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SINGLE COVARIATE LOG-LOGISTIC MODEL ADEQUACY WITH RIGHT AND INTERVAL CENSORED DATA

(Kecukupan Model Log-Logistik Kovariat Tunggal dengan Data Tertapis Kanan dan Selang)

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ABSTRACT

This research aims to analyze and examine the adequacy of the log-logistic model for a covariate, right, and interval censored data by using various types of imputation methods. We started by incorporating a covariate to the log-logistic model with right and interval censored data and obtained its parameter estimates via maximum likelihood estimation (MLE). Performance of the parameter estimates using the left, mid, and right point imputation methods is assessed and compared at various sample sizes and censoring proportions via a simulation study. The best imputation method is chosen based on minimum values of standard error (SE), and root mean square error (RMSE). Also, newly proposed Modified Cox-Snell residuals based on the geometric mean (GMCS) and harmonic mean (HMCS) were compared with Cox-Snell (CS) and Modified Cox-Snell (MCS) residuals via simulation study by comparing the range of residual's intercept, slope, and R-square at different settings. Conclusions are then made based on the simulation results. The proposed residual worked well with real data and provided simple and easy interpretation of the results using log(-log(estimated survivor function of residual)) versus log(residual) plot. The results show the data is fitted well with the log-logistic model and gender of patients is not giving any significant impact on the development of diabetic nephropathy.

Keywords: log-logistic; covariate; interval censored

ABSTRAK

Tujuan kajian ini dijalankan adalah untuk menyiasat kebagusan penyuaian model log-logistik bagi data berkovariat dan data tertapis kanan dan selang menggunakan pelbagai kaedah imputasi yang berbeza. Analisis dimulakan dengan menggabungkan kovariat ke dalam model log logistik dengan data tertapis kanan dan selang dengan anggaran parameter model diperoleh melalui penganggaran kebolehjadian maksimum (MLE). Prestasi parameter yang dianggarkan melalui kaedah imputasi titik kiri, tengah dan kanan dibandingkan dengan sampel pelbagai saiz dan kadar tapisan berbeza melalui kajian simulasi. Kaedah imputasi terbaik dikenal pasti melalui nilai minimum ralat piawai dan punca min kuasa dua ralat. Di samping itu, reja baharu yang dicadangkan dinamakan sebagai reja Cox-Snell Terubah suai min Geometri dan reja Cox-Snell Terubah suai min Harmonik dibandingkan dengan reja Cox-Snell dan reja Cox-Snell Terubah suai melalui kajian simulasi menggunakan tetapan berbeza pada julat reja pintasan, kecerunan dan kuasa dua R. Kesimpulan seterusnya dibuat berdasarkan keputusan simulasi. Reja yang dicadangkan berfungsi dengan baik ke atas data sebenar dan memberikan tafsiran hasil yang mudah menggunakan plot log(-log(fungsi kemandirian teranggar untuk reja)) lawan log(reja). Hasil kajian menunjukkan data berkenaan adalah sesuai digunakan dalam model log-logistik dan jantina pesakit tidak memberikan kesan yang signifikan terhadap perkembangan nefropati diabetes.

Kata kunci: log-logistik; kovariat; tertapis selang

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1. Introduction

Log-logistic (LL) model is one of the commonly used parametric survival models in handling survival analysis with non-monotonic hazard function. Non-monotonic hazard function occurs frequently in medical data, such as the curability of breast cancer study (Langlands *et al.* 1979), the AIDS infection rate study (Byers *et al.* 1988), and adjuvant chemotherapy regimes in breast cancer study (Faradmal *et al*. 2010). Besides the medical field, LL regression is widely used in other fields, i.e. in networking field, fitted delays transmission of sensory data to predict future times of arrival in networked telerobot (Gago-Benítez *et al*. 2013).

Adnan and Arasan (2018) investigated the left-truncation and right-censoring effect on LL model, and the results showed that standard error (SE) of parameter estimates increases as truncation level and censoring proportions increases. They also showed that SE and RMSE decreases as sample size increases. Loh *et al*. (2017) studied inferential procedures for LL distribution with doubly interval censored data, and they stated that Wald outperformed the likelihood ratio and jackknife inferential procedures by using the results in coverage probability study.

