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Performance of Variance Corrected Models and Frailty Model in Recurrent Event Data: A Simulation Study

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ABSTRACT

Events in a survival data are independent. However, some health outcomes of a person may occur several times, such as infections and asthma attacks, etc., during the study follow up period. Such events are known as recurrent events. Recurrent event data analysis is most commonly used in biomedical research. This paper examines the performance of variance corrected models with frailty models through simulation with varying degree of correlation, treatment effect and sample sizes. Results were evaluated by comparing the risk ratio estimates, average standard errors (SE), Mean square error (MSE), AIC and log-likelihood values. The Prentice William and Peterson-Counting Process model had better fit among variance corrected models. The Andersen Gill model had very high AIC values and log-likelihood values in the simulation data and in the real time datasets. The frailty model had very high coverage probability which exceeded 95% nominal level in all the circumstances. The Relative Sampling Bias (RSB) and mean square error with beta -1 were not very different for all the models, in all scenarios. The PWP-CP model seemed to have lower AIC, less bias, minimum MSE and optimal coverage probability than all other models for different degree of correlations, varying sample sizes and treatment effects from the simulated data.

Keywords: Counting process; Cox Proportional hazard model; Frailty; Recurrent events; Relative sampling bias; Variance corrected model

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1. Introduction

The Cox Proportional hazard model is commonly used to analyze time-to-event data in biomedical sciences, where events are assumed to be independent [1]. However, some health outcomes of a person may occur several times during the course of follow up. For example, a person experiences repeated occurrences of the same type of event such as asthma attacks, recurrence of bladder cancer tumours and recurrent opportunistic infections in HIV patients. Such outcomes are often called 'recurrent' events or 'repeated' events [2-4]. Researchers use the standard Cox model for recurrent events data which actually deals with time to single event, without realizing that the observations are not independent. The recurrent events within an individual and their corresponding time are expected to be correlated. Ignoring this correlation is expected to bias the regression coefficient and its standard error. This correlation should be considered as a rule rather than an exception which must be taken into account for analysis in order to obtain the correct inference [5, 6]. This led to the development of a number of models for analyzing correlated survival data. These models are often an extension of the standard Cox model used for analyzing independent survival data. Such models are classified as marginal models/variance corrected models and random effects models. Marginal models focus on estimating the effect of the covariates on the marginal expectation of the response by either specifying a correlation structure (Generalized Estimating Equations) or by adjusting the estimated variance of the regression coefficients. Random effects models attempt to model the dependent structure by including a random effect besides accounting for unobserved heterogeneity. This heterogeneity could arise from unobserved covariates. Random effect models are subject-specific models or cluster-specific models [7]. Survival models with random effects are called frailty models [8]. There are a few other methods to handle recurrent event data based on independent increment such as Andersen Gill Model(AG), Wei, Lin and Weissfeld (WLW); Prentice, Williams and Peterson, Counting Process(PWP-CP) and gap time (PWP-GT); and Lee, Wei and Amato (LWA) [3, 8-13].

The Cox extension methods for the analysis of recurrent events are commonly evaluated using simulated data. Kelly and Lim [14] explained the application and the comparison of various recurrent event time models. Villegas et al., [15] simulated recurrent time data with varying degree of correlation, censoring and number of recurrences. Researchers in the applied field (epidemiology or clinical epidemiology) explore a robust method from the variance corrected models and frailty model.

However, there are no studies that compare frailty models to the recurrent event models. Also, there is still a dearth of evidence to select the best method/model for analyzing recurrent event data using simulated and real time data. Hence the objective of this paper was to apply and appreciate the differences between the recurrent event models, including frailty models, through simulation with varying degree of correlation, treatment effect and sample sizes. Two real time datasets were also used to demonstrate the same objective comprehensively.

2. Methods

2.1 Cox proportional hazard model

The standard Cox proportional hazard model for the survival data specifies the hazard function for the individual *i* is modeled as

$$\lambda_i(t) = \lambda_0(t)\exp(\beta' X_i), \qquad (2.1)$$

where t represents time, X_i is the vector of covariates of the i^{th} individual, β' is the vector of regression coefficients and $\lambda_0(t)$ denotes the baseline hazard function obtained for an individual with $X = 0$. $\lambda_i(t)$ is the hazard of individual *i* to experience an

event at time *t*. We could obtain an estimator $\hat{\beta}$ for β based on the assumption that the events in each subject were independent [1]. Let T_{ij} be the time when the j^{th} failure occurs for the i^{th} subject. C_i is the censoring time for individual *i*. The minimum of (T_{ij} , C_i) i.e., Z_{ij} equals T_{ij} if the event was observed (coded 1) and C_i if it is censored (coded 0).

2.2 Extended Cox models

The extended Cox models were used to model recurrent time-to-event outcomes within a subject more comprehensively than the Cox model. The extended Cox models are: 1) Andersen-Gill counting process (AG-CP), 2) Prentice-Williams-Peterson counting process (PWP-CP), 3) PWP - Gap time (PWP-GT) model; and 4) random effect/frailty model. The variance corrected models take into account the recurrent structure of the data and the random effect model uses a frailty term to account for the unobserved heterogeneity besides taking into account the recurrent structure of the data.

These four models were applied to a simulated data and two real time datasets. The model results were evaluated by comparing the risk ratio estimates, average standard errors (SE), Mean square error (MSE), AIC and log likelihood values.

2.2.1 Andersen Gill model

The counting process model of Andersen Gill (AG) is a generalized Cox Model. The AG model assumes that recurrent events are independent. Hence, the baseline hazards for all events are common. The assumption of mutual independence of the events within a subject is equivalent to the assumption of independent increments in the counting process within each subject. The counting process style of data input is seen in AG models where each subject is represented as a series of observation with recurrence time which is given as $(t_0, t_1]$, $(t_1, t_2]$ (t_m , last follow-up time].Each recurrent event (*j*) for an individual *i* is assumed to follow a proportional hazard model where the hazard function is given as

$$\lambda_i(t) = \lambda_0(t)\exp(\beta' X_i(t)) \qquad (2.2)$$

where $\lambda_0(t)$ represents the common baseline hazard function (that is $\lambda_0 = \lambda_0$ for all *j*). Under this model, the risk of recurrent event for a subject follows the usual Cox proportional hazards assumption, assuming each event as independent. Every subject risk interval contributes to the risk set for every event, irrespective of the number of events for each individual. The AG model provides more powerful inference for a covariate effect than the standard Cox model for the time to first event, but requires stronger assumptions than the other models, such as common baseline hazards. A robust sandwich method is used in the estimation of standard errors [2, 16].

2.2.2 Prentice, William and Peterson models (PWP)

Another model for analyzing recurrent events is the Prentice, William and Peterson model. The PWP model analyses recurrent events by stratification, based on the prior number of the events during the follow-up period (10). There are two types of PWP models, they are: 1. PWP counting process model (PWP-CP) and 2. PWP gap time model (PWP-GT). The total time and the gap time models look similar in certain aspects, yet there are important conceptual differences. In the PWP-CP model, the time scale is measured from the beginning of the study to a specified event. It assumes that a subject is not at risk for the k^{th} event until he/she has experienced event *j*-1. The PWP-CP model is similar to the AG-CP model but stratified by events. The baseline hazards vary from event to event, the hazard function for the j^{th} event for i^{th} subject with the standard proportional hazards form is written as

$$\lambda_{ij}(t) = \lambda_{0j}(t)\exp(\beta_j' X_i(t)), \quad (2.3)$$

$i = 1,...,n,\ j = 1,...,k_i, k_i \le k.$ The PWP-GT model describes an intensity process from the occurrence of an immediately preceding event, with the gap time defined as $(t - t_{j-1})$; therefore, each survival process defines a different rank order for a specific risk set on the occurrence of a recurrent event. Both PWP approaches are conditional models as an individual is not considered in the risk set for the j[th] event until experiencing the $(j-1)$[th] event

$$\lambda_{ij}(t) = \lambda_{0j}(t - t_{j-1})\exp(\beta_j' X_i(t)), \quad (2.4)$$

$i = 1,...,n,\ j = 1,...,k_i, k_i \le k,$ where t_{j-1} is the time of the $(j-1)$[th] event(with $t_0 = 0$), and $\lambda_{0j}(t)$ represents the event-specific baseline hazard for the j[th] event over time. Equations (2.2), (2.3) and (2.4) assume that the repeated events are related. Therefore, these estimates are presented by using the sandwich type estimators and hence they are known as variance corrected models [17].

2.2.3 Random effect/frailty model

The frailty model is an extension of the Cox PH model, in which the hazard function depends on an unmeasured random variable [2, 8, 18]. In a frailty model, individuals in the same group share the same frailty value which generates dependence between those individuals who share those frailties. The term 'frailty' means that each subject has his/her own disposition to failure, in addition to any effects that will be quantified using regression. Hazard function $\lambda_{ij}(t)$ for the recurrent time of the j[th] event in the i[th] subject $(j = 1,...,i; i = 1,2,...,n)$ conditional on the frailty Z_i follows the standard proportional hazards form and is given by:

$$\lambda_{ij}(t) = z_i \lambda_0(t)\exp(\beta' X_i(t)), t > 0, \quad (2.5)$$

where, (t) is the common baseline hazard function, X_i is a vector of observable covariates and β is a vector of unknown regression coefficients. Frailty Z_i is the unobserved (random) common risk factor shared by all subjects i and is assumed to be independent and identically distributed with unit mean and unknown variance θ. Each subject could have different values of random effects. Variability in the Z_i reflect the heterogeneity of risk across the subjects. If the value of the frailty Z_i is zero, then events from the same subject are independent. The variance of the random effect lies between 0 to infinity. Mostly the frailty variable is assumed to follow gamma distribution [18-22]. The density function of gamma frailty distribution results in the following form,

$$f(z) = \begin{cases} \dfrac{z^{(1/\theta)-1}\exp(-z/\theta)}{\theta^{1/\theta}\Gamma(1/\theta)}, & if\ z > 0 \\ 0, & otherwise \end{cases}$$

with Γ the gamma function. Note that there is heterogeneity if $\theta > 0$. So, large values of θ reflect a greater degree of heterogeneity among groups or clusters and a stronger association within groups or clusters. The semi parametric gamma frailty model can also be fitted by the penalized partial log likelihood approach [5, 23-25]. The gamma frailty model is equivalent to a penalized Cox model with penalty function $\rho(z) = (1/\theta)\sum[Z_i - \exp(Z_i)]$. The Z's are distributed as the log of i.i.d gamma random variables and the tuning parameter θ as their variance. For the gamma frailty distribution, the correlation of subjects within groups (Kendall's tau) is $\theta/(2+\theta)$.

