Original Research Article

An Introspective Overview of the Dynamics of Recurrent Events Data Analysis

In many biometric studies, the outcome variable of interest is a recurrent event. Recurrent events can be explained as events of defined interest that can occur to same person more than once during the study period. This study presents an overview of different pertinent recurrent models for analyzing recurrent events.

Aims: To introduce, compare, evaluate and discuss pros and cons of four models in analyzing recurrent events, so as to validate previous findings in respect of the superiority or appropriateness of these models.

Study design: A simulation-based comparison of recurrent event models applied to a tertiary data on cancer studies.

Methodology: R codes are provided for simulating four recurrent events models, namely; The Andersen and Gill model; Prentice, Williams and Peterson models; Wei, Lin and Weissferd*;* and Cox frailty model. Finally, these models were used to analyze the first twenty subjects from a study of Bladder Cancer Tumors. The data set contained the first four recurrences of the tumor for each patient, and each recurrence time was measured from the patient's entry time into the study. Each time to an event or censoring was a separate risk interval.

Results: The choice and usage of any of the models lead to different conclusions, but the choice depends on: risk intervals; baseline hazard; risk set; and correlation adjustment or simplistically, type of data and research question. The PWP-GT model could be used if the research question is focused on whether treatment was effective for the kth event since the previous event happened. However, if the research question is designed to find out whether treatment was effective for the kth event since the start of treatment, then we could use the PWP- TT. The AG model will be adequate if a common baseline hazard could be assumed, but the model lacks the details and versatility of the event-specific models. The WLW model is very appropriate for data where there are different types of events for the same person, and the baseline hazard is potentially different for each type.

Conclusion: PWP-GT has proven to be the most useful model for analyzing recurrent event data.

Keywords: Keywords: Bladder cancer; Cox model; recurrent events; survival analysis; simulation.

1. INTRODUCTION (ARIAL, BOLD, 11 FONT, LEFT ALIGNED, CAPS)

Survival Analysis belongs to the class of statistical methods intended for studying and analyzing longitudinal data with the view of unearthing the timing and nature of occurrences of events. The method is used to find the survival probabilities of individuals from a point in

time until the event of interest occurs. In many biomedical research, the outcome variable of interest is a recurrent event. Recurrent events refer to events of interest experienced repeatedly by a given individual. These events may all be homogenous or heterogenous. Two features may define recurrent event data, these include events ordering and the exposure of an individual to risk for only one such an event at a time.

This paper is devoted to the study of survival functions of recurrent events. Special emphasis is placed upon how recurrent events vary over time and across treatments in the population. There are many research settings in which individual subjects may experience the event of interest more than once within the study period, the occurrences of such events may either follow a probability distribution or may be purely due to chance. In order to mitigate and or eradicate the effects of these occurrences to life and properties, it is deemed expedient to subject events of such nature to empirical studies. Event data analyses have implications and applications to real life situations. Applying the theories behind recurrent events, reveal trends in recurrent event data which invariably leads to the introduction of interventions to curb further occurrences. It is useful for predictions in maintaining optimal maintenance policies in engineering; medical; and biomedical studies. It also has the added advantage of being used as a research design for other research works. The paper is organized as follows: it reviews the dynamics of recurrent events, it considers some theoretical underpinnings of the present study, discussed each of the four models in detail and presented the data layout of each of the models, we did some simulation studies to identify which of the models provided standard results, discussed the results and drew the needed conclusions.

1.1 Dynamics of Recurrent Events

Recurrent event connotes the occurrence of events more than once per subject over the follow up period. In other words, the event of interest can occur multiple times during the lifetime of subjects. In recurrent events the subjects remain in the risk set until the last interval is completed. Subsequent reoccurrence is influenced by previous occurrences, therefore in the analysis, the correlation between the reoccurrence's must be investigated. What characterizes recurrent event is that the same event is observed multiple times with a single subject. Recurrent events data arise in diverse settings with each setting having its own goals; the goal in one setting may be to describe the relationship of recurrent event rates to the individual's preceding history, or the relationship to the covariate history that may include treatment choices or repair activities carried out on a machine intended to reduce the risk of further events. In studies associated with recurrent events, researchers are often interested in underscoring or exploring the effects of covariates on some features of the processes generating the recurrent event data. In this process the assumption is that the events are independent, more so, there is this assumption that there are no tied event times, furthermore, as long as a subject is under observations, it contributes to the risk set till the event occurs. According to this model, the follow-up time is segmented into the time each event occurred, this model can also accommodate time–dependent covariates of any kind. Data obtained from such studies are often referred to as recurrent event data. The structure of the data obtained in such recurrent events is a special case of multivariate survival data, with the event times for each subject ranked in order of occurrences. Survival analysis of past and current occurrences may affect future failure processes. For most requirements, event times are a key factor in the analysis, not only that, but the number of events can affect the recurrent process [1].

Classical examples of recurrent event data used in modern literature follows: In medical studies, we could have recurring- migraines, seizures, heart attacks, strokes, cancers. HIV patients may experience recurrent opportunistic infections [2]. There could be multiple infections of malaria for individuals living in mosquito prune areas. There could be re-infection of sexually transmitted diseases, there could be multiple infection times among leukemia patients receiving bone marrow transplant. In Reliability studies, there could be

repeated breakdowns of machines. brake re-failures, circuit breakers and valve seats [3]. In quality control, researchers could investigate the rate at which production units fail to satisfy consumer taste. Of particular concern to recent researchers is the methodology associated with the modeling of such data. Various models have been proposed in the literature of survival analysis, they include but not limited to the following; marginal intensity models and conditional intensity models [4-5]. Research has shown that for recurrent event data, the mean number of events is more interpretable than the event intensity or the hazard of recurrent event data, to that end researchers have modeled the mean and rate functions under the assumption that the covariates act multiplicatively on the unspecified baseline rate functions. In [6], the simplest modeling approach called the counting process is proposed. Description of counting process could be done by using time intervals, event indicators and strata [7]. In another development, semi-parametric additive model for the marginal recurrent event rates were developed under the assumption that the covariate effects were added to the unspecified baseline rate function. It has been assumed that in the proportional means and rate models, the covariates have a fixed multiplicative effect on the mean and rate function, however, in many applications, it is not reasonable to assume that the effects of the covariates measured at the beginning of the study will remain fixed over time, a more acceptable assumption proposed in [8] was that the effects of the covariates converge as time increases; violation of the proportional means and rates assumption for recurrent event data leads to bias and wrong conclusions.

Reference [9] noted in general that, two types of events were often encountered in health research: non-reversible events and reversible events. Non-reversible events were those events which were chronic in nature and occur to an individual only once (e.g., hypertension, AIDS, diabetes and cystic fibrosis). While other types of events were reversible and acute in nature and could occur to an individual more than once. Reversible events could further be divided into multiple events and recurrent events. Multiple events are those repeated events that are not of exactly the same type but somewhat related, such as repeated hospitalization due to different reasons (hospitalization due to road accident, hospitalization due to fall, hospitalization due to fever, etc.). Unlike multiple events, recurrent events are those repeated events, which are of the same type such as acute exacerbations in asthmatic children, seizures in epileptics, low back pain in women, skin cancer, myocardial infarctions, migraine pain, and sports injuries.