For LL model adequacy study, O'Quigley and Struthers (1982) studied both logistic and log-logistic models with censored survival data. They also applied residual plots in model checking to identify how well the model fit for the data. Silva *et al*. (2011) used residual plots to check violation of model assumption and existence of outlier for log-Burr XII model with censored data. They suggested that modified martingale-type residual can be applied to log-Burr XII regression model with censored data by using the standard approach of residual analysis that commonly applied in standard linear regression models. Since LL model is a special case for log-Burr XII model, these residuals are also applicable for LL model adequacy checking.

When compare to general linear model, residual for survival data is not easy to define and will be influenced by not only sample size, but also censoring proportion and censoring type in the survival data (Naslina *et al*. 2020). Cox-Snell residual is the most general practice to evaluate the model adequacy. In this research, newly proposed modified Cox-Snell residuals were applied in the log-logistic model with covariate, right and interval censored data by using the best imputation method that was obtained via simulation study.

2. Methodology

2.1. *The log-logistic (LL) model*

A single covariate log-logistic accelerated failure time model can be expressed as below:

$$In(t) = \beta_0 + \beta_1 x + \sigma\varepsilon \tag{1}$$

where β_0 is the shape parameter, β_1 is the single covariate, t is the lifetime, σ is the scale parameter and ε indicates the error term which follows the standard log-logistic distribution.

The log-logistic survivor function is as shown below:

$$S(t, x, \beta, \sigma) = [1 + exp(z)]^{-1} \tag{2}$$

where $z = \frac{y - \beta_0 - \beta_1 x}{\sigma}$ and $y = In(t)$

In this research, we were going to use three approaches to analyze interval censored data for comparison purpose. These three approaches are left, mid, and right imputations. Suppose there is a random sample of size n, let t_i denotes as failure time of the i^{th} observation and δ_i its censoring indicator, then the general likelihood function of model with uncensored, right censored and interval censored lifetime data for left, mid, and right imputation methods are given by,

$$L(\theta) = \prod_{i=1}^{n}[f(t_i)]^{\delta_{E_i}}[S(t_{R_i})]^{\delta_{R_i}}[f(\tilde{t}_i)]^{\delta_{I_i}} \quad (3)$$

where t_{R_i} is the right censored failure time, $\tilde{t}_i$ is the midpoint /right point /left point of an interval, δ_{E_i} = 1 if exact survival time is observed, 0 otherwise, δ_{R_i} = 1 if subject is right censored, 0 otherwise, and δ_{I_i} = 1 if subject is interval censored, 0 otherwise.

The log-likelihood function using imputation methods for i = 1, 2, …, n observations with right and interval censored is,

$$In[L(\beta,\sigma)] = \sum_{i=1}^{n}\delta_{E_i}\{-In(\sigma) + z_i - 2In[1+exp(z_i)]\} - \delta_{R_i}In[1+exp(z_i)] + \delta_{I_i}\{-In(\sigma) + \tilde{z}_i - 2In[1+exp(\tilde{z}_i)]\} \quad (4)$$

where $\tilde{z} = \frac{\tilde{y}-\beta_0-\beta_1 x}{\sigma}$, and $\tilde{y} = In(\tilde{t})$

2.2. *Residuals in survival analysis*

Cox-Snell (CS) residual is one of the most widely used residual in survival analysis for uncensored data, it can be defined as a negative natural log of survival probability for individual i when the survival function has been estimated. The formula is shown as below:

$$r_{C_i} = \hat{H}(t_i) = -\log\left(\hat{S}(t_i)\right) \quad (5)$$

When dealing with censored data, modified Cox-Snell (MCS) residual is used. Crowley and Hu (1977) stated that CS residual is biased when dealing with censored data, and MCS residual can remedy this issue. Instead of adding an unity of exponential for censored observations, median of excess residual is suggested, where log(2) = 0.693 should be added for censored data.

In this research, we proposed 2 modifications to the CS residual as given in the following.