2.3 Simulation

The survival time was generated based on the Cox Proportional Hazard model that was proposed by Bender et al. [26]. However, there is no straight forward method to generate time-to-event till date. In the

Cox PH model, the effects of the covariate have to be translated into survival time from the hazard rate. It is simpler to convert or translate the regression coefficient for hazard to survival time only if the baseline hazard function has a constant hazard, which means that the survival times follow an exponential distribution and thereby this is one of the reasons that most simulations are based on exponential distribution.

2.3.1 Simulation of survival time

From equation (2.1), the survival function of the Cox PH model is given as

$$\lambda(t/X) = \exp\{-\lambda_0(t)\exp(\beta' X)\}. \quad (2.6)$$

Based on the cumulative hazard function and the distribution function of the Cox PH model, equation (2.6) can be rewritten as

$$F(t/X) = 1-\exp\{-\lambda_0(t)\exp(\beta' X)\}. \quad (2.7)$$

Let us consider Y to be a random variable with distribution function F, then $U = F(Y)$ follows a uniform distribution with the interval [0,1] which can be written as $U \sim U[0,1]$. If $U \sim U[0,1]$ then $(1-U) \sim U[0,1]$ also follows uniform distribution. Then the equation is expressed as

$$T = 1/\lambda_0\{-\log(U)/\lambda\exp(-\beta' X)\}\}, \quad (2.8)$$

where U is a random variable with $U \sim U[0,1]$. This can be transformed into survival time following a specific Cox model [4], which can be rewritten in the form of exponential distribution as follows:

$$T = -\log(U)/\lambda\exp(\beta' X).$$

The corresponding hazard function of the Cox model is given by

$$H(t \mid X) = \lambda\exp(\beta' X). \quad (2.9)$$

Thus, the Cox PH model [2.1] with constant baseline hazard results in an exponentially distributed survival time with scale parameters $\lambda(x) = \lambda\exp(\beta' X)$, which are dependent on the regression coefficient. The exponential distribution has a similar correlation structure, with correlation ρ between adjacent recurrence times [15, 27].

$$W = \frac{\pi(\log 2)^2}{\pi(\log 2)^2 + (1-\log 2)^2}, \quad (2.10)$$

$$P_0 = \frac{-\omega + \sqrt{\omega^2 + 2p(1-\omega)}}{1-\omega}. \quad (2.11)$$

Based on equations 2.10 and 2.11 using R software (Version 3.1.2) [28], recurrent survival time was generated based on rho, which was multiplied with time, until it reached a maximum follow-up time of 24 months. A covariate 'treatment' was generated using random Bernoulli with treatment arm to be 60% and the control arm to be 40%. Each and every individual had a start and a stop time based on the above condition using exponential distribution. If the individual did not get any event within 24 months and/or if the follow-up time exceeded 24 months, such individuals were considered as censored. Also, occurrences of censoring were fixed to be 0%, 10%,15% and 20%, respectively. Data was generated with the above specified criteria and repeated for 1000 times with varied sample size, correlation, betas and censoring.

2.4 Model robustness, accuracy, estimation and evaluation

2.4.1 Robustness

The robustness of the generated recurrent event data was measured using true coverage of 95 and the relative sampling bias of the β estimator for the generated data. The relative sampling bias is defined as

$$\text{Re}\,\textit{lative Sampling Bias} = \frac{1}{m}\sum_{i=1}^{m}\frac{\hat{\beta}_i - \beta}{\beta}.$$

2.4.2 Accuracy

The most common criterion in evaluating the performance of a statistical model is based on its accuracy with respect to the

fitted data. Thus, the model accuracy is assessed by the closeness of the estimates to the exact (or observed) value. The most widely used measure of accuracy is the mean-squared error (MSE). Smaller values indicate a more accurate and reliable model.

$$MSE = \frac{1}{m}\sum_{i=1}^{m}(\hat{\beta}_i - \beta)^2,$$

where m is the number of simulation ($m = 1,000$), $\hat{\beta}_i$ is the estimator from the simulated data and β is the given estimate.

2.4.3 Estimation and evaluation

The Information Criterion (IC) is used for comparison between models. The model with the lower IC indicates better fit of the model. The Akaike Information Criterion (AIC) was calculated for each simulated data. The AIC is one of the most commonly used fit statistics.

$$\text{AIC} = -2\,\text{Log}(L) + 2k,$$

where *k* is the number of predictors, including the intercept in the model and L is the maximized value of the likelihood function for the estimated model.

3.Results

3.1 Simulation

We generated a series of simulations using exponential distribution with different sample sizes, correlation and hazard levels. The different sample sizes considered were $n = (100, 200, 300, 400, 500)$. The correlation within subjects and treatment effects considered were $\rho = (0.1, 0.4, 0.6, 0.8, 1)$ and $\beta = 0.2, 0.4, 0.6, 0.8, 1$ and -1, respectively. Survival time was truncated at 24 months in all the series of simulated data.

Table 1 shows the results of estimates, robustness of the standard error and accuracy of the models for the simulated recurrent event data. The naive standard error was always slightly higher than the robust standard error in all the models with increasing correlations and sample sizes. The standard errors (naive and robust) were large when the sample size was small ($n = 100$). The variance of the frailty increased with increasing correlations irrespective of the sample size. The β coefficient from the frailty model was nearly close to the true value when the sample size was small and when correlation was high. When the sample size was large, the beta value and the true value were similar for varying correlations. A similar kind of trend was also seen with all the remaining β as well. The simulation results are presented in the appendix.

The model fit was assessed for the simulated data using the Akaike Information Criterion (AIC). The AIC seems to be consistently increasing with increase in sample size and decreasing with increasing correlation levels within each of the sample sizes. Of the four models, the PWP-CP model had lower AIC and log likelihood values. The AG model had very high AIC and log-likelihood values in all the circumstances. The PWP-GT model had lower AIC values than the frailty model for all sample size and varying correlations. The frailty model had coverage probability greater than the nominal level of 95% than all other models in many situations (Fig. 1).

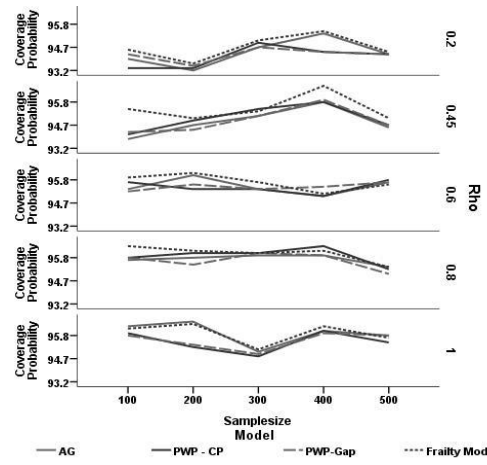

Fig. 1. Coverage Probability for beta -1 with varying rho's and varying sample size.

The Relative Sampling Bias (RSB) and mean square error (Fig. 2) with fixed

treatment effect of -1 were not very different for all the models, in all situations.

3.2 Bladder cancer data

The bladder cancer data are listed in [11], and used as a primary example for these methods. There were 85 cancer patients with recurrent bladder cancer tumours followed up for 64 months after transurethral excision [2].

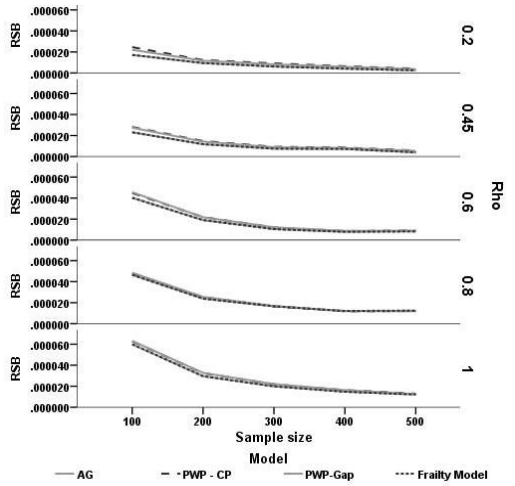

Fig. 2. Explains the Relative Sampling Bias (RSB) for the recurrent event models. With varying sample size and varying correlation.

Of them, 47 and 38 were assigned to placebo and intervention groups, respectively. The risk factors considered in the model were the "treatment"," number of tumours" and "size of the tumours". The main purpose of considering this example was to compare the recurrent event models rather than providing the estimates of recurrent bladder cancer data. Table 2 presents the treatment effect (β) model standard error, robust standard error, AIC, -2 log likelihood and frailty variance for the AG, PWP-CP, PWP-GT and frailty models.

The β value in frailty model was slightly higher (-0.460) than the AG model (-0.412) but the treatment effects of the remaining models were smaller than the frailty and AG models. This suggests that the risk of recurrent bladder cancer was event dependent(correlated). The model fitness characteristics such as AIC and -2 log-likelihood were lower in PWP-CP (AIC = 637.96-2 log-likelihood = -315.99) model as compared to other models. The additional information provided by the frailty model was variance of the random effect (θ= 0.567, p=0.036). This significant heterogeneity suggested that some patients were prone to disease recurrence more quickly than other patients.

