A Comparative Study of Mixture Cure Models with Covariate

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Abstract. In survival analysis, the survival time is assumed to follow a non-negative distribution, such as the exponential, Weibull, and log-normal distributions. In some cases, the survival time is influenced by some observed factors. The absence of these observed factors may cause an inaccurate estimation in the survival function. Therefore, a survival model which incorporates the influences of observed factors is more appropriate to be used in such cases. These observed factors are included in the survival model as covariates. Besides that, there are cases where a group of individuals who are cured, that is, not experiencing the event of interest. Ignoring the cure fraction may lead to overestimate in estimating the survival function. Thus, a mixture cure model is more suitable to be employed in modelling survival data with the presence of a cure fraction. In this study, three mixture cure survival models are used to analyse survival data with a covariate and a cure fraction. The first model includes covariate in the parameterization of the susceptible individuals survival function, the second model allows the cure fraction to depend on covariate, and the third model incorporates covariate in both cure fraction and survival function of susceptible individuals. This study aims to compare the performance of these models via a simulation approach. Therefore, in this study, survival data with varying sample sizes and cure fractions are simulated and the survival time is assumed to follow the Weibull distribution. The simulated data are then modelled using the three mixture cure survival models. The results show that the three mixture cure models are more appropriate to be used in modelling survival data with the presence of cure fraction and an observed factor.

INTRODUCTION

Survival analysis consists of two types of survival models, which is parametric and nonparametric models. In parametric models, the survival data are assumed to follow a non-negative distribution. Exponential, Weibull, and log-normal distribution are the popular distributions used in survival analysis. Parametric survival models rely on assumptions that the data are drawn from a given probability distribution. Whereas, nonparametric survival models make very few assumptions about the model. Therefore, nonparametric distributions can be used to model a wide variety of survival data. Kaplan-Meier is the most popular nonparametric survival approach used to estimate the survival function. For example, Michalak et al. [1] proposed a bootstrapped Kaplan-Meier estimate for survival curve smoothing. Whereas, Wileyto et al. [2] employed Kaplan-Meier to estimate the survival function and Price and Manatunga [3] applied Kaplan-Meier approach to show the positive asymptote of the survival function which hints the possible existence of a cure fraction.

In survival analysis, it is common to assume that all individuals will eventually experience death or the event of interest. However, this assumption may not hold true in every case. In some cases, cure is possible. A number of individuals will not experience the event of interest. For instance, time-to-recurrent of certain cancer disease, some

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individuals will never experience recurrent and they are considered cured from the disease. The usual survival models are no longer appropriate to be applied in these cases. Hence, a survival model that takes into account the cure fraction is developed and it is well known as cure model. The cure model was first introduced by Boag [4] and is increasingly popular in the medical field, especially in the studies of cancer. This is because the curability of many cancer diseases is becoming a reality. There are two types of cure models, mixture and non-mixture cure models. Most of the studies use mixture cure models. For example, Angelis et al. [5] and Yao and Ng [6] applied mixture cure model to estimate the cure fraction. Achcar et al. [7] applied both mixture and non-mixture models and their finding showed that the results obtained by both models are very similar. Besides that, Peng and Dear [8] employed a nonparametric mixture model to estimate the cure fraction.

Survival data are often affected by observed and unobserved factors. For instance, the time-to-employment is often affected by the academic performance and working experience. The observed factor is incorporated in survival analysis as covariate while the unobserved factor is well known as frailty. Hougaard [9] and Shih and Louis [10] used frailty survival models to include the effect of unobserved factors and Hanagal [11] and Yin [12] used frailty mixture cure survival model to incorporate both frailty and cure fraction.

This study aims to compare the performance of mixture cure models in modelling survival data with the presence of a cure fraction and a covariate. The survival time of susceptible individuals is assumed to follow a Weibull distribution. The Weibull distribution is chosen because it has two parameters and this allows for more flexibility.