2.2.1. *Modified Cox-Snell residual based on geometric mean (GMCS)*

Let G be geometric mean of uncensored CS residual.

$$G = \left(\prod_{i=1}^{n} x_i\right)^{\frac{1}{n}} \quad (6)$$

Habib (2012) stated that geometric mean is useful in dampen the inflation effect and perform better than the median in the estimation of the scale parameter of the LL distribution. Hence, GMCS residual was proposed and can be written as below,

$$r^*_{G_i} = \begin{cases} r_{C_i} & \text{for observed event time} \\ r_{C_i} + G & \text{for censored event time} \end{cases} \quad (7)$$

2.2.2. *Modified Cox-Snell residual based on harmonic mean (HMCS)*

Let H be harmonic mean of uncensored CS residual.

$$H = \frac{n}{\frac{1}{x_1}+\frac{1}{x_2}+\cdots+\frac{1}{x_n}} \tag{8}$$

Harmonic mean having same advantages as geometric mean, where both means are calculated based on all the observations, and they are not heavily impacted by sample fluctuation. Bian and Tao (2008) stated that harmonic mean is performing better than geometric mean in handling classification problem in Fisher's linear discriminant analysis. This inspired us that harmonic mean should be another proposed solution to compare with geometric mean. The proposed HMCS residual can be written as below,

$$r^*_{H_i} = \begin{cases} r_{C_i} & \text{for observed event time} \\ r_{C_i} + H & \text{for censored event time} \end{cases} \tag{9}$$

3. Simulation Study

A simulation was conducted using $N = 1000$ replications with sample sizes $n = 30$, 50, 100, and 200 to compare the performance of the MLE for the parameters of the LL model. Besides that, four levels of approximate censoring proportions (CP) were applied which are 0.05, 0.1, 0.2 and 0.3. The values for parameters $\beta_0, \beta_1,$ and σ were specifically set at 2.87, 0.05, and 0.5 respectively to mimic the lung cancer data, and interval period is 4 months which was used to simulate 4 months follow up period for lung cancer patient. Let $F(t_i) = U$ be CDF for LL distribution, where U is a uniform variable on (0,1), and the lifetime, t_i was generated using inverse transformation, and can be written as below:

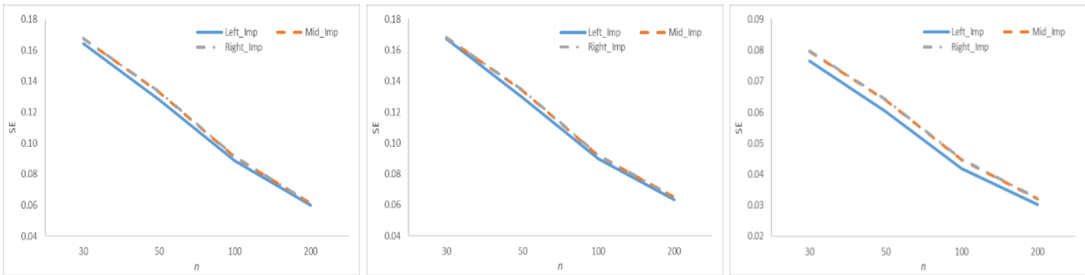
$$t_i = \sigma\left(\frac{1}{u_i} - 1\right)^{-1/\beta} \tag{10}$$

Interval censoring occurs when the lifetime of a subject is only known to fall within an interval $[L_i, R_i]$, where L_i and R_i are knowns as left and right endpoints. In this case, the imputation methods can be used to estimate the true lifetime. Left, mid, and right point imputation methods can be generated as $Y_i = L_i$, $Y_i = \frac{L_i+R_i}{2}$, and $Y_i = R_i$ respectively. For performance study, a set of measures will be used to evaluate performance of parameters $\beta_0, \beta_1,$ and σ. Standard error (SE), and root mean square error (RMSE) were used to evaluate the accuracy, precision, and stability of estimator's performance.

Best imputation method was chosen based on simulation results and applied in the next simulation study. Following that, four type of residuals were applied, which are CS, MCS, GMCS and HMCS residuals. Three selection criterions were used to compare performance of residuals, which are the intercept, slope and R-square values of the plot of log(-log $S(t)$) against log(t). Range of simulated intercept, slope and R-square were obtained, and residual that produce smaller range of desired value is preferred.