3.3 Cystic fibrosis data

This example data is from the study that assessed the effects of rhDNase - pulmozyme (DNase I), acloned and highly purified recombinant DNase I designed to mimic that produced by the human body, deoxyribonuclease-on the incidence of pulmonary exacerbations [29]. The double blind, placebo-controlled study was conducted in 1992. There were 956 patients with cystic fibrosis and all exacerbations were collected for 196 days. Of them 43% of the placebo and 33 % of the rhDNase patients experienced an exacerbation during the follow up period. Table 2 presents the treatment effect β, model standard error, robust standard error, AIC, -2 loglikelihood and frailty variance for the AG, PWP-TT, PWP-GT and frailty models for cystic fibrosis data. The robust standard errors obtained using PWP-CP and frailty models were lowest and exactly the same. It was highest in the AG model followed by the PWP-GT model. The treatment effect was statistically significant in all models except the PWP-GT model. The variance of the frailty was found to be very high (θ = 1.19) and statistically significant (p = 0.001). A frailty variance of more than 1 indicates that the heterogeneity is high. The correlation between recurrent events from the same patient was estimated as $\rho = 0.3748$. The AIC and -2 log-likelihood were also lower in the PWP-CP model compared to other models.

Table 1. Simulation results for $\beta = -1$, varying sample size and varying correlation.

n	β	ρ	Model	β	SE	RSE	AIC	-2LL	FV	CP	RSB	RMSE
100	-1	0.2	AG	-1.0007	0.1776	0.1754	1269.76	-633.88	-	94.0	0.00001559	0.00005210
			PWP-CP	-1.0093	0.1919	0.1893	952.61	-475.30	-	93.5	0.00000979	0.00005632
			PWP-GT	-1.0093	0.1915	0.1886	994.23	-496.11	-	94.2	0.00000955	0.00005558
			Frailty	-1.0007	0.1806	0.1777	1263.29	-630.65	0.026	94.6	0.00001559	0.00005210
		0.45	AG	-1.0137	0.2679	0.2642	570.13	-284.06	-	93.9	0.00002323	0.00007929
			PWP-CP	-1.0205	0.2772	0.2723	476.96	-237.48	-	94.1	0.00001903	0.00008265
			PWP-GT	-1.0206	0.2771	0.2725	482.31	-240.15	-	94.2	0.00001913	0.00008255
			Frailty	-1.0138	0.2721	0.2680	564.22	-281.11	0.058	95.5	0.00002323	0.00007929
		0.6	AG	-1.0243	0.3125	0.3090	426.67	-212.33	-	95.4	0.00002494	0.00001449
			PWP-CP	-1.0291	0.3205	0.3154	367.56	-182.78	-	95.7	0.00002235	0.00001487
			PWP-GT	-1.0277	0.3206	0.3157	370.11	-184.05	-	95.3	0.00002385	0.00001485
			Frailty	-1.0243	0.3180	0.3127	420.33	-209.16	0.089	95.9	0.00002494	0.00001449
		0.8	AG	-1.0174	0.3610	0.3567	323.91	-160.96	-	95.7	0.00004611	0.00001869
			PWP-CP	-1.0237	0.3789	0.3626	286.53	-142.26	-	95.8	0.00004195	0.00001925
			PWP-GT	-1.0227	0.3679	0.3627	287.49	-142.74	-	95.8	0.00004293	0.00001919
			Frailty	-1.0174	0.3675	0.3612	317.69	-157.84	0.120	96.3	0.00004611	0.00001869
200	-1	0.2	AG	-0.9991	0.1249	0.1242	2931.63	-1464.82	-	93.2	0.00000960	0.00003818
			PWP-CP	-1.0023	0.1343	0.1332	2288.73	-1143.36	-	93.5	0.00000749	0.00004044
			PWP-GT	-1.0023	0.1339	0.1327	2372.34	-1185.17	-	93.6	0.00000745	0.00004033
			Frailty	-0.9991	0.1262	0.1250	2329.69	-1460.84	0.015	93.7	0.00000960	0.00003818
		0.45	AG	-1.0061	0.1874	0.1858	1314.59	-656.29	-	94.7	0.00001138	0.00005374
			PWP-CP	-1.0109	0.1935	0.1914	1125.58	-561.79	-	94.9	0.00000751	0.00005483
			PWP-GT	-1.0107	0.1935	0.1915	1136.22	-567.11	-	94.4	0.00000775	0.00005483
			Frailty	-1.0060	0.1893	0.1875	1306.92	-652.46	0.036	95.0	0.00001138	0.00005374
		0.6	AG	-1.0119	0.2174	0.2161	985.87	-491.94	-	96.0	0.00001034	0.00009068
			PWP-CP	-1.0144	0.2225	0.2203	865.52	-431.76	-	95.4	0.00000857	0.00006201
			PWP-GT	-1.0135	0.2226	0.2206	870.65	-434.32	-	95.6	0.00000949	0.00006224
			Frailty	-1.0119	0.2199	0.2174	976.96	-487.48	0.057	96.1	0.00001034	0.00006090
		0.8	AG	-1.0065	0.2509	0.2497	745.44	-371.72	-	95.8	0.00002538	0.00007574
			PWP-CP	-1.0088	0.2554	0.2537	669.27	-333.64	-	96.0	0.00002380	0.00007652
			PWP-GT	-1.0086	0.2554	0.2538	671.40	-334.70	-	95.5	0.00002422	0.00007661
			Frailty	-1.0066	0.2542	0.2509	736.04	-367.02	0.083	96.1	0.00002538	0.00007573
	-1	0.2	AG	-0.9985	0.1018	0.1014	4732.84	-2366.42	-	94.7	0.00000688	0.00003032
			PWP-CP	-1.0012	0.1092	0.1086	3766.62	-1882.31	-	94.9	0.00000506	0.00003273
			PWP-GT	-1.0013	0.1090	0.1082	3892.97	-1945.48	-	94.7	0.00000494	0.00003253

			Frailty	-0.9985	0.1026	0.1018	4725.41	-2361.71	0.012	95.0	0.00000688	0.00003032
		0.45	AG	-1.0065	0.1527	0.1516	2121.72	-1059.86	-	95.1	0.000005467	0.00004431
			PWP-CP	-1.0113	0.1576	0.1565	1838.11	-918.05	-	95.5	0.000001184	0.00004547
			PWP-GT	-1.0109	0.1575	0.1565	1853.85	-925.92	-	95.1	0.000001507	0.00000333
			Frailty	-1.0065	0.1538	0.1527	2113.41	-1055.71	0.025	95.4	0.000005467	0.00004431
		0.6	AG	-1.0088	0.1767	0.1757	1594.41	-796.20	-	95.4	0.000006273	0.00000411
			PWP-CP	-1.0122	0.1809	0.1797	1414.01	-706.00	-	95.4	0.000003429	0.00000424
300			PWP-GT	-1.0119	0.1809	0.1798	1421.28	-709.64	-	95.4	0.000003753	0.00000425
			Frailty	-1.0088	0.1782	0.1768	1584.89	-791.44	0.039	95.7	0.000006273	0.00000411
		0.8	AG	-1.0087	0.2039	0.2029	1202.69	-600.35	-	95.9	0.000001164	0.000005527
			PWP-CP	-1.0123	0.2076	0.2064	1088.76	-543.38	-	96.0	0.000008664	0.000005654
			PWP-GT	-1.0115	0.2076.	0.2065	1091.91	-544.96	-	96.0	0.000009351	0.000005649
			Frailty	-1.0087	0.2059	0.2040	1192.19	-595.09	0.058	96.0	0.000001164	0.000005527
	-1		AG	-1.0002	0.0882	0.0879	6631.10	-3314.55	-	95.4	0.00000391	0.00002629
		0.2	PWP-CP	-1.0026	0.0945	0.0942	5338.37	-2668.18	-	94.4	0.00000221	0.00002826
			PWP-GT	-1.0024	0.0943	0.0939	5506.94	-2752.47	-	94.4	0.00000237	0.00002826
			Frailty	-1.0002	0.0887	0.0882	6621.66	-3309.82	0.009	95.5	0.00000391	0.00002629
			AG	-0.9998	0.1319	0.1314	2974.74	-1486.37	-	95.8	0.00000875	0.00003813
		0.45	PWP-CP	-1.0024	0.1361	0.1354	2594.66	-1296.33	-	95.8	0.00000661	0.00003937
400			PWP-GT	-1.0022	0.1360	0.1354	2616.05	-1307.02	-	95.9	0.00000687	0.00003942
			Frailty	-0.9998	0.1326	0.1319	2966.40	-1482.20	0.019	96.5	0.00000875	0.00003813
			AG	-1.0052	0.1525	0.1520	2237.23	-1117.62	-	95.0	0.00000641	0.00004433
		0.6	PWP-CP	-1.0069	0.1561	0.1554	1994.63	-996.32	-	95.0	0.00000513	0.00004501
			PWP-GT	-1.0069	0.1561	0.1554	2004.612	-1001.31	-	95.5	0.00000509	0.00004493
			Frailty	-1.0052	0.1537	0.1525	225.37	-1111.68	0.036	95.1	0.00000641	0.00004433
			AG	-1.0058	0.1760	0.1752	1686.29	-842.15	-	95.9	0.00000959	0.00005164
		0.8	PWP-CP	-1.0089	0.1791	0.1783	1533.56	-765.78	-	96.3	0.00000708	0.00005237
			PWP-GT	-1.0085	0.1791	0.1784	1537.96	-767.98	-	95.9	0.00000751	0.00005236
			Frailty	-1.0058	0.1774	0.1760	1674.19	-836.09	0.049	96.1	0.00000959	0.00005164
	-1		AG	-1.0006	0.0788	0.0786	8604.20	-4301.10	-	94.2	0.00000286	0.00002376
		0.2	PWP-CP	-1.0027	0.0845	0.0842	6982.98	-3491.49	-	94.2	0.00000127	0.00002546
500			PWP-GT	-1.0025	0.0842	0.0840	7195.66	-3596.83	-	94.2	0.00000143	0.00002540
			Frailty	-1.0006	0.0793	0.0788	8592.65	-4295.32	0.087	94.4	0.00000286	0.00002376
		0.45	AG	-1.0016	0.1179	0.1176	3855.41	-1926.70	-	94.6	0.00000563	0.000001918
			PWP-CP	-1.0031	0.1217	0.1212	3379.38	-1688.69	-	94.7	0.00000434	0.000001972

			PWP-GT	-1.0028	0.1260	0.1213	3405.91	-1701.95	-	94.7	0.00000461	0.000001968
			Frailty	-1.0016	0.1185	0.1180	3846.39	-1922.19	0.016	95.0	0.00000632	0.000001918
		0.6	AG	-1.0019	0.1361	0.1358	2903.86	-1450.93	-	95.7	0.00000741	0.000002504
			PWP-CP	-1.0029	0.1393	0.1388	2599.94	-1298.97	-	95.8	0.00000669	0.000002582
			PWP-GT	-1.0029	0.1393	0.1388	2612.39	-1305.19	-	95.7	0.00000678	0.000002588
			Frailty	-1.0019	0.1369	0.1361	2892.36	-1445.18	0.027	95.6	0.00000741	0.000002504
		0.8	AG	-1.0047	0.1570	0.1565	2188.52	-1093.26	-	95.4	0.00000726	0.000003258
			PWP-CP	-1.0066	0.1598	0.1591	1996.75	-997.38	-	95.3	0.00000569	0.000003343
			PWP-GT	-1.0066	0.1598	0.1592	2002.50	-1000.25	-	95.0	0.00000571	0.000003341
			Frailty	-1.0047	0.1580	0.1571	2176.49	-1087.25	0.039	95.4	0.00000725	0.000003257

Note: SE: Standard error, RSE: Robust Standard error, FV: Frailty Variance, CP: Coverage Probability, RSE: Relative Sampling Bias, RMSE: Root Mean square error

4. Discussion

Recurrent event data has two main issues which need to be accounted for, viz., (i) dependence between repeated events within a subject and (ii) heterogeneity across the subjects. With this in mind, recurrent event models were examined using simulation without fixing the number of events and also using real time data.