They further noted that recurrent event data have two main characteristics which are: within-subject correlation and time varying covariates. Recurrent events within-subject were very unlikely independent, they were related. Two possible sources have been identified with this within-subject correlation, one was due to event dependency and the other due to heterogeneity. Within-subject correlation due to event dependency refers to a situation where an event itself accelerates or decelerates the rate of subsequent event, a case in point is that with the occurrence of a first heart attack to a subject, chances of having a second heart attack is increased because during the first heart attack some part of the heart might have been damaged. Within- subject correlation due to heterogeneity refers to the situation whereby some subjects were more prone to experiencing a larger number of events than other subjects because of some unknown, unmeasured or immeasurable reasons. This phenomenon also causes within-subject correlation. Proper adjustment of within-subject correlation was essential in order to correct estimation of standard error; if we treat correlated observation as uncorrelated, we would overstate the amount of information each observation provided leading to incorrect estimates of standard errors. Another important concern of recurrent event analysis is how to deal with time-varying covariates. In many studies there are some covariates which are subject to change over time. For example, in the case of asthma management, dose and type of drugs are subject to change during the course of time which have direct effect on outcome.

1.2 Risk Intervals

Risk Intervals define the hazard of obtaining the event of interest within a given time scale. There are basically three formulations of the risk intervals: Counting process; gap time; and total time formulation. Some authors use the term counting process time or calendar time to further specify the risk intervals that are to be used in the regression analysis [10-11]. A total time scale is also known as counting process.

Gap time is the time from the prior event. In order words, the hazard process (that is, the clock) restarts to zero after every event.

Total time is the time from a chosen point, usually the time from the start of treatment. This means that the hazard process is defined from some starting point, for instance, the beginning of some disease.

In both gap time and counting process formulations, the subject is at risk for the same length of time. The risk interval for the first event is the same for all other risk intervals.

The risk interval determines whether a model is marginal or conditional. The gap time and counting process formulation are both conditional, which is to say that, the subject is at risk conditional on previous events. Total time falls within the marginal domain, because the subject is at risk from the start of the treatment and does not depend on any previous events.

Even though the need has been indicated in [12] to investigate statistical methods under different event generation processes and correlation structures, little attention has been given to the time scale that is applied for subsequent events. It was noted in particular that simulation studies often generated data from the gap time perspective, where the time and for that matter the risk process is reset after each event, this simplifies the simulation process. But in many clinical applications the total time perspective is deemed to be appropriate, i.e., where the hazard for experiencing a particular recurrent medical condition depends on the time since some starting point. They noted some discordance between the two approaches and subsequently derived a flexible simulation plan that could improve the accordance between the two approaches.

1.3 Risk Sets

The risk set contains the subjects who are at risk for the kth event. Three risk sets are referred to in the literature: unrestricted; restricted; and semi-restricted. In defining the risk set, we incorporate the choice of baseline hazard. The risk set at any given point in time depends on two conditions: subjects included in the set; and risk interval (i.e., when those subjects were at risk). For unrestricted risk set, the subject's risk intervals may contribute to the risk set for any given event regardless of the number of events experienced by each subject. An unrestricted risk set has a common baseline hazard function for all events. For a restricted risk set, contributions to the kth risk set are restricted to only include the kth event risk intervals of those subjects who had experienced $(k-1)th$ events. For example, only subjects who have had two events will be considered to be at risk for the third event. A restricted risk set has event-specific baseline hazards. Semi-restricted risk sets have event-specific baseline hazards but allow subjects who have had fewer than $(k-1)th$ events to be at risk for the kth event through the creation of 'dummy' risk intervals. Thus, a subject who has had none or one event can be considered at risk of a third event. However, a semi-restricted risk set does not allow information from the kth event risk interval to contribute to the risk set for an earlier event. This third kind of risk set applies to the counting process and total time with event-specific baseline hazards [13].

1.4 Theoretical Perspectives Underpinning the Study

Reference [14] underscored the fact that many different statistical methods exist for analyzing recurrent events, and that the different statistical techniques could be divided into naive techniques and longitudinal techniques. The "Naive techniques" were explained to

have been characterized either by ignoring the existence of recurrent events or ignoring the fact that the recurrent events within subjects or patients were correlated, while, the longitudinal techniques are characterized by the fact that the whole pattern of recurrent events over time is analyzed, taking into account that the recurrent events were correlated within subjects or patients. Despite the fact that there were many statistical techniques available to analyze recurrent event data, [14] expressed surprise that most researchers rather found it difficult to choose the proper technique to answer the research question they were interested in. Most of them chose the naive statistical techniques to analyze their study outcomes. They proposed to give an overview of easily applicable statistical techniques that were available to analyze recurrent event data; to compare the results of naive and longitudinal techniques with each other; and to give some recommendations on how to analyze recurrent event data, given a certain research question. Reference [15] aimed at evaluating the performance of existing recurrent event models for specific data situation of a composite endpoint which was characterized by the following properties:

- For each event type, recurrent or terminal, there exist separate event processes that might be correlated or not;
- the event-specific treatment effects related to the different event types may deviate;
- after occurrence of an event, the instantaneous baseline risk for a subsequent event, fatal or non-fatal, increases;
- the instantaneous risk for a subsequent event depended on the time when the previous event occurred; and
- after occurrence of an event, the relative treatment effect for a subsequent event (in terms of the hazard ratio) may change.

They identified three most frequently used models for analyzing recurrent event data. The first is the Andersen and Gill model which was based on the common Cox proportional hazards model. The model assumes independence between all observed event times irrespective of whether these event times corresponded to the same patient or not. The second is the Prentice, Williams, and Peterson, this model incorporates the order of events. There are two different time scales needed to handle this model, the gap time and the total time scale. The gap time approach investigates the time since the last event occurs, whereas the calendar or total time scale considers the time since study entry. The third is the unconditional marginal model which was proposed by Wei, Lin, and Weissfeld. This model ignores the order of occurrence of the events. Therefore, for each subsequent event all individuals would be at risk independent of a preceding event. The model by Wei et al. is based on a total time scale. The focus of [15] was the comparison of the three most common models of analyzing recurrent data. The investigation was done using two different data sets - one recurrent non-fatal event and the other a fatal event. The comparison was done based on the statistical properties of the models' treatment effect estimator and their correct interpretation. This comparison was done to enable them to proffer recommendations for the choice of an appropriate analysis model which could address the specific data structure of clinical trials with composite endpoints. A total of *n* individuals was allocated in a 1:1 ratio to the experimental group (E) and to the control group (C). The group allocation of subjects was expressed by the covariate X_i which equals 1 whenever the patient belongs to the experimental group and 0 otherwise. Each individual $i = 1,2 \dots n$ could experience up to $j = 1,2 \dots k$ events of the same or of differing types. In this case, k which was the maximal number of considered events per patient was restricted for the sake of simplicity. Their process for the occurrence of the event could be described by a multi-state model, that is to say, an individual entered the study at an initial state 0. Every time an event occurred, the individual leaves the previous state and entered a new event state. If this observed event was non-fatal, the individual could experience more subsequent non-fatal events or the fatal event. The instantaneous risk to experience a jth event at time t given that the individual