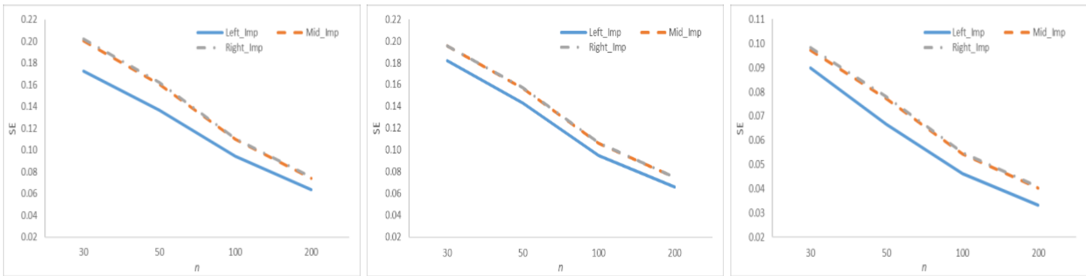
4. Simulation Result and Discussion

Figures 1 to 8 clearly show that the values of SE and RMSE for β_0, β_1 and σ decrease as the sample size increases but an opposite trend occurs as censoring proportions increases. The results also show that left imputation method outperforms by having the lowest SE and RMSE value compared to midpoint and right imputation methods.



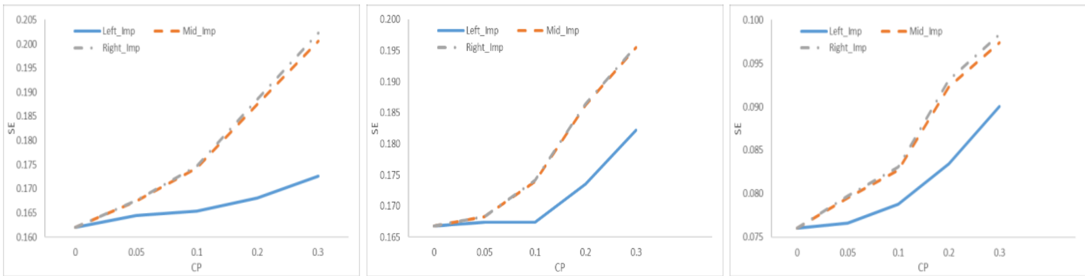
(a) (b) (c)

Figure 1: Line plot of SE for (a) $\hat{\beta}_0$, (b) $\hat{\beta}_1$ and (c) $\hat{\sigma}$ at CP = 0.05



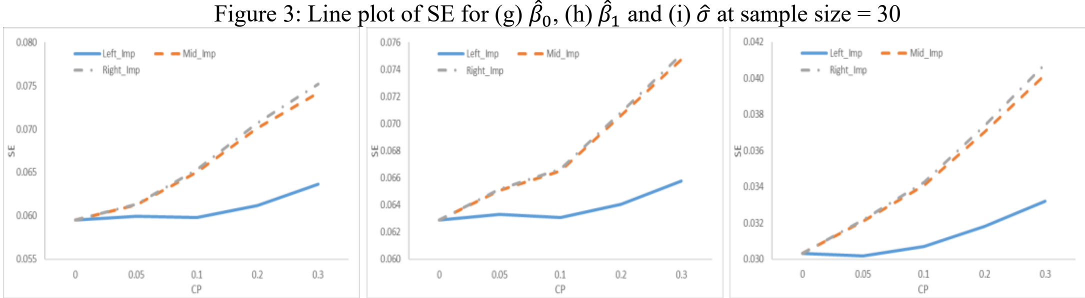
(d) (e) (f)

Figure 2: Line plot of SE for (d) $\hat{\beta}_0$, (e) $\hat{\beta}_1$ and (f) $\hat{\sigma}$ at CP = 0.30



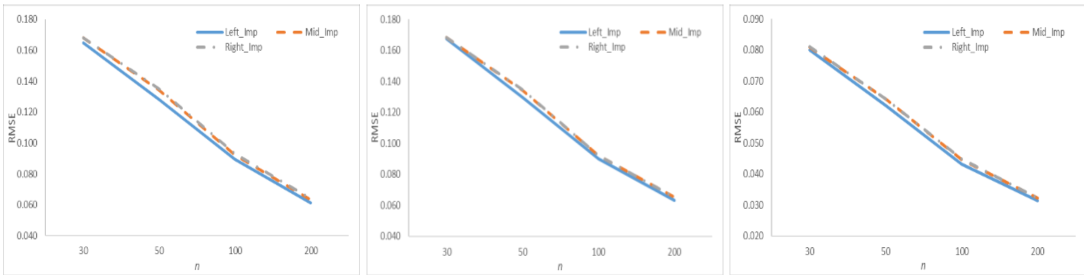
(g) (h) (i)