Table 2. Treatment effect, Standard error (SE), robust standard error (RSE), AIC, loglikelihood (LL) and frailty variance using bladder cancer data and Cystic fibrosis data.

Model	Estimate (β)ab	Standard Error	Robust Std Error	AIC	Log likelihood	P value	θ
Bladder Cancer data							
AG	-0.412	0.199	0.249	919.9	-456.9	0.097	-
PWP-CP	-0.333	0.216	0.205	637.9	-315.9	0.103	-
PWP-Gap	-0.279	0.207	0.216	723.9	-358.9	0.195	-
Frailty	-0.460	0.276	0.209	841.2	-417.6	0.095	0.567
Cystic fibrosis datab							
AG	-0.295	0.106	0.131	4527.5	-2261.8	0.024	-
PWP-CP	-0.216	0.107	0.108	3909.3	-1952.6	0.046	-
PWP-Gap	-0.215	0.107	0.112	3982.7	-1989.4	0.055	-
Frailty	-0.333	0.141	0.108	4010.4	-2003.2	0.018	1.199

a treatment effect is adjusted for number of tumours and size of the tumours.
b treatment effect is adjusted for FEV.

The simulation results show that all the models have different degree of robustness with variations in sample size and correlation. With increasing correlation, all the models overestimated the value for lower sample sizes but the value of β was equivalent to -1 with the increasing sample size. The AG and frailty models provided exact β values (as fixed) and different robust standard errors and PWP models overestimated β values with low correlation levels. However, Kelly and Lim reported that AG and PWP models overestimated β values with low correlation levels. The AIC values were very high for low correlation while AIC values were low for increasing correlation in all of the samples. The AG model had highest AIC values than other models in all situations. Although AG model is recommended by Therneau et al. because of its simplicity, robustness and efficiency, Kelly and Lim (2000) stated that robust variance alone was not adequate to account for within subject correlations [13]. With respect to AIC and log-likelihood values, PWP-CP followed by PWP-GT model performed better than other models in both simulated and real time data. As stated in the literature [2, 14], the PWP-CP model is more appropriate when the dependence from the past recurrent events is strong and consistent whereas the PWP-GT is more appropriate when one wants to preserve the order of the events in the creation of the risk set and account for event dependence [30-32].

The variance corrected models such as AG and PWP models have been compared by various authors (e.g., Lin,1994; Gao and Zhou, 1997; Therneau and Hamilton, 1997: Villegas et al, 2013, Jahn EA et al, 2015) [15, 29, 31, 33-34] using real time data and simulated data, and found that these models give different findings for the same data set like the present study. This was not indeed unexpected because all these models have different underlying assumptions.

The random effect/frailty model had smaller AIC and log-likelihood values than the AG model. A study by Ullah et al (2012) showed that there was no statistical difference between AG and frailty models in terms of model selection and goodness of fit or accuracy both for simulated data and Australian National Rugby League recurrent injury data [35]. Kelly and Lim (2000) also recommended the use of a frailty model which incorporates random effect to account for heterogeneity as well as event dependence. The coverage probability for the frailty model was very much higher than 95% in all the circumstances. To our knowledge, this was one of the few studies in health data which used simulated recurrent event data to explore frailty models.

Variance corrected models and random effects/frailty model comparison should also consider risk interval, risk set, baseline hazard and within person correlation to decide on an appropriate model.

4.1 Limitation of the study

This study dealt with simulation data with sample sizes of 100, 200, 300, etc., However in real life situations survival analysis often deals with small sample sizes such as 25, 50 and 75. Our study conclusions may not be valid with a small sample size. Also, the maximum censoring rate in this study simulation was 20%. The recommended censoring rate in survival analysis is maximum 50%. Unfortunately, our study did not deal with maximum recommended simulation. However, that decision should be made on the basis of our research question and interest in choosing the model and purely on simulation finding.

5. Conclusion

The PWP-CP model had lower AIC, less bias, minimum MSE and optimal coverage probability than all other models specified for different degree of correlation and varying sample sizes or treatment effects from the simulated data; hence we strongly recommend the PWP-CP model.

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Appendix

Table 1. Simulation result for Beta 0.2, varying sample size and varying correlation without censoring.

n	β	p	Model	Est	SE	RSE	AIC	-2LL	FV	CP	RSB	RMSE
100	0.2	0.2	AG	0.2045	0.1315	0.1300	2372.21	-1185.11	-	93.7	0.00001472	0.00002847
			PWP-CP	0.2059	0.1350	0.1319	1700.96	-849.48	-	94.2	0.00001660	0.00003021
			PWP-GT	0.2053	0.1347	0.1319	1825.09	-911.55	-	94.0	0.00001589	0.00002982
			Frailty	0.2045	0.1339	0.1315	2365.14	-1181.57	0.015	94.9	0.00001472	0.00002847
		0.45	AG	0.1992	0.1973	0.1939	1067.03	-532.51	-	93.8	0.00002045	0.00006478
			PWP-CP	0.1981	0.2001	0.1962	857.08	-427.54	-	93.4	0.00001996	0.00006668
			PWP-GT	0.1981	0.2000	0.1960	874.12	-436.06	-	93.4	0.00001980	0.00006597
			Frailty	0.1992	0.2008	0.1973	1060.20	-529.10	0.035	95.1	0.00002045	0.00006478
		0.6	AG	0.2051	0.2277	0.2244	803.93	-400.96	-	94.9	0.00003327	0.00009176
			PWP-CP	0.2058	0.2305	0.2267	667.50	-332.75	-	95.3	0.00003415	0.00009193
			PWP-GT	0.2058	0.2304	0.2265	675.89	-336.95	-	94.8	0.00003435	0.00009290
			Frailty	0.2051	0.2318	0.2277	797.14	-397.57	0.047	95.8	0.00003327	0.00009176
		0.8	AG	0.2060	0.2635	0.2599	606.27	-302.13	-	95.4	0.00004283	0.00012160
			PWP-CP	0.2062	0.2662	0.2627	518.72	-258.36	-	95.0	0.00004421	0.00012566
			PWP-GT	0.2065	0.2662	0.2626	522.36	-260.18	-	95.0	0.00004466	0.00012584
			Frailty	0.2060	0.2684	0.2635	599.55	-298.77	0.064	96.8	0.00004283	0.00012160
200	0.2	0.2	AG	0.2013	0.0926	0.0919	5447.78	-2722.89	-	94.6	0.00000671	0.00001299
			PWP-CP	0.2012	0.0941	0.0929	4096.01	-2047.00	-	95.5	0.00000672	0.00001339
			PWP-GT	0.2012	0.0940	0.0928	4344.07	-2171.03	-	95.1	0.00000665	0.00001319
			Frailty	0.2013	0.0937	0.0926	5438.56	-2718.28	0.097	95.8	0.00000671	0.00001299
		0.45	AG	0.1974	0.1386	0.1372	2443.54	-1220.77	-	93.4	0.00000947	0.00000338
			PWP-CP	0.1978	0.1399	0.1383	2022.38	-1010.19	-	93.8	0.00000100	0.00000345
			PWP-GT	0.1975	0.1398	0.1382	2056.39	-1027.19	-	93.4	0.00000987	0.00000348
			Frailty	0.1974	0.1401	0.1386	2435.35	-1216.67	0.0198	93.9	0.00000947	0.00003389
		0.6	AG	0.2002	0.1597	0.1580	1844.61	-921.30	-	94.9	0.00001447	0.00004087
			PWP-CP	0.2021	0.1609	0.1594	1570.93	-784.47	-	94.3	0.00001662	0.00004205
			PWP-GT	0.2018	0.1609	0.1592	1587.35	-792.67	-	94.6	0.00001639	0.00004225
			Frailty	0.2002	0.1613	0.1596	1836.71	-917.35	0.026	95.1	0.00001447	0.00004088