CURE MODEL

The survival function of non-mixture survival function can be written as

$$S(t) = (1-p)^{F_0(t)} \tag{1}$$

where $0 < (1\text{-}p) < 1$ is the probability of cure fraction and $F_0(t)$ is the cumulative distribution function of the susceptible individuals. It is known that

$$F_0(t) = 1 - S_0(t) \tag{2}$$

where $S_0(t)$ is the survival function of the susceptible individuals. Therefore (1) can be expressed as

$$S(t) = \frac{(1-p)}{(1-p)^{S_0(t)}} \tag{3}$$

The mixture cure model assumes that, the study population can be divided into two subpopulations, long-term and short term survivors. The long-term survivor refers to the cure fraction with probability *(1-p)* while the short-term survivor refers to susceptible individuals with a proper survivor function $S_0(t)$ with probability p. The survival function of mixture cure model is given as

$$S(t) = (1-p) + pS_0(t) \tag{4}$$

and the density function is

$$f(t) = pf_0(t) \tag{5}$$

where $f_0(t)$ is the density function of $S_0(t)$. The Weibull distribution is chosen as the distribution of the susceptible individuals in this study. The survival function of the Weibull distribution is

$$S(t) = \exp\left\{-(t/\alpha)^{\beta}\right\} \tag{6}$$

where $\alpha>0$ is the scale parameter and $\beta>0$ is the shape parameter. The density function of the Weibull distribution is

$$f(t) = \frac{\beta}{\alpha}\left(\frac{t}{\alpha}\right)^{\beta-1} \exp\left\{-(t/\alpha)^{\beta}\right\} \tag{7}$$

From equation (4) and (6), the Weibull mixture cure model can be written as

$$S(t) = (1-p) + p\exp\left\{-(t/\alpha)^{\beta}\right\} \tag{8}$$

and the associated density function is obtained by combining (5) and (7),

$$f(t) = p\frac{\beta}{\alpha}\left(\frac{t}{\alpha}\right)^{\beta-1} \exp\left\{-(t/\alpha)^{\beta}\right\} \tag{9}$$

In the light of the above discussion, survival data are often affected by observed and unobserved factors. This study has focused on survival data which is affected by an observed factor. The influence of the observed factor is incorporated in the model as covariate *x*.

Covariate can be incorporated in the Weibull survival function through scale parameter *α* and shape parameter *β*. However, this study examines only cases with the shape parameter depends on covariate. Covariate is included in the scale parameter *α* using the following function

$$\alpha_i = \exp(b_0 + b_1 x_i) \tag{10}$$

Covariate can also be included in the cure fraction through a logit function as follows

$$p_i = \frac{\exp(a_0 + a_1 x_i)}{1 + \exp(a_0 + a_1 x_i)} \tag{11}$$

with p_i is the probability of cure of *ith* individual.

This study aims to compare three Weibull mixture cure models with covariate. The three Weibull mixture cure models are referred as Model 1, 2, and 3.

Model 1: Weibull mixture model with *α* depends on covariate.
The survival function is a combination of (8) and (10) while the corresponding density function can be obtained by combining (9) and (10).

Model 2: Weibull mixture cure model with cure fraction depends on covariate.
The survival function is a combination of (8) and (11) while the corresponding density function is obtained by combining (9) and (11).

Model 3: Weibull mixture model with both cure fraction and α depend on covariate.
The survival function is a combination of (8), (10), and (11) while the corresponding density function can be obtained by combining (9), (10), and (11).

These three models are used to model survival data with different characteristics in this study.

LIKELIHOOD FUNCTION

Maximum likelihood estimation approach is utilized to obtain the estimation of parameters in Weibull mixture cure models. Suppose f_i is the true failure time and c_i is the potential censoring time, then $t_i = \min(f_i, c_i)$. An observation is then consists of t_i and d_i, where d_i is the censored indicator. $d_i = 1$ if $f_i \le c_i$, an uncensored observation and $d_i = 0$ if $f_i > c_i$, a censored observation.