Figure 3: Line plot of SE for (g) $\hat{\beta}_0$, (h) $\hat{\beta}_1$ and (i) $\hat{\sigma}$ at sample size = 30



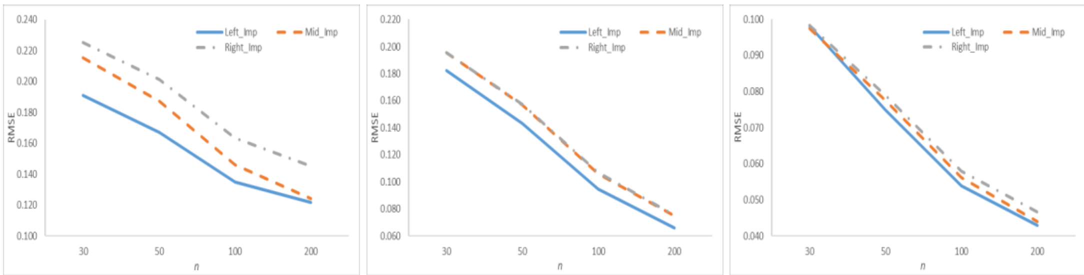
(j) (k) (l)

Figure 4: Line plot of SE for (j) $\hat{\beta}_0$, (k) $\hat{\beta}_1$ and (l) $\hat{\sigma}$ at sample size = 200



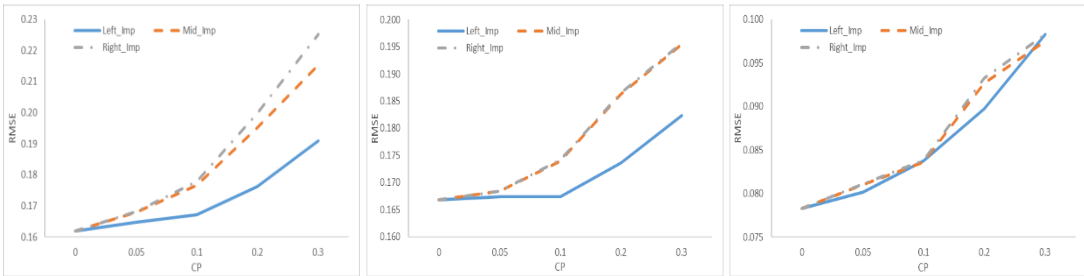
(m) (n) (o)

Figure 5: Line plot of RMSE for (m) $\hat{\beta}_0$, (n) $\hat{\beta}_1$ and (o) $\hat{\sigma}$ at CP = 0.05



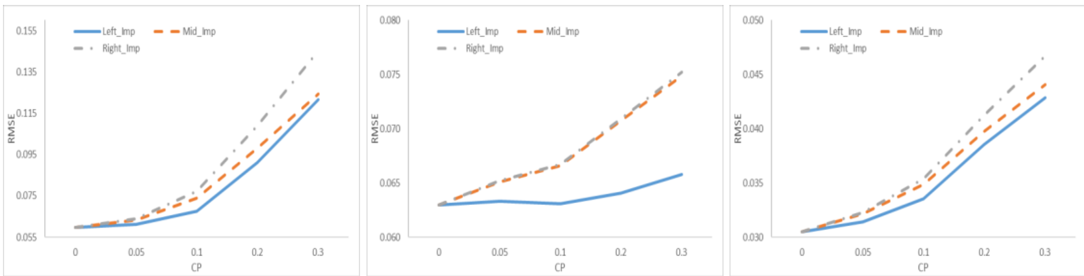
(p) (q) (r)

Figure 6: Line plot of RMSE for (p) $\hat{\beta}_0$, (q) $\hat{\beta}_1$ and (r) $\hat{\sigma}$ at CP = 0.30



(s) (t) (u)