has experienced $j-1$ non-fatal events was parameterized. In [16], two methods of analyzing recurrent events were described: non-parametric and semiparametric methods. Their focus was on the functions that were modeled in the analysis. They indicated that, the data structure for recurrent events represented a special case of multivariate survival data, where the failure times for a subject were ordered. Hence, recurrent event data had often been analyzed using methods of multivariate survival analysis. Five Cox-based models for recurrent event data were underscored in [17]: Andersen and Gill (AG); Wei, Lin and Weissfeld (WLW); Prentice, Williams and Peterson, total time (PWP-TT) and gap time (PWP-GT); and Lee, Wei and Amato (LWA). It was mentioned that some authors have compared these models by observing differences that arose from fitting the models to real and simulated data. It was opined that no author had attempted to systematically identify the components of the models that are appropriate for recurrent event data. They proposed a systematic way of characterizing such Cox-based models using four key components: risk intervals; baseline hazard; risk set, and correlation adjustment. From their definitions of risk interval and risk set, they conceptualized two new variant models termed as: 'total time – restricted' (TT-R) and 'gap time – unrestricted' (GT-UR) models. In their study they determined which of the models were appropriate for recurrent event data using the key components. The models were fitted to simulated data sets and to a data set of childhood recurrent infectious diseases. It was concluded that the LWA model was not appropriate for recurrent event data because it allowed a subject to be at risk several times for the same event. The WLW model was said to overestimate treatment effect and was not recommended. It was then recommended that the PWP-GT and TT-R were useful models for analyzing recurrent event data. Reference [18] has underscored the fact that though there had been a considerable amount of discussion on methods of analysis for recurrent or repeated events, still inefficient or inappropriate statistical approaches were used to analyze such types of data. They mentioned that the most well-known approach for analysis of survival data was the Cox proportional hazards model, which due to the independence assumption, was only appropriate for modeling time to the first event. They indicated that this model was inefficient because data from later events were discarded. Another approach of modeling the number of events for each patient according to [18] was to fit Poisson or negative binomial models, which were recently integrated into the generalized estimating equations (GEE). The third approach they mentioned was the random effects models which consider the correlation of events. Even though this third model had its inefficiencies. They climaxed their discussion by alluding to the fact that extensions of the original Cox model have been proposed for analyses of recurrent event data: Andersen-Gill (AG); Prentice, Williams and Peterson (PWP) (total and gap times); Wei, Lin and Weissfeld (WLW); and frailty models. Other analysis strategy was modelling the mean number of events or their occurrence rate. They concluded by showing that, more recently, multi-state models (MSM) have been extended for recurrent events. Reference [19] mentioned that over the past few decades, lots of statistical advancements had taken place in the field of recurrent event data analysis. It was asserted that several approaches had been proposed for the analysis of such data. These newly developed techniques were far better than traditional statistical techniques (such as t-test, logistic regression, multiple linear regression, and Cox's Proportional Hazard regression) just to mention a few. It was revealed that despite several powerful techniques available for analysis of the recurrent event data, most researchers were still using traditional statistical techniques for analyzing their research questions where outcome of interest was recurrent in nature. It was alluded that the application of sub-optimal suitability could lead to loss in terms of internal validity and precision of the results.

Reference [20] considered outcome events that may occur more than once over the follow-up time for a given subject, known in the literature as "recurrent events." They surmised that modeling such type of data could be carried out using a Cox proportional hazard model with the data layout constructed so that each subject would have a line of

data corresponding to each recurrent event. They noted that a variation of this approach uses a stratified Cox proportional hazard model, which stratifies on the order in which recurrent events occur. It was concluded that regardless of which approach was used, the investigator should consider adjusting the variances of estimated model coefficients for the likely correlation among recurrent events on the same subject. Such adjusted variance estimates were called “robust variance estimates.” A parametric approach for analyzing recurrent event data that includes a frailty component was also described and illustrated.

Our purpose in this current study is to undertake another extensive investigation using a different dataset of recurrent Bladder Cancer Tumors [26-27] to compare, evaluate and discuss pros and cons of four models of recurrent events; The Andersen and Gill model; Prentice, Williams and Peterson models; Wei, Lin and Weissferd*;* and Cox frailty model. This will aid to further illustrate the characteristics of these four models so as to consolidate and validate previous findings in respect of the superiority or appropriateness of these models.

2. MATERIAL AND METHODS / EXPERIMENTAL DETAILS / METHODOLOGY (ARIAL, BOLD, 11 FONT, LEFT ALIGNED, CAPS)

2.1 Study design

A simulation-based comparison of recurrent event models was applied to tertially data on cancer studies. Data was extracted from the first twenty (20) subjects on the study of recurrent Bladder Cancer Tumors [21-22] reproduced in the book authored by [20]. The data consist of 86 patients with superficial bladder tumors, which were removed when the patients entered the study. Of these patients, 48 were randomized into the placebo group, and 38 were randomized into the group receiving thiotepa. Many patients had multiple recurrences of tumors during the study, and new tumors were removed at each visit. The data set contained the first four recurrences of the tumor for each patient, and each recurrence time was measured from the patient’s entry time into the study. Each time to an event or censoring was a separate risk interval. Extending the database as mentioned above for purposes of exemplification will assist the researchers to further shed more light on the points that have been raised by earlier researchers.

2.2 Statistical Model Formulation

Four different models were used to model recurrent event data, we propose that the final choice we make must depend on the type of data and research question.

The first model discussed was the counting process model, each event was assumed to be independent. A subject contributed to the risk set for an event as long as it was under observation at the time the event occurred. We described the data for each subject with multiple events as data for multiple subjects where each subject had a delayed entry and was followed until the next event. We ignored the order of the events, leaving each subject to be at risk for any event as long as they were under observation. Implicitly, a subject could be at risk for a subsequent event without having experienced prior events. We used the same time as that of total time and recognized that a subject may have a delayed entry or censored period before the subject becomes at risk for the event. We again noted that in the counting process formulations, subjects were at risk for the same duration of time.

The second model we considered was conditional (referred to in some literature as conditional 1 or A). It is so called because of the assumption that it was not possible for a subject to be at risk for a next event without experiencing the previous event. We used a strata variable to indicate the event number. We started the time interval of a subsequent event at the end of the time interval for the previous event. This model helped us to model the full-time course of the recurrent event.

The third model we considered was also conditional (referred to in some literature as conditional 2 or B). This model only differs from the conditional 1 model in the way the time intervals were structured. We started each time interval at zero and ended at the length of time until the next event. Implicitly, the risk sets for each of the events were completely different. This model is very useful for modeling the time between each of the recurring event rather than the full-time course of the recurrent event process.
The fourth model we considered was the marginal model. We considered each event as a separate process. The time for each event started at the beginning of follow-up time for each subject. Each subject was considered to be at risk for all events, regardless of how many events each subject actually experienced. Thus, this model considered each event separately and modelled all the available data for the specific events.