The log-likelihood function can be expressed as

$$L = \ln(l) = d_i \sum_{i=1}^{n} f(t_i) + (1 - d_i) \sum_{i=1}^{n} S(t_i) \tag{12}$$

DATA SIMULATION

A number of survival data are simulated to achieve the aim of this study. The data are simulated based on the characteristics of Model 1, 2, and 3. The survival function of the short-term survivors is assumed to follow a Weibull distribution. The details of the survival data are as follows:

- **Survival 1**: Model 1, *α* depends on covariate.
- **Survival 2**: Model 2, cure fraction depends on covariate.
- **Survival 3**: Model 3, both cure fraction and α depend on covariate.

Survival 2 and Survival 3 are simulated with different sample sizes *n* while Survival 1 is simulated with different samples sizes and cure fractions *(1-p)*. The sample sizes used are 100, 500, and 1000 whereas the cure fractions used are 0.2, 0.3, and 0.4. The simulation size used is 1000 for each data with varying sample sizes and cure fractions. These data are then modelled by using Model 1 (M1), Model 2 (M2), and Model (M3). Weibull survival model (W) and Weibull mixture cure model (W+C) which do not take into account the influence of covariate have also been used to model the data.

RESULTS AND DISCUSSION

Mean square errors of the estimators are calculated to compare the performance of the models in estimating the parameters. Whereas, Akaike Information Criterion (AIC) is used to compare the performance of the models in modelling survival data.

The sampling variance of the cure fraction in Model 2 and Model 3 are equal. This is because both models employed a logit function to include the covariate in the cure fraction. As depicted in Table 1, all the sampling variances are smaller than 0.09, this indicates that all p_i is closed to its average value. Therefore, $\widehat{p}$ in Model 2 and Model 3 is estimated using the average of p_i.

TABLE 1. The Sampling Variance of Cure Fraction in Model 2 and Model 3

Sample size, *n*	Survival 1			Survival 2	Survival 3
	(1-p)=0.4	*(1-p)=0.3*	*(1-p)=0.2*		
100	0.06821	0.05286	0.03151	0.08835	0.03869
500	0.06696	0.05093	0.03038	0.08549	0.03774
1000	0.06692	0.05044	0.03023	0.08503	0.03748

As shown in Table 2, Table 3, and Table 4, the mean square errors of the Weibull survival model are the largest. This is because the Weibull survival model includes the effect of cured individuals in the survival function of susceptible individuals. Besides that, $\widehat{a}_0$ and $\widehat{a}_1$ in Model 2 and Model 3 are equal. This is because both Model 2 and Model 3 allowed the cure fraction to depend on covariate by using (11).