Figure 7: Line plot of RMSE for (s) $\hat{\beta}_0$, (t) $\hat{\beta}_1$ and (u) $\hat{\sigma}$ at at sample size = 30



(v) (w) (x)

Figure 8: Line plot of RMSE for (v) $\hat{\beta}_0$, (w) $\hat{\beta}_1$ and (x) $\hat{\sigma}$ at sample size = 200

Collett (1994) stated that model adequacy procedure is mainly based on residuals. This is because the residuals of each subject in the study can be calculated and the characteristics of the data can be identified. The plot of log(-log($S(t)$)) against log(t) is a commonly used method to evaluate model adequacy. If the model is fit correctly, then the CS residual should follows exponential distribution with parameter one, *exp*(1). A well fit model should have an intercept that approaches to 0, and slope and R-square approach to 1.

From Tables 1 to 3, we can clearly see that the range of intercept, slope, and R-square values decrease as sample sizes increase but there are having an opposite trend as censoring proportions increase. This result is applicable for all the four residuals, which again leads to the conclusion that the residuals perform well in model diagnosis when sample size is large and censoring proportion is small.

When comparing the performance of the residuals, GMCS residual was found to perform the best when sample sizes are large based on the range of slope values (Table 2), but HMCS residual performs the best in small sample size. From the intercept and R-square values (Table 1 and 3), we can observe that HMCS residual indicates better result compared to other residuals. Thus, we can conclude that HMCS residual outperforms all the other residuals.

Table 1: Range of intercept for various residuals

		Residuals							
CP	*n*	CS		MCS		GMCS		HMCS	
		Min	Max	Min	Max	Min	Max	Min	Max
0.05	30	-0.3023	0.1161	-0.3034	0.0845	-0.2968	0.0845	-0.2815	0.0953
	50	-0.2874	0.0771	-0.2512	0.0494	-0.2305	0.0499	-0.1989	0.0632
	100	-0.2712	0.0488	-0.2009	0.0233	-0.1944	0.0262	-0.1776	0.0353
	200	-0.2021	0.0337	-0.1739	0.0058	-0.1651	0.0093	-0.1118	0.0222
0.1	30	-0.5327	0.1465	-0.4882	0.0744	-0.4395	0.0797	-0.3454	0.0957
	50	-0.3960	0.0763	-0.3829	0.0338	-0.3537	0.0361	-0.2850	0.0473
	100	-0.3205	0.0405	-0.3316	-0.0031	-0.2989	0.0012	-0.2248	0.0337
	200	-0.2627	0.0279	-0.2788	-0.0365	-0.2523	-0.0291	-0.1609	0.0164
0.2	30	-0.6625	0.1104	-0.8590	0.0354	-0.6959	0.0409	-0.5016	0.1029
	50	-0.6082	0.0943	-0.7249	-0.0223	-0.6576	-0.0151	-0.5955	0.0534
	100	-0.4108	0.0603	-0.5248	-0.0719	-0.4723	-0.0482	-0.3301	0.0180
	200	-0.3699	-0.0115	-0.4658	-0.1274	-0.4138	-0.0927	-0.2773	-0.0073
0.3	30	-0.8620	0.1373	-1.1870	0.0045	-0.9353	0.0176	-0.6338	0.1312
	50	-0.7854	0.0687	-0.9711	-0.1086	-0.8643	-0.0778	-0.7126	0.0837
	100	-0.5535	0.0177	-0.7769	-0.1887	-0.6520	-0.1453	-0.4639	0.0075
	200	-0.4849	-0.0206	-0.6833	-0.2478	-0.5349	-0.2008	-0.3557	-0.0263