2.3 Models of Recurrent Events

Starting from a time origin which is well defined, we will observe the points $T_1, T_2, \ldots, T_n$ for a given subject, where T_1 is the time to the subject's first failure, T_2 is the time from the origin to the subject's second failure with follow-ups continuing to a total follow-up time *C* that right censors the point process. There may also be a covariate vector or covariate process *x,* which is a function of *u* having history $X(t) = \{x(u), 0 \le u < t\}$ for the subject. Denoting by $\tilde{N}(t)$ the number of failures on the subject by follow up time *t*, and by $N(t)$ the corresponding observed number of failures in (0, t], because of censoring $N(t)$ may be less than $\tilde{N}(t)$. Recurrence rates that condition on the preceding failure and covariate histories for the subject constitutes a logical starting point for modeling recurrent event data. For absolutely continuous event times, one can define the hazard or intensity process as $\lambda(t)$ at follow-up time t, given the covariate history $X(t)$, by

$$\lambda(t)dt = P[d\tilde{N}(t) = 1 \mid \tilde{N}(u), 0 \le u < t, X(t)].$$

(1)

The expression in (1) assumes that jumps in $\tilde{N}$ are of unit size only, however recurrent event data sometimes include jumps of size greater than one, as more than one event is recorded for an individual at a specific follow-up time. This typically occurs because event times from an underlying continuous process are grouped. It is also possible to consider continuous-time counting processes having jump sizes greater than one, for example in queuing models that counts the arrival time of customers in continuous time, but where customers arrive in groups of various sizes, one natural approach to modeling counting processes with jumps that may exceed one is to model the mean jump in $\tilde{N}$ across time. Models that care for such increments are presented below;

$$d\Lambda(t) = E[d\tilde{N}(t) \mid \tilde{N}(u), 0 \le u < t, X(t)].$$

(2)

Where Λ is the cumulative intensity process, Equation (2) is referred to as the failure intensity at time *t*, and is defined as the expected number of events on a subject, Equations (1) and (2) are equivalent to

$$\Lambda(t) = \int_0^t \lambda(u)\, du.$$

(3)

for cases of continuous-time processes having only unit jumps. Whenever reoccurrence times are being restricted to be absolutely continuous, we assume that $d\tilde{N}(t) \le 1$.

In most applications, interest is often placed on the assessment of the effects of covariates on the marginal recurrent event rates. The multiplicative rates model is written as:

$$E[d\tilde{N}(t) \mid X(t)] = \exp\{\beta_0' X(t)\}\lambda_0(t)dt .$$

(4)

Where β_0 is a p-vector of unknown regression parameters and λ_0 is an unspecified baseline rate function. The additive rates model takes the form;

$$E[d\tilde{N}(t) \mid X(t)] = \beta_0' X(t)dt + \lambda_0(t)dt$$

(5)

Equation (5) was subjected to regression analysis by [23] they came out with the regression parameters and the baseline rate, and they also showed that the proposed estimators were consistent and asymptotic Gaussian [24].

The Cox proportional hazards model could be generated from Equations (2) and (3):

$$\Lambda(t) = \int_0^t \lambda(u)\, du$$

$$d\Lambda(t) = d\Lambda_0(t)\, exp[(Y(t)'\beta] \Longrightarrow d\int_0^t \lambda(u)\, du = d\int_0^t \lambda(u)\, du.exp[(Y(t)'\beta]$$

(6)

where $Y(t)' = Y_1(t), Y_2(t), \ldots Y_P(t)$ are made up of functions of $X(t)$ and $[N(u); 0 \le u < t]$ and product terms with *t.*

When Equation (6) is calculably manipulated

$$\lambda(t) = \lambda_0(t)\, exp[(X(t)'\beta].$$

(7)

Where $X(t)' = X_1(t), X_2(t), \ldots X_i(t)$.

.

Five methods of modelling recurrent events have been discussed in [25-26]: Andersen and Gill model; Prentice, Williams and Peterson models; marginal means/rates model; frailty model; and multi-state models. We present brief description of four of the models.

2.3.1 The Andersen and Gill model (Counting process)

Andersen-Gill (AG) uses the counting process structure of data inputs. Each subject is represented as a series of observations with recurrent times given as $(t_0, t_1]\ (t_1, t_2] \ldots (t_{n-1}, t_n]$. Each recurrent event for the ith subject; $i = 0,1,2 \ldots n$; is assumed to follow the proportional hazards model. The outcome of interest is time since randomization for a treatment until an event occurs. It uses a common baseline hazard function for all events and estimates a global parameter for the factors of interest. The Andersen and Gill (AG) model assumes that the correlation between event times for a subject can be explained by past events, which implies that the time increments between events are conditionally uncorrelated, given the covariates. In simple terms we use this counting process when each event is assumed to be independent, moreover, a subject contributes to the risk set for an event as long as the subject is under observation at the time the event occurs. This model ignores the order of the events leaving each subject to be at risk for any event as long as they are still under observation at the time of the event. This further means that a subject could be at risk for a subsequent event without having experienced the prior event. The hazard function is given as:

$$\lambda_i(t) = \lambda_0(t)\exp\{\beta_k x_i(t)\}.$$

(8)

Under this model, the risk of recurrent event for a subject follows the Cox proportional hazards model assumption, but the number of recurrent events is not taken into consideration.

2.3.2 Prentice, Williams and Peterson models 1981 (Conditional 1 and 2)

The Prentice, Williams and Peterson (PWP) model do the analyses of ordered multiple events by stratification, based on the prior number of events during the follow-up period. All subjects are deemed to be at risk for the first stratum, but only those with an event in the previous stratum are at risk for the successive one. It is deemed impossible for a subject to be at risk for a subsequent event without having experienced the previous event (in other words, one cannot be at risk of event 2, without being at risk of event 1). The model can incorporate both overall and event-specific effects for each covariate. In practice, the data may need to be limited to a specific number of recurrent events if the risk set becomes very small for later strata and event-specific estimates become too unreliable. Besides using the same outcome (total time: TT) as in the AG model, the PWP model can also be usually defined in terms of gap time (GT), which is the time since the previous event occurred. When using a gap or waiting-time scale, the time index is reset to zero after each recurrence of the event, with assumption of a renewal process. Gaps between events are often useful with infrequent events, when a renewal occurs after an event or when the interest lies on prediction of a next event. Hence, two stratified PWP models can be fitted: PWP-TT, which evaluates the effect of a covariate for the kth event since the entry time in the study; and the PWP-GT, which evaluates the effect of a covariate for the kth event since the time from the previous event. Unlike the AG model, the effect of covariates may vary from event to event in the stratified PWP models. Therefore, the PWP models might be preferable to the AG model when the effects of covariates are different in subsequent events. The PWP -TT model for the hazard function for the kth event for the ith subject is given as:

$$\lambda_{ik}(t) = \lambda_0(t)\exp\{\beta_k x_i(t)\}. \quad (9)$$

The baseline hazards vary from event to event.