TABLE 2. The Mean Square Error of Parameters in Modelling Survival 1

(1-p)	*n*	Model	$\widehat{a}_0$	$\widehat{a}_1$	$\widehat{b}_0$	MSE	$\widehat{b}_1$	MSE	$\widehat{\alpha}$	$\widehat{\beta}$	MSE	$\widehat{p}$	MSE
0.4	***100***	W							43.7526	2.3621	159.7292		
		W+C							26.3060	4.8874	102.6167	0.5995	0.0024
		M1			0.5006	0.016685	0.0999	0.000023		15.5520	3.0158	0.5996	0.0024
		M2	-21.5494	0.8482					26.3060	4.8874	102.6168	0.5995	0.0024
		M3	-21.5494	0.8482	0.5006	0.016685	0.0999	0.000023		15.5520	3.0158	0.5995	0.0024
	500	W							43.7393	2.3463	160.1188		
		W+C							26.3143	4.7076	106.0032	0.5999	0.0005
		M1			0.4996	0.002873	0.1000	0.000004		15.1411	0.5085	0.5999	0.0005
		M2	-20.5076	0.8080					26.3143	4.7076	106.0032	0.5999	0.0005
		M3	-20.5076	0.8080	0.4996	0.002873	0.1000	0.000004		15.1411	0.5085	0.5999	0.0005
	1000	W							43.7559	2.3444	160.166		
		W+C							26.2962	4.6972	106.179	0.5993	0.0002
		M1			0.5003	0.001393	0.1000	0.000002		15.0669	0.23217	0.5993	0.0002
		M2	-20.4077	0.8040					26.2962	4.6972	106.179	0.5993	0.0002
		M3	-20.4077	0.8040	0.5003	0.001393	0.1000	0.000002		15.0667	0.23228	0.5993	0.0002
0.3	***100***	W							39.6661	2.2448	162.6998		
		W+C							26.3043	4.8484	103.3544	0.7010	0.0022
		M1			0.4972	0.011994	0.1001	0.000016		15.4764	2.4983	0.7010	0.0022
		M2	-19.4054	0.7829					26.3043	4.8484	103.3544	0.7010	0.0022
		M3	-19.4054	0.7829	0.4972	0.011996	0.1001	0.000016		15.4775	2.4986	0.7010	0.0022
	500	W							39.6807	2.2327	163.0052		
		W+C							26.3030	4.7125	105.8972	0.7006	0.0004
		M1			0.5030	0.002542	0.0999	0.000003		15.0737	0.4167	0.7006	0.0004
		M2	-18.4823	0.7464					26.3030	4.7125	105.8972	0.7006	0.0004
		M3	-18.4823	0.7464	0.5030	0.002542	0.0999	0.000003		15.0737	0.4167	0.7006	0.0004
	1000	W							39.7080	2.2313	163.04		
		W+C							26.2985	4.6946	106.232	0.6999	0.0002
		M1			0.5013	0.001174	0.0999	0.000002		15.0360	0.2096	0.6999	0.0002
		M2	-18.3279	0.7402					26.2985	4.6946	106.2321	0.6999	0.0002
		M3	-18.3279	0.7402	0.5013	0.001174	0.0999	0.000002		15.0360	0.2096	0.6999	0.0002
0.2	***100***	W							35.6428	2.2473	162.6352		
		W+C							26.3046	4.8492	103.2798	0.7992	0.0015
		M1			0.5020	0.010556	0.0999	0.000014		15.4258	2.0497	0.7992	0.0015
		M2	-17.0883	0.7137					26.3046	4.8492	103.2799	0.7992	0.0015
		M3	-17.0883	0.7137	0.5020	0.010556	0.0999	0.000014		15.4258	2.0497	0.7992	0.0015
	500	W							35.6050	2.2327	163.0042		
		W+C							26.2986	4.6959	106.2262	0.7999	0.0003
		M1			0.5003	0.002609	0.1000	0.000004		15.0817	0.3652	0.7999	0.0003
		M2	-16.0348	0.6721					26.2986	4.6959	106.2262	0.7999	0.0003
		M3	-16.0348	0.6721	0.4996	0.002069	0.1000	0.000003		15.0843	0.3596	0.7999	0.0003
	1000	W							35.6074	2.2326	163.0080		
		W+C							26.3052	4.6855	106.4159	0.8000	0.0002
		M1			0.5015	0.001642	0.0999	0.000002		15.0461	0.1838	0.8001	0.0002
		M2	-16.132	0.6758					26.3052	4.6855	106.4159	0.8000	0.0002
		M3	-16.132	0.6758	0.5008	0.001052	0.1000	0.000001		15.0493	0.1717	0.8000	0.0002

From Table 2, the mean square errors of $\widehat{b}_0$, $\widehat{b}_1$, and $\widehat{\beta}$ in Model 1 and Model 3 are decreasing when sample size increased and cure fraction decreased. This reveals that the abilities of these models in estimating the survival function of susceptible individuals are better for a bigger sample size and a smaller cure fraction. Besides that, $\widehat{p}$ in all the mixture cure models are equal and the mean square errors are smaller for bigger sample size and smaller cure fraction. This results shows that their abilities in estimating p is better for a bigger sample size and a smaller cure fraction.

Form Table 3, it can be seen that the differences between the estimation of the parameters for different sample sizes are small. Besides that, the mean square error of $\widehat{\beta}$ in Model 2 and the Weibull cure mixture model is the smallest for all sample sizes. As predicted, Model 2's estimators have the smallest mean square error for all sample sizes. This is because Survival 2 is simulated based on Model 2's characteristics.