Table 2: Range of slope for various residuals

		Residuals							
CP	*n*	CS		MCS		GMCS		HMCS	
		Min	Max	Min	Max	Min	Max	Min	Max
0.05	30	0.3374	1.2070	0.4603	1.3570	0.4603	1.3580	0.4603	1.3280
	50	0.3881	1.1810	0.5333	1.2340	0.5346	1.2400	0.5328	1.2120
	100	0.4979	1.1340	0.6568	1.1400	0.6581	1.1430	0.6448	1.1470
	200	0.5477	1.1010	0.7276	1.1230	0.7286	1.1250	0.6989	1.1270
0.1	30	0.2629	1.3530	0.4603	1.3640	0.4603	1.3570	0.4603	1.3510
	50	0.3449	1.2480	0.5418	1.3110	0.5431	1.3170	0.5270	1.2680
	100	0.4261	1.1430	0.6635	1.1780	0.6670	1.1840	0.5924	1.1530
	200	0.4915	1.0980	0.7371	1.1550	0.7392	1.1620	0.6536	1.1610
0.2	30	0.1980	1.3200	0.4640	2.0490	0.4643	1.9350	0.4440	1.3860
	50	0.2748	1.2320	0.5620	1.4430	0.5670	1.4520	0.5300	1.3360
	100	0.3400	1.1840	0.6484	1.3460	0.6545	1.3850	0.5450	1.2680
	200	0.4429	1.0700	0.7806	1.2000	0.7894	1.2140	0.6668	1.1980
0.3	30	0.1676	1.3880	0.4542	2.1420	0.4565	2.0670	0.4410	1.5000
	50	0.2376	1.5290	0.5687	1.6990	0.5800	1.7810	0.4761	1.6080
	100	0.2916	1.1620	0.6508	1.5040	0.6575	1.5090	0.5252	1.4070
	200	0.4061	1.0390	0.7909	1.3610	0.8023	1.3820	0.5613	1.2640

Table 3: Range of R-square for various residuals

CP	n	CS		MCS		GMCS		HMCS	
		Min	Max	Min	Max	Min	Max	Min	Max
0.05	30	0.6380	0.9947	0.6985	0.9947	0.6985	0.9947	0.6985	0.9947
	50	0.6537	0.9948	0.7487	0.9962	0.7473	0.9951	0.7445	0.9948
	100	0.6550	0.9969	0.7972	0.9963	0.7961	0.9965	0.8474	0.9969
	200	0.7568	0.9982	0.8362	0.9983	0.8359	0.9984	0.8769	0.9983
0.1	30	0.5656	0.9947	0.6699	0.9947	0.6727	0.9947	0.6944	0.9947
	50	0.6053	0.9942	0.7337	0.9952	0.7305	0.9954	0.7442	0.9962
	100	0.6233	0.9968	0.7810	0.9972	0.7780	0.9972	0.8439	0.9968
	200	0.7256	0.9979	0.8275	0.9981	0.8264	0.9981	0.8975	0.9982
0.2	30	0.5309	0.9946	0.6212	0.9925	0.6529	0.9929	0.6853	0.9944
	50	0.5461	0.9942	0.7396	0.9949	0.7296	0.9942	0.7537	0.9937
	100	0.6179	0.9960	0.7564	0.9971	0.7495	0.9967	0.8347	0.9964
	200	0.6913	0.9974	0.8793	0.9979	0.8804	0.9976	0.9354	0.9979
0.3	30	0.5215	0.9900	0.5391	0.9907	0.5654	0.9895	0.6030	0.9937
	50	0.4847	0.9940	0.6986	0.9941	0.6950	0.9931	0.7749	0.9931
	100	0.6536	0.9943	0.6532	0.9950	0.6460	0.9954	0.8537	0.9955
	200	0.6870	0.9964	0.8611	0.9961	0.8626	0.9969	0.9358	0.9966

5. Real Data Analysis

The data was obtained from the Steno Memorial Hospital from Denmark, and it describes the survival time for Type I diabetes patients to develop diabetic nephropathy (DN), where DN is a sign of kidney failure for the diabetes patient. The data consist of 731 patients, and all patients had developed DN by the end of study or at time of admission. There is no right censored in the dataset, but there are 136 interval-censored observations. There were 454 males and 277 females among 731 patients, gender (0 = male, 1 = female) and censoring indicator (1 = developed DN, 0 = interval censored), where 18.6% of interval censored in the data.

The left imputation technique was applied to the interval censored data. Following that, the non-parametric Kaplan Meier (KM) survivor function and *S(t)* based on the LL model were plotted on the same graph, and we can say that the LL distribution is appropriate for the diabetes data.