The PWP - GT model for the hazard function for the $(k-1)th$ event, a subject is not considered in the risk set for the kth event until it experiences the $(k-1)th$ event. The hazard function is given as:

$$\lambda_{ik}(t) = \lambda_0(t - t_{k-1})\exp\{\beta_k x_i(t)\}. \quad (10)$$

2.3.3 The marginal means/rates model (Wei, Lin and Weissferd, 1989)

This is an alternative model for analyzing recurrent events. This model can be interpreted in terms of the mean number of events when there are no time-dependent covariates. This approach does not specify dependence structures among recurrent event times within a subject. However, since the marginal means/rates model considers all recurrent events of the same subject as a single counting process and does not require time-varying covariates to reflect the past history of the process, this model is more flexible and parsimonious than AG model. If no time-dependent covariates are included in the AG model to account for all the influence of the prior events on future recurrences, point estimates from the means/rates model and the AG model will be the same. Nevertheless, the covariance matrix estimate for the regression coefficients for the marginal means/rates model uses score residuals in the middle of the sandwich estimate, which corrects for the dependency structure. This approach can be of interest in many medical applications when the dependence structure is complex and unknown, especially when it cannot be characterized by including time-varying covariates, as in the AG model. In the hazard model, it is of interest to note that all the time intervals start at zero. The hazard model allows a separate underlying hazard for each

event. When an event is set to zero, it means that subject is no longer at risk after the last given interval. The hazard is given by

$$\lambda_{ik}(t) = \lambda_0(t)\exp\{\beta_k x_i(t)\}. \quad (11)$$

2.3.4 The Cox frailty model

The frailty model also known as the random effects approach, introduces a random covariate into the model that induces dependence among the recurrent event times. The idea is that the random effect describes excess risk or frailty for distinct subjects, taking into account unmeasured heterogeneity that cannot be explained by observed covariates alone. The most commonly used frailty model is a shared frailty model with random effects assumed to follow a gamma distribution with mean equal to one and unknown variance. The model assumes that the recurrent event times are independent conditional on the covariates and random effects. When there is heterogeneous susceptibility to the risk of recurrent events, the frailty model can be applied. The Hazard function $\lambda_{ik}(t)$ for the recurrent time of the kth event of the subject ith $(j = 1.2 \dots k, i = 1,2 \dots n)$, conditional on the fraity Z_k, follows the proportional hazards model form and is given by:

$$\lambda_{ik}(t) = \lambda_{0k}(t)\, Z_i\{\exp\{\beta_k x_i(t)\}, t > 0. \quad (12)$$

Where $\lambda_{0k}(t)$ is the common baseline hazard function x_i is a vector of observable covariates, β is the vector of unknown regression coefficients, frailty Z_i is the unobserved common risk factors shared by all subjects in cluster i and is assumed to be fixed with unit mean and unknown variance.

2.4 Determining the Appropriate Model to Use

In addressing the question as to which model to choose in analyzing and modeling recurrent event data, there appears to be no end in sight as to which of the models is robust. Several authors have proposed one proportional hazards model over the other. Reference [27] had proposed that the choice of the most appropriate model depended on:

- Distribution of subsequent event times;
- Within person correlation of subsequent events;
- Frequency of occurrence; and
- Specific research questions.

In [17], a systematic way of characterizing the Cox-based models using four key components has been proposed. The components include risk intervals; baseline hazard; risk set, and correlation adjustment.

To help us to appreciate the model data layout, we will go through four different outlines for the start times and finish times of counting process, conditional 1, conditional 2 and marginal recurrent models. It should be noted that the choice of the appropriate model depends on how one defines the model characteristics, risk interval and risk set.

We will approach this by looking at a hypothetical data on two subjects 1 and 2. These subjects were observed for 33 weeks, the event of interest was time until reinfection of sexually transmitted disease. When a subject gets reinfested, he is immediately treated and discharged. It is assumed that subject 1 had reinfection on the following weeks of follow up: 10th, 15th and 31st weeks. Subject 2 experienced the event of interest at the 3rd and 12th weeks of follow-up and did not experience any event till the end of follow up. If a subject obtained an event of interest (E), $E = 1$, if a subject fails to obtain the event of interest, $E = 0$. It is assumed that each recurrent event is independent of the previous event, thus a stratum number (from 1 to 4) was accorded each event. This number was used to track the number of separate events that have occurred within the follow-up time. The data layout for subjects1 and 2 are shown in Table 1 below under the four recurrent event models:

Table 1: Hypothetical data layout for two subjects (Subjects 1 and 2) with recurrent event times 10, 15, 31 and 3, 12 weeks respectively after 33 weeks of follow-up under four recurrent event models

Model	**Subject 1**			**Subject 2**		
	Time Interval	Event	Stratum	Time Interval	Event	Stratum
The Andersen and Gill model (Counting process)	(0,10]	1	1	(0,3]	1	1
	(10,15]	1	1	(3,12]	1	1
	(15,31]	1	1	(12,33]	0	1
	(31,33]	0	1			
Prentice, Williams and Peterson (Total time, counting process, Conditional 1 or A)	(0,10]	1	1	(0,3]	1	1
	(10,15]	1	2	(3,12]	1	2
	(15,31]	1	3	(12,33]	0	3
	(31,33]	0	4			
Prentice, Williams and Peterson (Gap time - Conditional 2 or B)	(0,10]	1	1	(0,3]	1	1
	(0,5]	1	2	(0,9]	1	2
	(0,16]	1	3	(0,21]	0	3
	(0,2]	0	4			
Wei, Lin and Weissferd (Marginal)	(0,10]	1	1	(0,3]	1	1
	(0,15]	1	2	(0,12]	1	2
	(0,31]	1	3	(0,33]	0	3
	(0,33]	0	4	(0,33]	0	4

2.5 R Codes for all Models

The software for simulation was run on an x64 windows-based machine with the following specification: operating system: MS Windows 10; processor: 1.4GHz, and RAM Size: 4 GB. Software: All analysis were performed in R Software (R version 4.1.1). Packages installed were survival, survminer, and simrec

```
library(survival)
library(survminer)
library(simrec)
bcs <- read.csv ("flie_location/filename.csv" use.value.labels=TRUE)
```

2.5.1 AG Model:

```
AG <- coxph(Surv(Start,Stop, Event) ~ tx + num + size +cluster(id), robust=TRUE, data = bcs)
summary (AG)
Call:
coxph(formula = Surv(Start, Stop, Event) ~ tx + num + size, data = bcs,
    robust = TRUE, cluster = id)
  n= 38, number of events= 23
```

Stratification Models: The models below are stratified Models. The argument strata(intcount) identify the stratification variable to obtain their estimates. Estimates are obtained for event-specific covariates.