		0.8	AG	0.2095	0.1846	0.1831	1391.71	-694.85	-	95.7	0.00002784	0.00005485
			PWP-CP	0.2109	0.1858	0.1841	1215.15	-606.57	-	95.5	0.00002938	0.00005585
			PWP-GT	0.2114	0.1858	0.1840	1222.53	-610.26	-	95.7	0.00002999	0.00005631
			Frailty	0.2095	0.1868	0.1846	1382.67	-690.34	0.040	95.7	0.00002784	0.00005485
300	0.2	0.2	AG	0.2035	0.0755	0.0751	8807.69	-4402.85	-	95.4	0.00000732	0.00008084
			PWP-CP	0.2032	0.0765	0.0758	6767.0	-3382.5	-	95.1	0.00000713	0.00000829
			PWP-GT	0.2034	0.0764	0.0757	7142.3	-3570.15	-	95.3	0.00000732	0.00000832
			Frailty	0.2035	0.0762	0.0755	8796.80	-4397.40	0.007	95.6	0.00000732	0.00000808
		0.45	AG	0.1980	0.1129	0.1123	3941.18	-1969.59	-	94.3	0.00000587	0.00002056
			PWP-CP	0.1984	0.1137	0.1129	3307.74	-1652.87	-	94.5	0.00000626	0.00002070
			PWP-GT	0.1983	0.1137	0.1129	3358.59	-1678.29	-	94.4	0.00000624	0.00002077
			Frailty	0.1980	0.1138	0.1129	3932.43	-1965.22	0.014	94.6	0.00000587	0.00002056
		0.6	AG	0.2020	0.1302	0.1293	2968.95	-1483.47	-	94.3	0.00001198	0.00002710
			PWP-CP	0.2031	0.1310	0.1302	2558.96	-1278.48	-	94.5	0.00001323	0.00002768
			PWP-GT	0.2030	0.1310	0.1301	2583.23	-1290.62	-	94.1	0.00001314	0.00002782
			Frailty	0.2020	0.1312	0.1302	2960.78	-1479.39	0.018	94.6	0.00001198	0.00002710
		0.8	AG	0.2078	0.1502	0.1492	2246.19	-1122.09	-	95.7	0.00002021	0.00003511
			PWP-CP	0.2086	0.1509	0.1499	1981.18	-989.59	-	95.9	0.00002110	0.00003571
			PWP-GT	0.2091	0.1510	0.1499	1991.80	-994.90	-	95.1	0.00002175	0.00003609
			Frailty	0.2078	0.1515	0.1502	2236.44	-1117.22	0.028	95.8	0.00002021	0.00003511
400	0.2	0.2	AG	0.2031	0.0653	0.0650	12338.58	-6168.29	-	95.6	0.00000624	0.00000614
			PWP-CP	0.2033	0.0661	0.0656	9612.14	-4805.07	-	96.0	0.00000654	0.00000626
			PWP-GT	0.2031	0.0660	0.0655	10113.17	-5055.58	-	96.0	0.00000634	0.00000626
			Frailty	0.2030	0.0658	0.0653	12327.07	-6162.53	0.006	96.5	0.00000624	0.00000614
		0.45	AG	0.2018	0.0977	0.0974	5521.26	-2759.63	-	94.2	0.00000799	0.00001529
			PWP-CP	0.2023	0.0983	0.0977	4673.44	-2335.72	-	94.2	0.00000846	0.00001539
			PWP-GT	0.2019	0.0983	0.0977	4742.06	-2370.03	-	94.0	0.00000824	0.00001556
			Frailty	0.2018	0.0982	0.0977	5513.39	-2755.69	0.009	94.5	0.00000799	0.00001529
		0.6	AG	0.2010	0.1126	0.1120	4163.37	-2080.69	-	93.9	0.00000920	0.00002157
			PWP-CP	0.2021	0.1132	0.1126	3613.89	-1805.95	-	94.0	0.00001027	0.00002162
			PWP-GT	0.2020	0.1132	0.1126	3646.50	-1822.25	-	93.7	0.00001020	0.00002179
			Frailty	0.2010	0.1132	0.1126	4155.58	-2076.79	0.012	94.5	0.00000920	0.00002157
		0.8	AG	0.2072	0.1298	0.1293	3146.79	-1572.39	-	94.6	0.00001663	0.00002591
			PWP-CP	0.2074	0.1303	0.1297	2791.34	-1394.67	-	94.8	0.00001699	0.00002618
			PWP-GT	0.2076	0.1303	0.1296	2806.16	-1402.08	-	94.5	0.00001725	0.00002643
			Frailty	0.2071	0.1307	0.1298	3135.65	-1566.83	0.031	94.9	0.00001663	0.00002592

500	0.2	0.2	AG	0.2024	0.0584	0.0582	16004.63	-8001.32	-	95.8	0.00000514	0.00000475
			PWP-CP	0.2025	0.0589	0.0586	12590.33	-6294.16	-	96.1	0.00000528	0.00000482
			PWP-GT	0.2025	0.0589	0.0585	13217.57	-6607.78	-	95.9	0.00000523	0.00000483
			Frailty	0.2024	0.0587	0.0584	15993.19	-7995.59	0.0046	95.9	0.00000514	0.00000475
		0.45	AG	0.2016	0.0874	0.0871	7154.48	-3576.24	-	93.6	0.00000669	0.00001204
			PWP-CP	0.2019	0.0879	0.0875	6094.07	-3046.04	-	93.7	0.00000714	0.00001234
			PWP-GT	0.2019	0.0879	0.0875	6180.54	-3089.27	-	93.6	0.00000718	0.00001229
			Frailty	0.2016	0.0877	0.0874	7146.98	-3572.49	0.007	94.2	0.00000669	0.00001204
		0.6	AG	0.2005	0.1007	0.1003	5395.29	-2696.65	-	94.5	0.00000714	0.00001700
			PWP-CP	0.2008	0.1011	0.1007	4707.09	-2352.55	-	94.5	0.00000749	0.00001703
			PWP-GT	0.2009	0.1011	0.1006	4748.01	-2373.00	-	94.5	0.00000765	0.00001713
			Frailty	0.2005	0.1010	0.1007	5387.96	-2692.98	0.009	95.0	0.00000716	0.00001700
		0.8	AG	0.2058	0.1160	0.1157	4076.65	-2037.32	-	94.1	0.00001395	0.00002157
			PWP-CP	0.2056	0.1165	0.1159	3631.81	-1814.91	-	94.8	0.00001378	0.00002179
			PWP-GT	0.2057	0.1165	0.1159	3650.57	-1824.28	-	94.4	0.00001387	0.00002181
			Frailty	0.2058	0.1167	0.1160	4064.82	-2031.41	0.026	94.5	0.00001395	0.00002157

Note: Est-Estimated beta, SE:Standard error, RSE:Robust Standard error, FV:Frailty Variance, RSE:Relative Sampling Bias,-RMSE:Root Mean square error

Table 2. Simulation result for Beta 0.4, varying sample size and varying correlation without censoring.

n	β	p	Model	Est	SE	RSE	AIC	-2LL	FV	CP	RSB	RMSE
100	0.4	0.2	AG	0.4072	0.1276	0.1258	2702.51	-1350.25	-	93.9	0.00001702	0.00003989
			PWP-CP	0.4097	0.1327	0.1291	1882.34	-940.17	-	93.4	0.00002040	0.00004486
			PWP-GT	0.4085	0.1323	0.1290	2056.23	-1027.12	-	93.4	0.00001924	0.00004464
			Frailty	0.4072	0.1296	0.1276	2695.59	-1346.80	0.0131	94.6	0.00001702	0.00003989
		0.45	AG	0.4087	0.1914	0.1880	1214.94	-606.47	-	94.2	0.00002979	0.00009665
			PWP-CP	0.4095	0.1952	0.1911	954.86	-476.3	-	93.6	0.00003183	0.00010409
			PWP-GT	0.4096	0.1951	0.1910	980.99	-489.49	-	94.3	0.00003179	0.00010347
			Frailty	0.4087	0.1946	0.1914	1207.93	-602.97	0.0309	95.3	0.00002979	0.00009664
		0.6	AG	0.4108	0.2204	0.2172	914.99	-456.49		94.1	0.00003689	0.00012456
			PWP-CP	0.4111	0.2239	0.2197	744.95	-371.47	-	94.3	0.00003803	0.00012855
			PWP-GT	0.4120	0.2239	0.2193	757.59	-377.79	-	94.7	0.00003859	0.00012717
			Frailty	0.4108	0.2240	0.2204	908.27	-453.13	0.0395	95.1	0.00003689	0.00012456
		0.8	AG	0.4019	0.2540	0.2499	690.27	-344.14	-	95.5	0.00003465	0.00015738
			PWP-CP	0.4038	0.2573	0.2529	580.83	-289.41	-	95.4	0.00003703	0.00016100
			PWP-GT	0.4060	0.2573	0.2524	586.61	-292.30	-	95.9	0.00003963	0.00016334
			Frailty	0.4019	0.2584	0.2541	683.53	-340.76	0.0559	97.2	0.00003466	0.00015738
200	0.4	0.2	AG	0.4039	0.0896	0.0889	6200.31	-3099.16	-	94.5	0.00000953	0.00002010
			PWP-CP	0.4053	0.0924	0.0911	4549.62	-2273.81	-	93.6	0.00001136	0.00002215
			PWP-GT	0.4049	0.0922	0.0908	4896.16	-2447.08	-	94.1	0.00001093	0.00002200
			Frailty	0.4039	0.0905	0.0896	6191.52	-3094.76	0.0081	94.9	0.00000953	0.00002012
		0.45	AG	0.4039	0.1341	0.1329	2789.82	-1393.91	-	94.8	0.00001445	0.00004274
			PWP-CP	0.4052	0.1362	0.1348	2266.61	-1132.31	-	94.3	0.00001604	0.00004505
			PWP-GT	0.4055	0.1362	0.1346	2317.85	-1157.92	-	94.3	0.00001631	0.00004486
			Frailty	0.4039	0.1356	0.1342	2781.08	-1389.54	0.0185	95.1	0.00001445	0.00004274
		0.6	AG	0.4034	0.1547	0.1532	2098.23	-1048.12	-	95.5	0.00001664	0.00005618
			PWP-CP	0.4037	0.1547	0.1549	1757.98	-877.99	-	95.8	0.00001720	0.00005773
			PWP-GT	0.4045	0.1565	0.1548	1782.47	-890.24	-	95.7	0.00001802	0.00005757
			Frailty	0.4034	0.1562	0.1547	2089.99	-1043.99	0.0235	95.7	0.00001664	0.00005618
		0.8	AG	0.4077	0.1784	0.1764	1583.52	-790.76	-	95.7	0.00002500	0.00007743
			PWP-CP	0.4091	0.1802	0.1782	1363.44	-680.72	-	95.8	0.00002649	0.00007741
			PWP-GT	0.4093	0.1802	0.1779	1375.00	-686.80	-	95.6	0.00002673	0.00007782
			Frailty	0.4077	0.1801	0.1784	1575.84	-786.92	0.0300	96.2	0.00002500	0.00007743

