one with the highest expected gain. Lindley (1985) also proposed good introduction to the basic concepts in decision theory.

III. CENSORING

Data are censored if we do not know the exact value of each observation but do know the information about the value of each of the observation in relation to one or more bounds. Censoring plays a pivotal role in these phase-I clinical trial data and provides much scope for statistical inference. Censoring is present when we do not observe the exact length of the lifetime, but observe only that its length falls within some interval. For these medical studies we mostly consider type I censoring and type-II censoring.

➢ *Definition:*

- *Type-I Censoring:*

When the censoring time C*i* are available prior then this type is called Type-I censoring. The following is also a special case of random censoring.

- *Type-II Censoring:*

The mechanism driven by Type-II censoring calls for the continued observation until a predetermined number of deaths has occurred. This can be simplified because the number of events of interest is non-random.

Censoring in hand in the representational inference on the available observations with each instance. It pays attention to the effect of the analysis drawn from the plan of observation bringing into the light the concept of censoring.

Example:

If there is a strong proof during a medical trial experiment, that the investigation might have to end before the stipulated time period so that an improvised treatment can be rendered to all the subjects or entities under study or

have the inferior responses subjected to withdrawal from the treatment.

IV. KAPLAN-MEIER (PRODUCT-LIMIT) MODEL

A. Introduction

We shall firstly derive the empirical distribution function for censoring. So for this we shall consider the lifetimes as function of time without mention of the starting age the speciality is that this can be extended for a new born, a live aged x .With reference to the phase-I clinical trials we base our studies on time since the doses have been introduced to the patient .We can eventually model the age of the patient as required taking it to be an explanatory variable in regression model.

➢ *Remark:*

Per say, we would want to predict the future lifetime of the patient suffering from cancer, which would not only depend on age but on duration and cohort factors.

B. Assumptions and Notations

In our case let us consider a population with entities of a non-informative right censoring following say some m deaths in the observational plan. This assumption of non-informative censoring will ensure that the survival probabilities of the population under study is not systematically higher or lower that the survival probabilities of the lives taken into the account of censoring.

Let the time at which these deaths were observed given that they were ordered in a sequence be as

$t_1<t_2<t_3<$ ……$<t_o$

We do not assume that k=m, so that we include more than a single life dying on the same day. Suppose we observe d_i deaths are observed at time t_i Observation of the remaining n-m lives is censored. Suppose c_j lives are censored between times t_j and t_{j+1} where we define $t_0=0$ and $t_{k+1}=\infty$ to allow the censored observations after the last observation failure time then $c_0 +c_1 +....+c_k=n-m$. We can then define c_j as the number of lives that are withdrawn from the investigation between times t_j and t_{j+1} for the purpose other than those under study.

The Kaplan-Meier estimator has the following assumptions:

- The hazard rate is null except on the occasion when the event happens in the sample.
- The hazard of any event for a particular duration of time t_j is equal to

$$\frac{dj}{nj}$$

Where d_j is the number of individuals experiencing the event at instance t_j and n_j is the number of individuals subjected to the risk of experiencing the event just prior to duration t_j

- Indiviuals who are censored are withdrawn from the trial for that duration, save those who are censored immediately so that they still are subjected to the risk at that instance.

V. METHODOLOGY

We partition the duration into small intervals to avoid the occurrence of events at very large intervals. We are not assuming that the risk for the event happening in any of these trials is zero. We assume that for very small intervals of the event's occurrence the hazard is constant within each of these intervals, but variation is possible. We estimate the hazard within each interval containing the event duration as t_j given as.

$\lambda=\frac{dj}{nj}$

This is often expressed as the estimate arising from a MLE whose likelihood is expressed as

$$\prod_{j=1}^{k} \lambda_j^{d_j}(1-\lambda_j)^{n_j-d_j}\ldots$$

This proportional to the product of independent binomial likelihoods, so that the maximum is obtained by setting

$$\hat{\lambda} = \frac{d_j}{n_j}.$$

Where

$$1 \le j \le k.$$

VI. KAPLAN-MEIER ESTIMATE

If we assume that

$$1 - F(t) = \prod_{t_j \le t} (1-\lambda_j).$$

Since 1-F(t) is also the Survival function we can estimate this using the Kaplan-Meier Estimate.

$$\hat{S}(t) = \prod_{t_j \le t} (1-\hat{\lambda}_j)$$

To compute the Kaplan-Meier estimate of the survivor function we simply multiply the survival probabilities within each of the interval up to and including the duration. The survival probability at time t_j is estimate by

$$1 - \hat{\lambda}_j = \frac{n_j - d_j}{n_j}.$$

Due to the fact that these survival probabilities are multiplied together it is called as product-limit estimate. For better effect we can divide these intervals into finer partitions of time and estimate the survival function as the product of the probabilities surviving each sub-interval. The Kaplan-Meier estimate of the survival function is constant after the last duration at which an event is observed to occur.