As shown in Table 4, for Model 2 and Model 3, the mean square errors of $\widehat{a}_0$ and $\widehat{a}_1$ are decreasing when sample size increased. Whereas, for Model 1 and Model 3, the mean square errors of $\widehat{b}_0$, $\widehat{b}_1$, and $\widehat{\beta}$ are decreasing

TABLE 3. The Mean Square Error of Parameters in Modelling Survival 2

	$\widehat{a}_0$	MSE	$\widehat{a}_1$	MSE	$\widehat{b}_0$	$\widehat{b}_1$	$\widehat{\alpha}$	MSE	$\widehat{\beta}$	MSE	$\widehat{p}$
Survival 2											
n=100											
W							37.8437	168.3444	2.2949	161.4218	
W+C							24.9952	0.0414	15.2649	2.1653	0.7445
M1					3.1587	0.0020			14.9446	6.9920	0.7387
M2	-12.7749	11.6077	0.5316	0.0185			24.9952	0.0414	15.2649	2.1653	0.7445
M3	-12.7749	11.6077	0.5316	0.0185	3.2077	0.0004			15.3232	3.0307	0.7445
n=500											
W							37.8273	165.1880	2.2841	161.6943	
W+C							24.9989	0.0087	15.0491	0.3572	0.7452
M1					3.1345	0.0029			14.4578	6.7260	0.7368
M2	-12.1454	1.7464	0.5061	0.0027			24.9990	0.0087	15.0491	0.3572	0.7452
M3	-12.1454	1.7464	0.5061	0.0027	3.2158	0.0001			15.0643	0.5254	0.7452
n=1000											
W							37.8791	166.2197	2.2827	161.7289	
W+C							24.9988	0.0043	15.0229	0.1704	0.7439
M1					3.1484	0.0024			14.5159	5.5707	0.7369
M2	-12.0889	0.8043	0.5035	0.0013			24.9988	0.0043	15.0229	0.1704	0.7439
M3	-12.0889	0.8043	0.5035	0.0013	3.2168	0.0001			15.0241	0.3316	0.7439

TABLE 4. The Mean Square Error of Parameters in Modelling Survival 3

	$\widehat{a}_0$	MSE	$\widehat{a}_1$	MSE	$\widehat{b}_0$	MSE	$\widehat{b}_1$	MSE	$\widehat{\alpha}$	$\widehat{\beta}$	MSE	$\widehat{p}$
Survival 3												
n=100												
W									39.5008	2.6227	153.2078	
W+C									32.1429	3.5767	130.6528	0.8083
M1					0.5028	0.006444	0.0999	0.000008		15.3834	2.1776	0.8078
M2	-12.6060	14.8216	0.5237	0.0216					32.1381	3.5776	130.6316	0.8078
M3	-12.6060	14.8216	0.5237	0.0216	0.5028	0.006444	0.0999	0.000008		15.3833	2.1770	0.8078
n=500												
W									39.4282	2.6092	153.5330	
W+C									32.1315	3.4758	132.8401	0.8101
M1					0.5003	0.001248	0.1000	0.000002		15.0711	0.3347	0.8099
M2	-12.1600	2.5819	0.5064	0.0037					32.1312	3.4759	132.8378	0.8099
M3	-12.1600	2.5819	0.5064	0.0037	0.5001	0.001246	0.1000	0.000002		15.0698	0.3339	0.8099
n=1000												
W									39.4363	2.6087	153.5454	
W+C									32.1562	3.4577	133.2421	0.8105
M1					0.5001	0.001150	0.1000	0.000001		15.0330	0.1925	0.8103
M2	-12.0745	1.2183	0.5030	0.0018					32.1558	3.4579	133.2393	0.8103
M3	-12.0745	1.2183	0.5030	0.0018	0.4992	0.000616	0.1000	0.000001		15.0355	0.1830	0.8103

when sample size increased. These results shows that for a larger sample size, Model 2 and Model 3 perform better in estimating the cure fraction while Model 1 and Model 3 perform better in estimating the survival function of the susceptible individuals. Besides that, $\hat{p}$ in Model 1, Model 2 and Model 3 are equal. This shows that their abilities in estimating the cure fraction are the same. As predicted, the mean square errors of Model 3's estimators are the smallest for all sample sizes. This is because Survival 3 is simulated according to Model 3's characteristic.