	0.4		AG	0.4042	0.0731	0.0727	10019.1	-5008.95	-	94.1	0.00000827	0.00001308
		0.2	PWP-CP	0.4049	0.0751	0.0744	7531.09	-3764.55	-	93.7	0.00000919	0.00001388
			PWP-GT Frail	0.4051	0.0749	0.0742	8053.77	-4025.88	-	93.8	0.00000933	0.00001382
			ty	0.4041	0.0736	0.0731	10009.51	-5003.75	0.0063	94.2	0.00000827	0.00001309
			AG	0.4016	0.1093	0.1086	4498.01	-2248.00	-	94.9	0.00000870	0.00002681
		0.45	PWP-CP	0.4024	0.1108	0.1099	3711.62	-1854.81	-	94.7	0.00000960	0.00002732
300			PWP-GT Frail	0.4024	0.1107	0.1098	3788.81	1893.41	-	94.6	0.00000969	0.00002752
			ty	0.4016	0.1102	0.1093	4487.51	-2242.75	0.0145	95.2	0.00000870	0.00002681
			AG	0.4033	0.1261	0.1253	3383.26	-1690.63	-	95.6	0.00001286	0.00003880
		0.6	PWP-CP	0.4039	0.1261	0.1265	2872.20	-1435.10	-	95.0	0.00001359	0.00003949
			PWP-GT	0.4046	0.1274	0.1264	2908.27	-1453.13	-	95.2	0.00001433	0.00003958
			Frailty	0.4033	0.1269	0.1261	3375.05	-1686.52	0.0153	95.5	0.00001286	0.00003880
			AG	0.4053	0.1453	0.1442	2553.89	-1275.95	-	95.3	0.00001727	0.00005024
		0.8	PWP-CP	0.4059	0.1466	0.1455	2223.67	-1110.83	-	95.9	0.00001797	0.00005029
			PWP-GT	0.4063	0.1465	0.1454	2240.66	-1119.33	-	95.3	0.00001836	0.00005063
			Frailty	0.4053	0.1463	0.1453	2545.93	-1271.96	0.0201	95.8	0.00001727	0.00005024
	0.4		AG	0.4009	0.0632	0.0629	14045.8	-7021.89	-	93.7	0.00000440	0.00001016
		0.2	PWP-CP	0.4018	0.0649	0.0644	10719.66	-5358.83	-	93.4	0.00000542	0.00001074
			PWP-GT	0.4018	0.0647	0.0642	11416.6	-5707.29	-	93.5	0.00000538	0.00001075
			Frailty	0.4009	0.0636	0.0632	14035.26	-7016.63	0.0047	93.8	0.00000440	0.00001017
			AG	0.4024	0.0946	0.0942	6300.56	-3149.28	-	95.4	0.00000825	0.00002070
		0.45	PWP-CP	0.4026	0.0958	0.0952	5248.63	-2623.31	-	95.1	0.00000857	0.00002126
400			PWP-GT	0.4029	0.0957	0.0951	5352.05	-2675.03	-	94.8	0.00000879	0.00002124
			Frailty	0.4024	0.0951	0.0946	6290.61	-3144.30	0.0102	95.2	0.00000825	0.00002070
			AG	0.4019	0.1089	0.1084	4746.04	-2372.02	-	96.6	0.00000895	0.00002628
		0.6	PWP-CP	0.4025	0.1089	0.1094	4060.76	-2029.38	-	96.3	0.00000955	0.00002666
			PWP-GT	0.4025	0.1100	0.1094	4109.58	-2053.79	-	96.5	0.00000968	0.00002695
			Frailty	0.4019	0.1094	0.1089	4738.66	-2368.33	0.0103	96.8	0.00000895	0.00002628
			AG	0.4042	0.1255	0.1249	3583.11	-1790.55	-	95.0	0.00001362	0.00003819
		0.8	PWP-CP	0.4049	0.1265	0.1258	3139.43	-1568.71	-	94.9	0.00001444	0.00003837
			PWP-GT Frail	0.4049	0.1265	0.1257	3162.78	-1580.39	-	95.0	0.00001439	0.00003851
			ty	0.4042	0.1262	0.1255	3574.27	-1786.14	0.0166	95.1	0.00001362	0.00003819
	0.4		AG	0.4015	0.0565	0.0563	18219.59	-9108.75	-	94.6	0.00000446	0.00000768
		0.2	PWP-CP	0.4023	0.0579	0.0575	14034.55	-7025.77	-	94.3	0.00000538	0.00000825
			PWP-GT	0.4021	0.0578	0.0574	14925.32	-7461.66	-	93.8	0.00000823	0.00000725
			Frailty	0.4015	0.0568	0.0565	18207.39	-9102.69	0.0043	95.0	0.00000446	0.00000768

500		0.45	AG	0.4015	0.0845	0.0842	8166.21	-4082.11	-	95.3	0.00000639	0.00001659
			PWP-CP	0.4021	0.0856	0.0852	6850.71	-3424.35	-	94.9	0.00000708	0.00001700
			PWP-GT	0.4021	0.0855	0.0852	6980.05	-3489.03	-	95.3	0.00000707	0.00001691
			Frailty	0.4015	0.0849	0.0845	8156.27	-4077.14	0.0081	95.1	0.00000639	0.00001659
		0.6	AG	0.4034	0.0974	0.0971	6149.19	-3073.59	-	94.4	0.00000978	0.00002334
			PWP-CP	0.4037	0.0974	0.0979	5291.70	-2644.85	-	94.6	0.00001006	0.00002346
			PWP-GT	0.4037	0.0983	0.0979	5353.32	-2675.66	-	94.8	0.00001011	0.00002352
			Frailty	0.4034	0.0978	0.0975	6141.99	-3069.99	0.0080	94.7	0.00000978	0.00002334
		0.8	AG	0.4025	0.1122	0.1119	4642.36	-2320.18	-	94.9	0.00001022	0.00003012
			PWP-CP	0.4026	0.1130	0.1125	4086.97	-2042.48	-	94.9	0.00001036	0.00002999
			PWP-GT Frail	0.4028	0.1130	0.1125	4116.41	-2057.21	-	95.0	0.00001056	0.00003001
			ty	0.4025	0.1127	0.1122	4633.47	-2315.73	0.0131	95.3	0.00001022	0.00003012

Note: Est-Estimated beta, SE:Standard error, RSE:Robust Standard error, FV:Frailty Variance, RSE:Relative Sampling Bias,-RMSE:Root Mean square error

Table 3. Simulation result for Beta 0.8, varying sample size and varying correlation without censoring.

n	β	p	Model	Est	SE	RSE	AIC	-2LL	FV	CP	RSB	RMSE
100	0.8	0.2	AG	0.8097	0.1208	0.1192	3585.54	-1791.77	-	94.5	0.00001721	0.00007577
			PWP-CP	0.8150	0.1340	0.1303	2307.63	-1152.82	-	94.2	0.00002461	0.00009937
			PWP-GT Frail-ty	0.8129	0.1319	0.1285	2657.41	-1327.70	-	93.7	0.00002212	0.00009475
				0.8097	0.1225	0.1208	3578.83	-1788.42	0.0094	95.5	0.00001721	0.00007577
		0.45	AG	0.8047	0.1811	0.1783	1610.16	-804.08	-	93.9	0.00002313	0.00020142
			PWP-CP	0.8072	0.1892	0.1852	1194.63	-596.31	-	93.8	0.00002811	0.00023804
			PWP-GT Frail-ty	0.8066	0.1891	0.1847	1254.47	-626.23	-	93.5	0.00002746	0.00023659
				0.8047	0.1835	0.1811	1603.37	-800.68	0.0220	95.2	0.00002313	0.00020142
		0.6	AG	0.8183	0.2097	0.2060	1217.28	-607.64	-	95.0	0.00004029	0.00024136
			PWP-CP	0.8208	0.2168	0.2119	940.97	-469.49	-	95.0	0.00004482	0.00027173
			PWP-GT Frail-ty	0.8213	0.2168	0.2118	971.64	-484.82	-	95.0	0.00004564	0.00027588
				0.8183	0.2124	0.2098	1210.82	-604.41	0.0281	96.3	0.00004029	0.00024136
		0.8	AG	0.8162	0.2418	0.2381	913.12	-455.56	-	95.0	0.00004648	0.00034664
			PWP-CP	0.8162	0.2479	0.2427	732.95	-365.48	-	94.3.	0.00004789	0.00036637
			PWP-GT Frail-ty	0.8167	0.2479	0.2421	747.83	-372.92	-	94.9	0.00004843	0.00036728
				0.8162	0.2454	0.2418	905.89	-451.94	0.0430	95.6	0.00004648	0.00034664
300	0.8	0.2	AG	0.8035	0.0692	0.0689	13355.16	-6676.58	-	95.6	0.00000617	0.00002397
			PWP-CP	0.8061	0.0692	0.0752	9456.51	-4727.26	-	94.7	0.00000915	0.00002860
			PWP-GT Frail-ty	0.8052	0.0747	0.0740	10517.90	-5257.95	-	94.7	0.00000824	0.00002765
				0.8035	0.0696	0.0692	13346.16	-6672.08	0.0039	96.0	0.00000617	0.00002397
		0.45	AG	0.8020	0.1036	0.1030	5978.90	-2988.45	-	95.6	0.00000751	0.00005308
			PWP-CP	0.8034	0.1077	0.1068	4716.13	-2357.07	-	95.2	0.00000926	0.00005766
			PWP-GT Frail-ty	0.8029	0.1076	0.1065	4897.22	-2447.61	-	95.3	0.00000883	0.00005733
				0.8020	0.1043	0.1036	5968.62	-2983.31	0.0105	95.6	0.00000751	0.00005308
		0.6	AG	0.8029	0.1194	0.1185	4504.29	-2251.14	-	94.9	0.00001046	0.00007459
			PWP-CP	0.8042	0.1194	0.1217	3670.47	-1834.23	-	95.1	0.00001200	0.00007770
			PWP-GT Frail-ty	0.8044	0.1229	0.1216	3760.83	-1879.41	-	95.0	0.00001217	0.00007788
				0.8029	0.1201	0.1194	4494.73	-2246.36	0.0130	95.7	0.00001046	0.00007459
		0.8	AG	0.8070	0.1378	0.1370	3388.03	-1693.01	-	94.8	0.00001659	0.00009766
			PWP-CP	0.8065	0.1378	0.1395	2844.09	-1421.04	-	94.9	0.00001652	0.00010111
			PWP-GT Frail-ty	0.8068	0.1408	0.1394	2886.99	-1442.50	-	94.9	0.00001681	0.00010164
				0.8070	0.1386	0.1377	3378.74	-1688.37	0.0171	95.3	0.00001659	0.00009766