VII. COMPARISON

Since Kaplan-Meier estimates are often used to compare life time distributions of two or more populations.

➢ *Remark*

- For our phase-I clinical trials this is very helpful in estimating the statistical properties.
- For the purpose under study we have had an approximation of the variance using the Greenwood's formula.

$$var[\hat{F}(t)] = (1-\hat{F}(t))^2 \sum_{t_j \le t} \frac{d_j}{n_j(n_j-d_j)}.$$

VIII. HAZARD MODELS

A. Covariates

Estimates of any distribution here we considered it to be non-parametric are limited in their ability to deal with important questions in statistical analysis such as the effect of the covariates on the efficacy rate of the dose or in our case the Maximum Tolerated Dose.

A covariate is any quantity recorded in respect of each life such as age, sex, type of treatment which in our case is phase-I clinical trial, level of dosages, severity of symptoms or toxicity rates. If the covariates partition the population into a small heterogenous group it is possible to compare Kaplan-Meier in respect to each of the population.

B. Proportional Hazard Model

These are the most widely used regression models in recent era for proportional hazard models. Proportional hazards can be constructed using both parametric and non-parametric approaches to estimate the effect of duration on the hazard function. In a typical Proportional hazard model the hard function for the ith life may be given as

$$\lambda_i(t,z_i) = \lambda_0(t)g(z_i).$$

Where λ_0 is a function of only the duration t and $g(z_i)$ is a function of the covariates vector. The λ_0 is the hazard for an indiviual with a covariate vector equal to zero which is known as baseline hazard. Models can be specified in which effect of covariates changes with duration as

$$\lambda_i(t,z_i) = \lambda_0(t)g(z_i).$$

But because the hazard no longer factorises into two terms one depends only on duration and the other depends on the covariates are not Proportional Hazard Models. Since they can be more difficult and cumbersome to manually interpret these are usually preferable by some simulation. Here we have used the R-software to code these to estimate the values.

C. Cox Proportional Hazard Models

The general analysis for the Cox Proportional Hazard Models requires this formula to be satisfied

$$\lambda_i(t,z_i) = \lambda_0(t)exp(\beta(z_i)^T$$

Where λ_0 (t) is the baseline hazard. The utility of this model rises from the fact that the general shape of the hazard function for all individuals is determined by the baseline hazard, whilst the exponential terms account for the differences between individuals .So even if we are not primarily concerned with the precise form of the hazard but with the effect of the covariates we can ignore λ_0(t) and estimate β from the data irrespective of the shape of the baseline hazard which is a semi-parametric approach

IX. ESTIMATION OF REGRESSION PARAMETERS

To estimate β in the Cox Model it is usual to maximize the partial likelihood. The partial likelihood estimates the regression coefficients but avoids the need to estimate the baseline hazard.Moreover,since it is essentially like an ordinary likelihood it furnishes all the statistical information needed for standard inference on the regression coefficients.Let $R(t_j)$ denote the set of lives which are at risk just before the jth observed lifetime and for that instance we assume that there is only one death at each observed lifetime that is d_j=1.

$$L(\beta) = \prod_{j=1}^{k} \frac{exp(\beta z_j{}^T}{\sum_{i\varepsilon R(t_j)} exp(\beta z_i^T)}$$

Intuitively this gives that for each observed lifetime contributes to the probability that the life observed to die should have been the one out of $R(t_j)$ lives at risk to die, conditional on one death being observed at time t_j. We maximize this expression to proceed numerically for obtaining the maximum likelihood estimates.

➢ *Properties*

- The partial likelihood behaves much like a full likelihood it yields an estimate for β.
- This is asymptotically multivariate normal and unbiased
- It has an asymptotic variance matrix can be estimated by the inverse of the observed information matrix
- An efficient score function can also be included in particularly solving it which furnishes the maximum likelihood estimate of β.

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X. MODEL CONSTRUCTION

We can consider the likelihood ratio statistic on the basis of various model-building strategies in which

- We shall always start with the null model and add possible covariates one at a time
- We shall start with a full model which includes all the possible covariates and then try to eliminate those with no significant effect.

In addition, it is always necessary to test for interactions between covariates and the likelihood ratio statistic is a standard tool for model selection

Example:

For example in our case we have carried out the study of phase-I clinical trials of oncology and we have tried to ascertain the link between the Desirable Outcome,Anti-Factor,Dosages given and Dose Limiting Event .If we model the Dose Limiting event (DLE) using the Cox Regression Model which is to include the two covariates Dosages and the Anti Factor Rendered .The model then can be used to test for the two way interaction between these covariates and other factors of the group.