The AIC values of all models are shown in Table 5. For Survival 1 and Survival 3, Model 3 has the lowest AIC and followed by Model 1, Model 2, Weibull mixture cure model and Weibull survival model. This shows that Model 3 fits Survival 1 and Survival 3 better than other models. For Survival 2, Model 2 has the smallest AIC for all sample sizes and followed by Model 3, Weibull mixture cure model, Model 1, and Weibull survival model. This indicates that Model 2 fits Survival 2 better than other models. Besides that, Model 1 has larger AIC compared to the Weibull mixture cure model. This shows that the Weibull mixture cure model fits Survival 2 better than Model 1. Weibull survival model has the highest AIC for all data because it does not include the influences of covariate and cure fraction.

TABLE 5. AIC of Survival 1, Survival 2, and Survival 3

	Survival 1									**Survival 2**			**Survival 3**		
	(1-p) = 0.2			***(1-p) = 0.3***			***(1-p) = 0.4***								
Sample size, *n*	**100**	**500**	**1000**	**100**	**500**	**1000**	**100**	**500**	**1000**	**100**	**500**	**1000**	**100**	**500**	**1000**
W	408	2027	4050	421	2090	4178	429	2130	4258	412	2048	4095	408	2024	4045
W+C	304	1505	3005	284	1404	2801	259	1278	2550	214	1052	2098	342	1697	3393
M1	218	1068	2131	209	1023	2038	195	951	1896	219	1078	2142	232	1138	2272
M2	296	1460	2913	273	1340	2674	244	1201	2394	192	936	1864	332	1642	3281
M3	210	1024	2039	198	960	1911	181	874	1740	194	938	1867	222	1083	2159

CONCLUSION

This study aims to compare the performance of three mixture models in modelling survival data with different characteristics. A simulation study is conducted to achieve the aim of this study. The data are simulated based on the characteristic of the three survival models.

For Survival 1, AIC of Model 3 is the smallest and followed by Model 1. The mean square errors of these models are smaller for a larger sample size and a smaller cure fraction. This results proved that Model 3 is suitable in modelling survival data with covariate effect in survival function of short-term survivors and Model 1 could be considered as an alternative choice of model. Besides that, $\hat{p}$ in all the mixture cure models are equal. This results revealed that their abilities in estimating the cure fraction are not affected by covariate. However, the characteristic of Model 2 and Model 3 will allow the models to give a more accurate estimation of the survival function as each individual will has their own cure probability and this allows the survival function to be estimated based on the individual cure probability.

For Survival 2, the result of this study shows that Model 2 has the lowest AIC and followed by Model 3. The mean square errors of estimators in both models are smaller compare to others and decreasing when sample size is increased. Therefore, it can be concluded that Model 2 is the most suitable model to be used in modelling survival data with cure fraction depends on a covariate and Model 3 could be used as an alternative model. These models performed better for a bigger sample size.

For Survival 3, this study revealed that Model 3 has the smallest AIC and followed by Model 1. Besides that, the mean square errors of Model 3's estimators are smaller for a bigger sample size. Therefore, it can be concluded that Model 3 is the best model to be applied and its performance is better for a bigger sample size and the Model 1 could be used as an alternative model in cases with covariate effect in both cure fraction and survival function of short-term survivors.

This study shows that, Model 1, Model 2, and Model 3 are more appropriate to be used in modelling survival data with covariate effect compare to Weibull survival model and Weibull mixture cure model. Model 3 is suitable to be applied in survival data with the presence of cure individuals and a covariate. Model 2 is only suitable for cases which the cure depends on a covariate.

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