2.5.2 PWP-Total time Model:

```
PWP_TT <- coxph(Surv(Start,Stop, Event) ~ tx + num + size +cluster(id) + strata(int_count), data = bcs)
summary (PWP_TT)
Call:
coxph(formula = Surv(Start, Stop, Event) ~ tx + num + size +
    strata(int_count), data = bcs, cluster = id)
  n= 38, number of events= 23
```

2.5.3 PWP Gap time Model:

```
PWP_GP <- coxph(Surv(Stop - Start, Event) ~ tx + num + size +cluster(id) + strata(int_count), data = bcs)
summary (PWP_GP)
Call:
coxph(formula = Surv(Stop - Start, Event) ~ tx + num + size +
    strata(int_count), data = bcs, cluster = id)
  n= 39, number of events= 23
```

2.5.4 Marginal Model

```
Marginal_M <- coxph(Surv(Start,Stop, Event) ~ tx + num + size +cluster(id) + strata(int_count), data = bcs)
summary (Marginal_M)
Call:
coxph(formula = Surv(Start, Stop, Event) ~ tx + num + size +
    strata(int_count), data = bcs, cluster = id)
  n= 38, number of events= 23
```

2.5.5 Frailty Model:

By default, gamma distribution is associated with the random effect for frailty model in R. However, gaussian distribution may be specified.

```
 Frailty_M <- coxph(Surv(Start,Stop, Event) ~ tx + num + size + frailty(id, distribution = "gamma"), data = bcs)
summary (Frailty_M)
Call:
coxph(formula = Surv(Start, Stop, Event) ~ tx + num + size +
    frailty(id, dist = "gamma"), data = bcs)
  n= 38, number of events= 23
```

The R codes for the various models are used to simulate the data in Table 2.

Table 2: The first twenty (20) Subjects from Bladder Cancer Study (Byer,1980, and Wei Lin, Weissfield, 1989 reproduced in the book authored by [20]

Id	int_count	Event	Start	Stop	tx	num	Size
1	1	0	0	0	0	1	1
2	1	0	0	1	0	1	3
3	1	0	0	4	0	2	1
4	1	0	0	7	0	1	1
5	1	0	0	10	0	5	1
6	1	1	0	6	0	4	1
6	2	0	6	10	0	4	1
7	1	0	0	14	0	1	1
8	1	0	0	18	0	1	1
9	1	1	0	5	0	1	3
9	2	0	5	18	0	1	3
10	1	1	0	12	0	1	1
10	2	1	12	16	0	1	1
10	3	0	16	18	0	1	1
11	1	0	0	23	0	3	3
12	1	1	0	10	0	1	3
12	2	1	10	15	0	1	3
12	3	0	15	23	0	1	3
13	1	1	0	3	0	1	1
13	2	1	3	16	0	1	1
13	3	1	16	23	0	1	1
14	1	1	0	3	0	3	1
14	2	1	3	9	0	3	1
14	3	1	9	21	0	3	1
14	4	0	21	23	0	3	1
15	1	1	0	7	0	2	3
15	2	1	7	10	0	2	3
15	3	1	10	16	0	2	3
15	4	1	16	24	0	2	3
16	1	1	0	3	0	1	1
16	2	1	3	15	0	1	1
16	3	1	15	25	0	1	1
17	1	0	0	26	0	1	2
18	1	1	0	1	0	8	1
18	2	0	1	26	0	8	1
19	1	1	0	2	0	1	4
19	2	1	2	26	0	1	4
20	1	1	0	25	0	1	2

20	2	0	25	28	0	1	2

Note: Subjects with no event have a single observation. for instance, subject id from 1 to 5,7,11, and17 with start time equals to 0 and stops equal to follow-up time, whiles subjects with at least one event have two or more rows (ids 6, 8,9,10,12,13,14, 15, and 16)
The patient with id 2 has a censored time at a month (Stop=1). The patient with id number 6 on the other hand had an event at time t = 6 (event = 1) and censored at time t=10 (event=0).
Similarly, the subject with id number 16 had an event on the 3rd month and repeated on the 15th month and censored time at the 25th month.

Variables in solution

- Id = Patient Identit which identifies the patient;
- Int_count= Number of observations;
- Num = initial number of tumors;
- Size =initial size of tumors in centimeters;
- Event= event status (0=censored, 1=event);
- Tx =Treatment (0=placebo, 1=thiotepa);
- Start = Beginning of an interval where patient is at risk for an event (in months);
- Stop = End of interval due to an event (1) or censoring (0) (in months); and
- The Start, Stop is used to define the time interval of risks

3. RESULTS AND DISCUSSION

A pictorial view of the recurrent events is presented (Figure 1). The output is a plot of data with bullet (•) indicating a recurrent event, a circle(o) indicating censoring. Each time interval (in months) starts at zero and ends at a length of time until the next event.

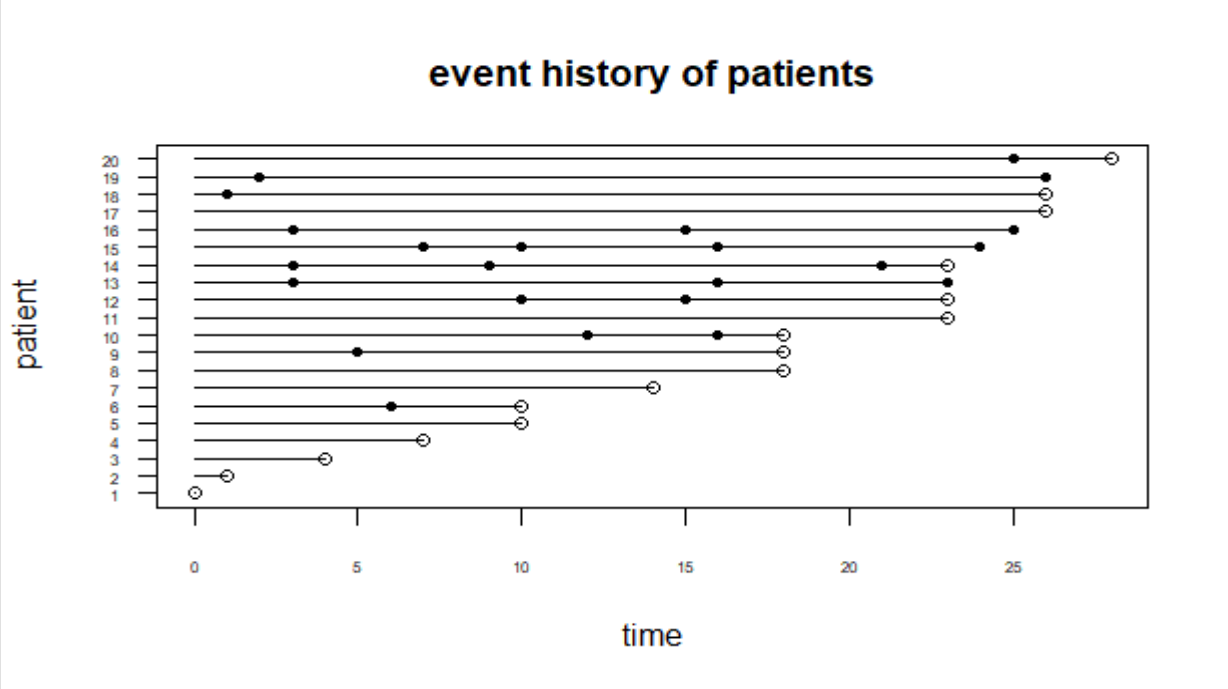

Figure1: Output of recurrent events of all 20 subjects Output.