XI. RESULT ANALYSIS

A. Simulation

Cohort	Subject	Dose (mg)	DLEs	Anti-factor Xa (units/ ML × 10)
1	1	10.5	0	0.43
	2	10.5	0	0.43
	3	10.5	0	0.36
	4	10.5	0	0.39
	5	10.5	0	0.37
2	6	35.0	0	0.73
	7	35.0	0	0.86
	8	35.0	0	0.81
	9	35.0	0	0.92
	10	35.0	0	0.84
3	1	87.5	0	1.14
	2	87.5	0	1.22
	3	87.5	0	1.08
	4	87.5	0	1.20
	5	87.5	0	1.13
4	6	262.5	0	1.54
	7	262.5	1	1.56
	8	262.5	1	1.43
	9	262.5	1	1.43
	10	262.5	1	1.55
5	1	700.0	0	1.91
	2	700.0	0	1.94
	3	700.0	0	1.83
	4	700.0	0	1.88
	5	700.0	0	1.89
6	6	1050.0	0	1.99
	7	1050.0	0	2.08
	8	1050.0	1	1.98
	9	1050.0	0	2.05
	10	1050.0	0	2.03

Fig 1:- Data Constructed Following the Anti-Factor X_a Study

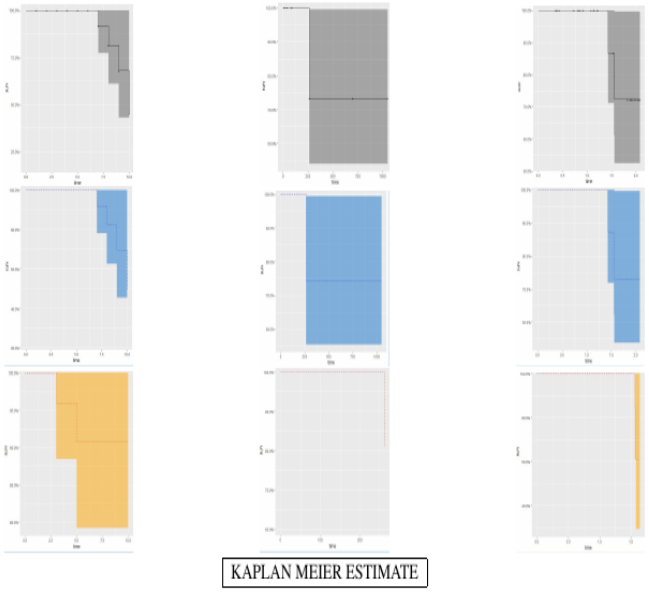

Fig 2:- Fitting of Cox Regression

From the graphs above figure shown in grey represent the Kaplan Meier Estimate of the data of the clinical trial followed by figures shown in blue wherein we fitted the data with Cox Regression Proportional Hazard Models .The figures in orange depict the recommended doses after the analysis which were again fitted using the Cox Regression .The stark difference obtained between figures in blue and orange talks of the decrement in the doses but which can effectively affect by adjusting other covariates considered. This therefore proves the efficacy of the doses administered could further be minimized which we have concluded using the utility function. These graphs have been modelled using the R Software for the phase-I clinical trial.

B. Implications

After fitting the model and analysing the likelihood ratio statistics we can make inferences about how each of the covariate affects the DLE which can eventually lead to the computation of the MTD. The information can be used in several ways:

- The model can be used to access the efficacy of the dose for the phase-I clinical trial and hence formulate on these bases the new dosages for limiting any unfortunate circumstances.
- These phase-I clinical trials are represented by a covariate which can be a quantitative measure of a dose or an indicator say taking into consideration dichotomous value representation of data.
- Individuals would also want to know the risk incurred in such trial with the mentioned dosages

The Cox Model thereby provides an estimate of the relative level of an individual's maximum tolerable dose in comparison to the baseline hazard. By making certain assumptions about the shape and the level of the baseline hazard we can then estimate the absolute level of the cohort's maximum level of dose toleration.

Remark

Another remarkable feature is that most whilst fitting the Cox-Model the information matrix is evaluated at β is usually produced as a by-product of the fitting process called as the Newton-Raphson algorithm so that some standard errors can also be available in evaluating the fit of a particular model

XII. CONCLUSION

Until now the recent researches on dose escalation have been elevated to the use of a binary DLE and a continuous DO using the Bayesian Approach where the prior distribution was already known. In this paper we have extended the concept of dose-escalation to a non-parametric distribution in contrast to the normal gamma distribution and estimated using the Kaplan-Meier estimate and evaluated the effect of the covariates like the doses ,anti-factor rendered before and after recommendation using the Cox-Regression and fitted the data using this model. It mainly concerns with the maximum level of dose tolerance that can be subjected to a patient undergoing a phase-I clinical trial.

These results have been simulated using a computer-extensive method and coded for obtaining a graphic visualization using the R-software for the same. Certain disadvantages to this are the uncertainty involved in the phase-I clinical trials which correspond to a N/A data which had to simulated in preference to the original value. Such missing values can lead to minute differences but this can be reduced by the method of optimization. We propose further research on this by adding constraints to the value of the covariates. Thus, by this line of reasoning we can make the assertion that our model can help oncologists make trade-offs on their decisions to the amount of cytostatic drug that should be administered.

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