500	0.8	0.2	AG	0.8008	0.0535	0.0533	24278.85	-12138.42	-	94.8	0.00000251	0.00001440
			PWP-CP	0.8022	0.0585	0.0581	17749.05	-8873.52	-	95.0	0.00000412	0.00001684
			PWP-GT	0.8017	0.0576	0.0572	19526.43	-9762.21	-	94.7	0.00000362	0.00001664
			Frailty	0.8008	0.0538	0.0535	24267.15	-12132.57	0.0030	95.1	0.00000251	0.00001440
		0.45	AG	0.8004	0.0801	0.0798	10873.14	-5435.57	-	94.4	0.00000399	0.00003353
			PWP-CP	0.8018	0.0832	0.0828	8759.14	-4378.57	-	94.6	0.00000565	0.00003647
			PWP-GT	0.8015	0.0831	0.0826	9062.15	-4530.08	-	94.5	0.00000535	0.00003640
			Frailty	0.8004	0.0805	0.0801	10860.85	-5429.42	0.0073	95.1	0.00000399	0.00003353
		0.6	AG	0.8037	0.0924	0.0921	8180.56	-4089.28	-	94.3	0.00000831	0.00004356
			PWP-CP	0.8043	0.0951	0.0946	6786.18	-3392.09	-	94.2	0.00000905	0.00004575
			PWP-GT	0.8042	0.0950	0.0946	6936.72	-3467.36	-	94.1	0.00000899	0.00004581
			Frailty	0.8037	0.0928	0.0924	8169.77	-4083.88	0.0087	94.8	0.00000831	0.00004356
		0.8	AG	0.8063	0.1065	0.1062	6168.15	-3083.08	-	94.1	0.00001236	0.00005884
			PWP-CP	0.8059	0.1088	0.1082	5254.49	-2626.24	-	94.0	0.00001204	0.00005969
			PWP-GT	0.8058	0.1088	0.1082	5328.45	-2663.23	-	94.2	0.00001187	0.00005947
			Frailty	0.8063	0.1068	0.1065	6159.79	-3078.90	0.0091	94.4	0.00001236	0.00005884

Note: Est-Estimated beta, SE:Standard error, RSE:Robust Standard error, FV:Frailty Variance, RSE:Relative Sampling Bias,-RMSE:Root Mean square error

Table 4. Simulation result for Beta 1, varying sample size and varying correlation without censoring.

n	β	p	Model	Est	SE	RSE	AIC	-2LL	FV	CP	RSB	RMSE
100	1	0.2	AG	1.0077	0.1182	0.1160	4171.41	-2084.70	-	95.1	0.00001732	0.00010135
			PWP-CP	1.0162	0.1379	0.1333	2558.89	-1278.44	-	95.6	0.00002910	0.00015859
			PWP-GT	1.0116	0.1338	0.1292	3054.52	-1526.26	-	96.0	0.00002354	0.00014138
			Frailty	1.0077	0.1194	0.1182	4165.41	-2081.70	0.007	95.9	0.00001732	0.00010135
		0.45	AG	1.0092	0.1774	0.1747	1866.49	-932.24	-	94.9	0.00002981	0.00030839
			PWP-CP	1.0136	0.1892	0.1843	1335.12	-666.56	-	94.2	0.00003743	0.00037554
			PWP-GT	1.0127	0.1889	0.1843	1427.14	-712.57	-	94.2	0.00003647	0.00037261
			Frailty	1.0092	0.1795	0.1774	1859.73	-928.87	0.0187	95.8	0.00002981	0.00030839
		0.6	AG	1.0140	0.2050	0.2018	1409.39	-703.70	-	94.7	0.00003985	0.00039425
			PWP-CP	1.0184	0.2149	0.2101	1055.92	-526.96	-	94.2	0.00004681	0.00044655
			PWP-GT	1.0188	0.2149	0.2098	1103.66	-550.83	-	93.9	0.00004750	0.00045280
			Frailty	1.0140	0.8073	0.2051	1403.25	-700.62	0.0226	94.8	0.00003985	0.00039425
		0.8	AG	1.0224	0.2372	0.2335	1064.41	-531.20	-	94.8	0.00005455	0.00059210
			PWP-CP	1.0248	0.2455	0.2403	830.41	-414.20	-	94.7	0.00005828	0.00052200
			PWP-GT	1.0254	0.2455	0.2401	854.58	-426.29	-	94.8	0.00005886	0.00052274
			Frailty	1.0224	0.2399	0.2372	1057.89	-527.95	0.0321	95.7	0.00005455	0.00049210
300	1	0.2	AG	1.0009	0.0677	0.0673	15530.16	-7764.08	-	96.1	0.00000616	0.00003276
			PWP-CP	1.0042	0.0779	0.0770	10608.96	-5303.48	-	95.2	0.00001029	0.00004579
			PWP-GT	1.0028	0.0757	0.0747	12115.37	-6056.68	-	95.3	0.00000859	0.00004160
			Frailty	1.0009	0.0681	0.0677	15521.13	-7759.57	0.003	96.0	0.00000616	0.00003276
		0.45	AG	1.0056	0.1015	0.1008	6951.64	-3474.82	-	94.8	0.00001402	0.00008293
			PWP-CP	1.0074	0.1077	0.1066	5333.94	-2665.97	-	94.7	0.00001657	0.00009445
			PWP-GT	1.0076	0.1074	0.1063	5612.59	-2805.29	-	94.6	0.00001665	0.00009396
			Frailty	1.0056	0.1020	0.1015	6941.94	-3469.97	0.0084	95.8	0.00001402	0.00008293
		0.6	AG	1.0016	0.1168	0.1161	5246.78	-2622.39	-	94.4	0.00001121	0.00009972
			PWP-CP	1.0037	0.1220	0.1210	4170.94	-2084.47	-	94.8	0.00001395	0.00011095
			PWP-GT	1.0033	0.1219	0.1208	4314.51	-2156.25	-	95.2	0.00001348	0.00011060
			Frailty	1.0016	0.1175	0.1168	5236.89	-2617.44	0.0115	95.3	0.00001121	0.00009972
		0.8	AG	1.0056	0.1347	0.1336	3955.90	-1976.90	-	94.5	0.00001820	0.00014781
			PWP-CP	1.0072	0.1391	0.1378	3247.12	-1622.56	-	94.7	0.00002002	0.00015093
			PWP-GT	1.0072	0.1391	0.1377	3318.66	-1658.33	-	94.7	0.00002007	0.00015163
			Frailty	1.0056	0.1355	0.1348	3946.75	-1972.38	0.0142	95.1	0.00001820	0.00014781

500	1	0.2	AG	1.0020	0.0524	0.0522	28226.9	-14112.45	-	95.7	0.00000644	0.00002014
			PWP-CP	1.0037	0.0614	0.0597	19986.30	-9992.15	-	96.1	0.00000848	0.00002598
			PWP-GT	1.0027	0.0584	0.0579	22508.12	-11253.06	-	95.5	0.00007446	0.00002465
			Frailty	1.0020	0.0526	0.0524	28215.74	-14106.87	0.002	95.8	0.00000644	0.00002014
		0.45	AG	1.0034	0.07844	0.0781	12655.87	-6326.94	-	95.5	0.00000959	0.00004638
			PWP-CP	1.0042	0.0832	0.0827	9943.24	-4970.62	-	95.6	0.00001079	0.00005313
			PWP-GT	1.0044	0.0829	0.0824	10411.26	-5204.63	-	95.1	0.00001094	0.00005289
			Frailty	1.0034	0.0788	0.0784	12643.64	-6320.82	0.0062	95.4	0.00000959	0.00004638
		0.6	AG	1.0021	0.0904	0.0900	9542.67	-4770.34	-	95.5	0.00000931	0.00006200
			PWP-CP	1.0034	0.0943	0.0938	7741.01	-3869.51	-	95.7	0.00001091	0.00006769
			PWP-GT	1.0030	0.0942	0.0937	7980.89	-3989.45	-	95.4	0.00001048	0.00006728
			Frailty	1.0021	0.0907	0.0904	9531.19	-4764.59	0.0078	95.8	0.00000931	0.00006200
		0.8	AG	1.0065	0.1042	0.1039	7191.31	-3594.66	-	94.4	0.00001512	0.00008474
			PWP-CP	1.0074	0.1076	0.1071	6004.00	-3000.99	-	94.7	0.00001620	0.00008787
			PWP-GT	1.0074	0.1076	0.1070	6124.48	-3061.24	-	94.7	0.00001611	0.00008717
			Frailty	1.0065	0.1046	0.1043	7181.20	-3589.60	0.0092	94.5	0.00001512	0.00008474

Note: Est-Estimated beta, SE:Standard error, RSE:Robust Standard error, FV:Frailty Variance, RSE:Relative Sampling Bias,-RMSE:Root Mean square error

Table 5. Simulation result for beta -1, varying sample size and varying correlation with 10% censoring.