We note that the robust standard error for the initial number of tumors (row 2 for each model, column 5) for AG; PWP-TT; PWP-GT; and Marginal models were respectively: 0.08; 0.075; 0.09; and 0.075, the standard errors were approximately the same. In respect of the initial size of tumor (row 3 for each model, column 5) for AG; PWP-TT; PWP-GT; and Marginal models, the robust standard errors were respectively: 0.209; 0.174; 0.197; and 0.174, we note again that the standard errors did not differ considerably from each other. The hazard ratios for the initial number of tumors and size of tumor (row 2 for each model, column 8) are interpreted model by model as follows: For AG, the hazard ratio for the initial number of tumors indicates that for every unit increase in number of tumors, the rate of bladder cancer episode increases by 9%, the hazard ratio for initial size of tumor indicates that the subjects in the control group experience bladder cancer episodes at a rate which is 6% higher than the treatment group. For PWP-TT, the hazard ratio estimates for initial number of tumors indicate that for every unit increase in number of tumors, the rate of bladder cancer episode increases by 0.5%, the hazard ratio for initial size of tumor indicates that the subjects in the control group experience bladder cancer episodes at a rate which is 95.5% higher than the treatment group. For PWP-GT, the hazard ratio estimates for initial number of tumors indicate that for every unit increase in number of tumors, the rate of bladder cancer episode increases by 6.6%, the hazard ratio for initial size of tumor indicates that the subjects in the control group experience bladder cancer episodes at a rate which is 94.3% higher than the treatment group. For the Marginal model, the hazard ratio estimates for initial number of tumors indicate that for every unit increase in number of tumors, the rate of bladder cancer episode increases by 0.5%, the hazard ratio for initial size of tumor indicates that the subjects in the control group experience bladder cancer episodes at a rate which is 95.5% higher than the treatment group. (Table 3 for AG; PWP-TT; PWP-GT) and (Table 3B for Marginal models).

Table 3A: Results generated from the R platform for four models for analyzing recurrent events

	Coef.	exp(coef)	se(coef)	robust se	z	Pr(>|z|)	exp(-coef)	lower .95	upper .95
The Andersen and Gill model (Counting Process) AG									
tx	N/A	N/A	0.000	0.000	N/A	N/A	N/A	N/A	N/A
num	-.086	0.917	0.119	0.080	-1.073	0.283	1.090	0.784	1.074
size	-.059	0.943	0.212	0.209	-0.283	0.777	1.061	0.626	1.419
Prentice, Williams and Peterson models1981 (Conditional 1) PWP- Total Time									
tx	N/A	N/A	0.000	0.000	N/A	N/A	N/A	N/A	N/A
num	-.005	0.995	0.129	0.075	-0.061	0.951	1.005	0.860	1.153
size	.046	1.047	0.229	0.174	0.264	0.792	0.955	0.744	1.473
Prentice, Williams and Peterson models1981 (Conditional 2) PWP- Gap Time									
tx	N/A	N/A	0.000	0.000	N/A	N/A	N/A	N/A	N/A
num	-.064	0.938	0.143	0.090	-0.713	0.476	1.066	0.787	1.118
size	.059	1.061	0.234	0.197	0.301	0.764	0.943	0.721	1.560
The Marginal Means/Rates Model (Wei, Lin and Weissferd, 1989) WLM									
tx	N/A	N/A	0.000	0.000	N/A	N/A	N/A	N/A	N/A
num	-.005	0.995	0.129	0.075	-0.061	0.951	1.005	0.860	1.153
size	.046	1.047	0.229	0.174	0.264	0.792	0.955	0.744	1.473

Table 3B: Results generated for Frailty model for analyzing recurrent events

The Frailty Model

	Coef	se(coef)	se2	Chisq	dF	p	exp(-coef)	lower .95	upper .95
tx	.000	0.000	1.00				N/A	N/A	N/A
num	-.093	0.138	0.122	0.45	1.0	0.50	1.097	0.698	1.153
size	-.053	0.239	0.207	0.05	1.0	0.82	1.055	0.594	1.153

We have the results from the R platform showing the various significant test results (Tables 4 and 4B). Of particular interest now is the results listed at row one of Table 4, the standard error (se) of the models AG; PWP total time; PWP gap time and marginal are given respectively as: se = 0.07; se = 0.08; se = 0.06; se = 0.08. A small robust standard error means there is more variation within subjects than between subjects, while a big robust standard error means there is less variation within subjects than between subjects. From the simulated results, the robust standard errors of all four models were small regardless of whether events were independent within subjects. On the basis of the ongoing analysis, we note that the results from the PWP-GT model stands out clearly. We are of the candid opinion that if the within subject events are independent, then we need to use the PWP-GT model to analyze recurrent event data. As has been stated earlier, the choice of a model depends to a large extent on the research question and type of data available. The PWP-GT model could be used if the research question purports to find out whether the treatment was effective for the kth event since the previous event happened. However, if the research question is designed to find out whether treatment was effective for the kth event since the start of treatment, then we could use the PWP- TT. The AG model will be adequate if a common baseline hazard could be assumed, but the model lacks the details and versatility of the event-specific models. Applying a robust variance may not be adequate when there is within-subject correlation. The WLW model is very appropriate for data where there are different types of events for the same person, and the baseline hazard is potentially different for each type, such as multi-type event data. The WLW model overestimates treatment effect and is not recommended.

Table 4A: Concordance, Likelihood, Walt test, Score test and Robust Results.

	AG	**PWP- Total time**	**PWP- Gap time**	**Marginal**
Concordance	0.5(se = 0.07)	0.48(se = 0.08)	0.51(se = 0.06)	0.48(se = 0.08)
Likelihood ratio test	0.58,2 df, p=0.7	0.05, 2 df, p=1	0.42, 2 df, p=0.8	0.05, 2 df, p=1
Wald test	1.35,2 df, p=0.5	0.12, 2 df, p=0.9	3.12, 2 df, p=0.2	0.12, 2 df, p=0.9
Score (logrank) test	0.54,2 df,p=0.8,	0.05,2 df, p=1	0.4,2 df, p=0.8	0.05, 2 df, p=1
Robust	0.69 p=0.7	0.11 p=0.9	1.84 p=0.4	0.11, p=0.9

Note: For all Models: The likelihood ratio and score tests assume independence of observations within a cluster, the Wald and robust score tests do not.

Table 4B: Concordance, Likelihood Results generated from the for the Frailty Model

Variance of random effect	= 0.2007005 I-likelihood = -56.5
Degrees of freedom for terms	= NaN 0.8 0.8 2.9
Concordance	= 0.731 (se = 0.079)
Likelihood ratio test	= 8.09 on NaN df, p=NA

Iterations: 9 outer, 37 Newton-Raphson

Figure 2 gives the survival experiences using the four different models, while Figures 3 and 4 give pictorial views of the hazard's ratios of the first ten subjects from the bladder cancer data.