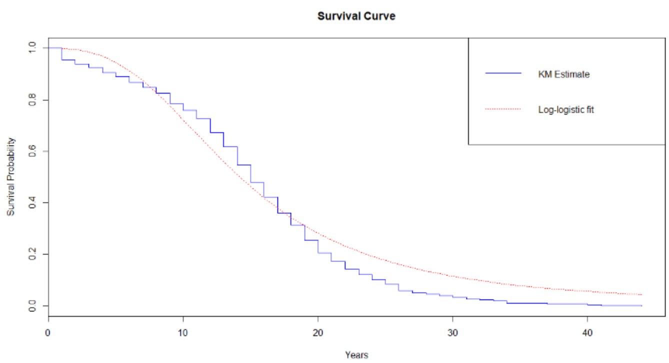


Figure 9: Survival Curve

LL model with and without covariate were generated, and p-value was used to conclude the effect of gender on survival time. Table 4 shows the R program output for the LL model, and the p-value for gender in model fitting is larger than alpha value of 0.05, which we can conclude that gender does not give impact to the survival time. The result is similar with Kim (2003) and

Zhao *et al*. (2008), which both articles concluded that gender of patients is not giving any significant impact on development of DN.

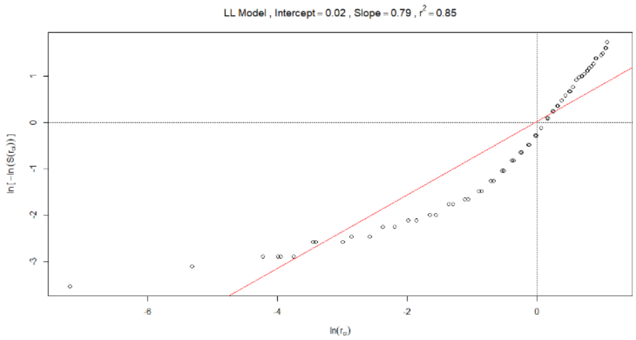


Figure 10: Plot for log (-log(estimated survivor function of residual)) versus log (residual)

Table 4**:** Estimated parameters for LL model

Type	Parameters	values	Standard Error	z-value	p-value
With Covariate	Intercept, $\hat{\beta}_0$	2.6681	0.0290	92.139	0.000
	Gender, $\hat{\beta}_1$	-0.0416	0.0466	-0.894	0.371
	Log(scale), σ	-0.9991	0.0323	-30.903	1.09×10^{-209}
Without Covariate	Intercept, $\hat{\beta}_0$	2.652	0.0228	116.3	0.000
	Log(scale), σ	-0.998	0.0323	-30.9	1.71×10^{-209}

Model adequacy diagnosis was carried out by using HMCS residual due to it is the best performing residual in the simulation study. Figure 10 shows plot for log(-log(estimated survivor function of residual versus log(residual), and the plot shows that there is a linear relationship between log(-log(estimated survivor function of residual)) and log(residual) with slope = 0.79, and intercept = 0.02. These values are fall within the range of simulation study for sample size of 200 and censoring proportion of 20 percent. HMCS residual has range of intercept (-0.1380, 0.0419), and range of slope (0.6751, 1.3282) based on our simulation study.

6. Conclusion

The performance of the parameter estimates was evaluated at various sample sizes and censoring proportions via the value of standard error and root mean square error. In the case of right censored and interval censored simulation study, large sample sizes and small censoring proportions always provide more accurate estimation. In the simulation study which included interval censored data, left point imputation outperforms midpoint and right point imputations by having smallest values of standard error and root mean square error.

Based on the model adequacy study, we found out that HMCS residual outperforms CS, MCS and GMCS residuals. When sample sizes are larger, range of simulated slope, intercept and R-square values are narrower, whereas increase in censoring proportions gave opposite results for all residuals. For the analysis of real data, we showed that the LL model fitted the diabetes data well. The preliminary analysis showed that survival probability of male patient is slightly higher than female, however, log-likelihood ratio test result showed that gender does not give significant impact on Type I diabetes patient to develop into diabetic nephropathy.

In this paper, we only focused on LL model with single covariate, right and interval censored data. Hence, log-logistic model with more covariate can also be used in the future to see whether similar results will be obtained. We can also investigate what is the impact on using dimension reduction method on large amount of covariate in LL model. Furthermore, time-dependent covariate that vary over time can also be incorporated.

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