n	β	ρ	Model	Estimate β	Standard Error	Robust Standard Error	AIC	-2log likelihood	FV	CP	Relative Sam-pling Bias	Mean Squared Error
100	-1	0.2	AG	-1.0031	0.1874	0.1851	1143.91	-570.95	-	93.6	0.00001537	0.00005541
			PWP_TT	-1.0119	0.2010	0.1982	872.09	-435.05	-	93.6	0.00000957	0.00005928
			PWP_GT	-1.0317	0.1997	0.2008	921.53	-459.76	-	93.2	0.00000964	0.00005949
			Frailty	-1.0031	0.1905	0.1875	1137.39	-567.69	0.030	94.6	0.00001537	0.00005541
		0.45	AG	-1.0137	0.2831	0.2791	512.64	-255.32	-	94.4	0.00002691	0.00008314
			PWP_TT	-1.0206	0.2918	0.2864	433.90	-215.95	-	94.4	0.00002264	0.00008631
			PWP_GT	-1.0242	0.2913	0.2879	442.62	-220.31	-	94.5	0.00001954	0.00008644
			Frailty	-1.0137	0.2876	0.2832	506.71	-252.36	0.066	95.1	0.00002691	0.00008314
		0.6	AG	-1.0243	0.3125	0.3090	426.66	-212.33	-	95.4	0.00002494	0.00009069
			PWP_TT	-1.0291	0.3205	0.3154	367.56	-182.78	-	95.7	0.00002235	0.00009199
			PWP_GT	-1.0277	0.3206	0.3157	370.10	-184.05	-	95.3	0.00002385	0.00009220
			Frailty	-1.0243	0.3180	0.3127	420.33	-209.16	0.089	95.9	0.00002494	0.00009069
		0.8	AG	-1.0251	0.3825	0.3776	291.80	-144.90	-	95.8	0.00004984	0.00011403
			PWP_TT	-1.0305	0.3889	0.3831	260.28	-129.14	-	95.4	0.00004610	0.00011459
			PWP_GT	-1.0310	0.3885	0.3837	262.69	-130.35	-	95.4	0.00004560	0.00011471
			Frailty	-1.0251	0.3893	0.3827	285.60	-141.80	0.134	96.5	0.00004984	0.00011403

200	-1	0.2	AG	-0.9994	0.1318	0.1311	2638.92	-1318.46	-	94.0	0.00001038	0.00004022
			PWP_TT	-1.0028	0.1406	0.1396	2088.73	-1043.36	-	94.1	0.00000819	0.00004250
			PWP_GT	-1.0219	0.1398	0.1416	2189.49	-1093.75	-	93.6	0.00000620	0.00004279
			Frailty	-0.9994	0.1331	0.1318	2630.86	-1314.43	0.018	94.5	0.00001038	0.00004022
		0.45	AG	-1.0044	0.1977	0.1961	1183.36	-590.68	-	94.9	0.00001464	0.00005692
			PWP_TT	-1.0089	0.2034	0.2013	1023.27	-510.63	-	95.7	0.00001109	0.00005787
			PWP_GT	-1.0132	0.2031	0.2022	1041.28	-519.64	-	95.2	0.00000707	0.00005839
			Frailty	-1.0044	0.1998	0.1977	1175.34	-586.67	0.042	95.3	0.00001464	0.00005692
		0.6	AG	-1.0119	0.2174	0.2160	985.88	-491.94	-	96.0	0.00001034	0.00009069
			PWP_TT	-1.0144	0.2226	0.2203	865.52	-431.76	-	95.4	0.00000857	0.00006201
			PWP_GT	-1.0135	0.2226	0.2206	870.65	-434.32	-	95.6	0.00000949	0.00006224
			Frailty	-1.0119	0.2199	0.2174	976.96	-487.48	0.057	96.1	0.00001034	0.00006090
		0.8	AG	-1.0066	0.2649	0.2636	671.28	-334.64	-	95.5	0.00002948	0.00008056
			PWP_TT	-1.0084	0.2692	0.2675	607.09	-302.55	-	95.8	0.00002831	0.00008093
			PWP_GT	-1.0097	0.2689	0.2679	612.33	-305.16	-	95.6	0.00002708	0.00008090
			Frailty	-1.0066	0.2683	0.2649	661.99	-329.99	0.093	95.6	0.00002948	0.00008056
300	-1	0.2	AG	-0.9993	0.1074	0.1070	4261.85	-2129.93	-	94.9	0.00000668	0.00003213
			PWP_TT	-1.0019	0.1144	0.1137	3433.40	-1715.70	-	94.4	0.00000500	0.00003412
			PWP_GT	-1.0210	0.1138	0.1155	3586.58	-1792.29	-	95.2	0.00000381	0.00003433
			Frailty	-0.9993	0.1082	0.1074	4252.67	-2125.33	0.013	95.4	0.00000668	0.00003213
		0.45	AG	-1.0063	0.1611	0.1599	1910.22	-954.11	-	94.8	0.00000682	0.00004627
			PWP_TT	-1.0108	0.1657	0.1645	1669.87	-833.93	-	95.1	0.00000283	0.00004693
			PWP_GT	-1.0152	0.1655	0.1652	1696.98	-847.49	-	94.8	0.00000139	0.00004714
			Frailty	-1.0063	0.1623	0.1611	1901.41	-949.70	0.030	95.2	0.00000682	0.00004627
		0.6	AG	-1.0087	0.1767	0.1757	1594.41	-796.20	-	95.4	0.00000627	0.00005019
			PWP_TT	-1.0122	0.1809	0.1797	1414.01	-706.00	-	95.4	0.00000343	0.00005095
			PWP_GT	-1.0119	0.1809	0.1798	1421.28	-709.64	-	95.4	0.00000375	0.00005110
			Frailty	-1.0087	0.1782	0.1767	1584.88	-791.44	0.039	95.7	0.00000627	0.00005019
		0.8	AG	-1.0082	0.2152	0.2142	1082.72	-540.36	-	95.1	0.00001495	0.00006306
			PWP_TT	-1.0113	0.2186	0.2175	986.75	-492.37	-	95.5	0.00001236	0.00006349
			PWP_GT	-1.0124	02185	0.2180	994.64	-496.32	-	95.5	0.00001122	0.00006336
			Frailty	-1.0082	0.2173	0.2153	1072.05	-535.03	0.066	95.6	0.00001495	0.00006306
400	-1	0.2	AG	-1.0010	0.0929	0.0927	5969.32	-2983.66	-	94.6	0.00000364	0.00002787
			PWP_TT	-1.0035	0.0990	0.0987	4863.04	-2430.52	-	93.8	0.00000182	0.00002982
			PWP_GT	-1.0228	0.0985	0.1001	5068.09	-2533.04	-	93.9	0.00000171	0.00003033
			Frailty	-1.0010	0.0935	0.0930	5959.74	-2978.87	0.010	94.7	0.00000364	0.00002787
		0.45	AG	-1.0004	0.1392	0.1386	2677.67	-1337.84	-	95.8	0.00000911	0.00004063
			PWP_TT	-1.0027	0.1431	0.1422	2355.61	-1176.81	-	95.7	0.00000731	0.00004159
			PWP_GT	-1.0070	0.1429	0.1430	2392.49	-1195.25	-	95.8	0.00000305	0.00004170

			Frailty	-1.0004	0.1400	0.1392	2668.31	-1333.15	0.023	96.3	0.00000911	0.00004063
		0.6	AG	-1.0052	0.1525	0.1520	2237.23	-1117.61	-	95.0	0.00000641	0.00004433
			PWP_TT	-1.0069	0.1561	0.1554	1994.63	-996.32	-	95.0	0.00000513	0.00004501
			PWP_GT	-1.0119	0.1809	0.1798	1421.28	-709.64	-	95.4	0.00000375	0.00005110
			Frailty	-1.0052	0.1537	0.1525	2225.37	-1111.68	0.036	95.1	0.00000641	0.00004433
		0.8	AG	-1.0058	0.1856	0.1848	1519.03	-758.51	-	95.2	0.00000117	0.00005477
			PWP_TT	-1.0086	0.1885	0.1877	1390.26	-694.13	-	95.0	0.00000959	0.00005550
			PWP_GT	-1.0099	0.1884	0.1881	1401.01	-699.50	-	95.2	0.00000837	0.00005554
			Frailty	-1.0058	0.1871	0.1856	1506.84	-752.42	0.056	95.7	0.00000117	0.00005477
500	-1	0.2	AG	-1.0015	0.0831	0.0829	7745.56	-3871.78	-	93.3	0.00000243	0.00002513
			PWP_TT	-1.0038	0.0885	0.0882	6360.04	-3179.02	-	94.1	0.00000269	0.00002697
			PWP_GT	-1.0229	0.0880	0.0895	6617.09	-3307.55	-	93.0	0.00000219	0.00002774
			Frailty	-1.0015	0.0835	0.0831	7735.09	-3866.55	0.001	93.7	0.00000243	0.00002513
		0.45	AG	-1.0017	0.1244	0.1241	3468.12	-1733.06	-	95.3	0.00000598	0.00003614
			PWP_TT	-1.0032	0.1279	0.1275	3065.35	-1531.67	-	95.4	0.00000478	0.00003664
			PWP_GT	-1.0076	0.1278	0.1281	3111.59	-1554.79	-	95.8	0.00000428	0.00003671
			Frailty	-1.0017	0.1251	0.1244	3458.19	-1728.09	0.020	95.4	0.00000598	0.00003614
		0.6	AG	-1.0019	0.1361	0.1358	2903.86	-1450.93	-	95.7	0.00000741	0.00003954
			PWP_TT	-1.0029	01393	0.1388	2599.94	-1298.97	-	95.8	0.00000669	0.000040067
			PWP_GT	-1.0029	0.1393	0.1388	2612.39	-1305.19	-	95.7	0.00000678	0.00004007
			Frailty	-1.0019	0.1369	0.1361	2892.36	-1445.18	0.028	95.6	0.00000741	0.00003954
		0.8	AG	-1.0047	0.1656	0.1649	1971.65	-984.83	-	94.4	0.00000881	0.00004797
			PWP_TT	-1.0066	0.1682	0.1674	1809.95	-903.97	-	95.2	0.00000736	0.00004896
			PWP_GT	-1.0083	0.1681	0.1677	1823.66	-910.83	-	95.3	0.00000569	0.00004905
			Frailty	-1.0047	0.1667	0.1656	1958.9	-978.45	0.045	94.6	0.00000881	0.00004797

Note: Est-Estimated beta, SE: Standard error, RSE:Robust Standard error, FV: Frailty Variance, RSE: Relative Sampling Bias,, RMSE: Root Mean square error