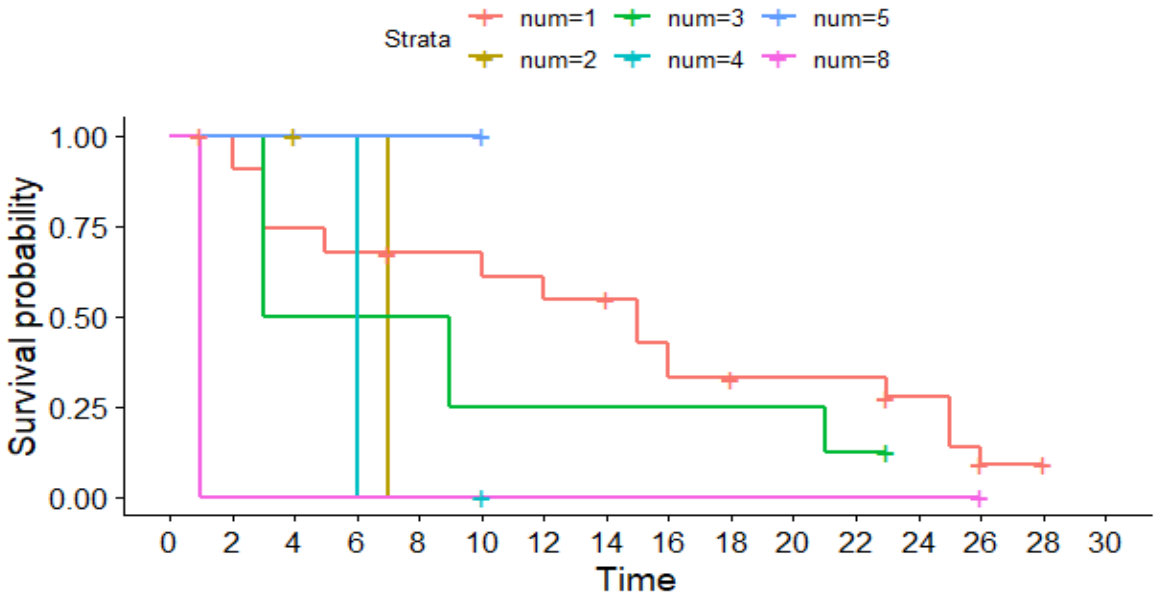

Figure 2: Display of the survival probabilities of the four models for analyzing recurrent data

Hazard ratios estimates along with confidence intervals and *p-values* are plotted for each variable. The means are shown as squares and confidence interval estimates as lines. The righthand side shows the *p-values* for the corresponding regression coefficients which can be obtained from summary (AG_Model). The variable tx is located around 1 hence, its effect is marginal or minimal (See Figure 3).

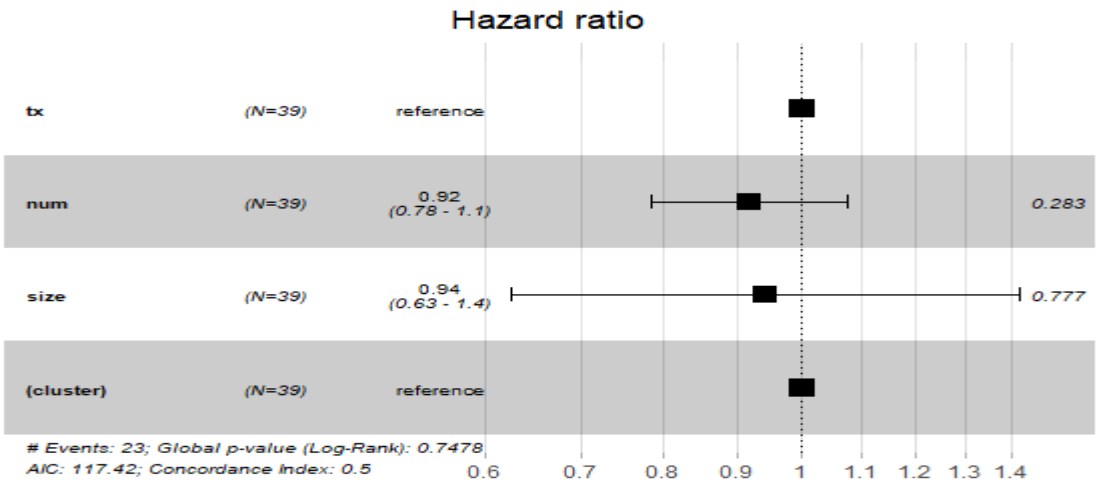

Figure 3: Forest plot of hazard ratios for a multivariate CPHM. (AG Model); Summary of a multivariate Cox Proportional Hazard Model (AG Model) results shown using a forest plot.

Similarly, hazard ratios estimates along with confidence intervals and *p-values* are plotted for each variable. The means are shown as squares and confidence interval estimates as lines. The righthand side shows the *p-values* for the corresponding regression coefficients which can be obtained from summary (Frailty Model). The variable tx is located around 1 hence, its effect is marginal (Figure 4).

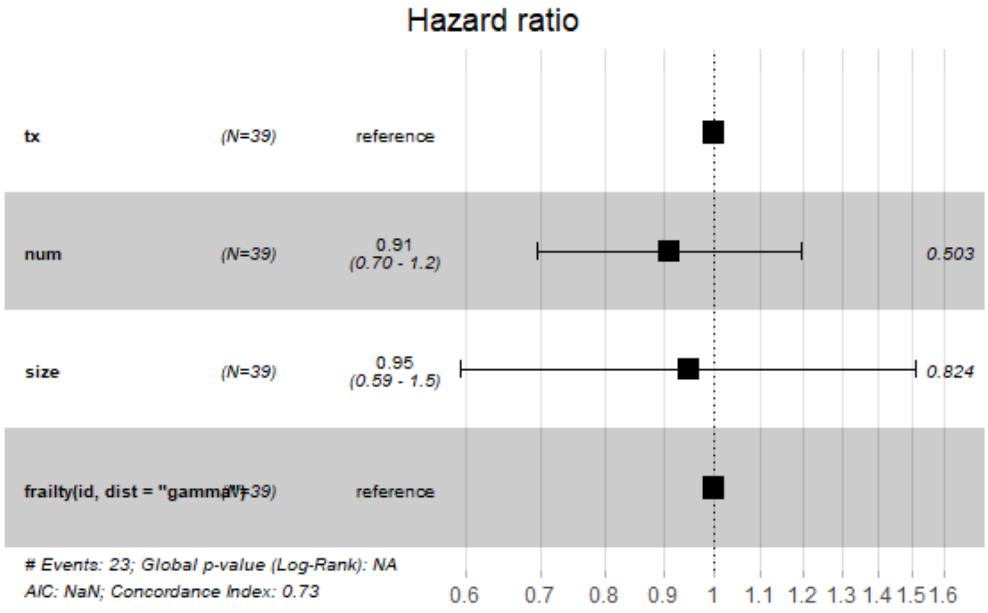

Figure 4: Summary of a multivariate Cox Proportional Hazard Model (Frailty model, distribution = gamma) results shown using a forest plot.

4. CONCLUSION

In conclusion, we join hands with earlier researchers and say that PWP-GT has proved to be the most useful model for analyzing recurrent event data, providing answers to slightly different research questions.

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