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Promotion time cure model with generalized Poisson-Inverse Gaussian Distribution

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ABSTRACT

Background & Aim: In the survival data with Long-term survivors the event has not occurred for all the patients despite long-term follow-up, so the survival time for a certain percent is censored at the end of the study. Mixture cure model was introduced by Boag, 1949 for reaching a more efficient analysis of this set of data. Because of some disadvantages of this model non-mixture cure model was introduced by Chen, 1999, which became well-known promotion time cure model. This model was based on the latent variable distribution of N. Non mixture cure models has obtained much attention after the introduction of the latent activating Scheme of Cooner, 2007, in recent decades, and diverse distributions have been introduced for latent variable.
Methods & Materials: In this article, generalized Poisson-inverse Gaussian distribution (GPIG) will be presented for the latent variable of N, and the novel model which is obtained will be utilized in analyzing long-term survival data caused by skin cancer. To estimate the model parameters with Bayesian approach, numerical methods of Monte Carlo Markov chain will be applied. The comparison drawn between the models is on the basis of deviance information criteria (DIC). The model with the least DIC will be selected as the best model.
Results: The introduced model with GPIG, with deviation criterion of 411.775, had best fitness than Poisson and Poisson-inverse Gaussian distribution with deviation criterion of 426.243 and 414.673, respectively.
Conclusion: In the analyzing long-term survivors, to overcome high skewness and over dispersion using distributions that consist of parameters to estimate these statistics may improve the fitness of model. Using distributions which are converted to simpler distributions in special occasions, can be applied as a criterion for comparing other models.

Introduction

In ordinary survival analysis, the main assumption is that all the patients are exposed to occurrence of event if time of follow up increasing, so the limit of the probability of event occurrence gets one when the time increase infinitely (1). However, in practice, thanks to the significant medical progressions and early diagnosis of cancer, a great number of people have a kind of survival like general population. In this type of data, due to the fact that there are people with long-time survival (cured), cure models should be applied (2).

Cure Mixture Model: This model, also known as standard cure model, was presented by Boag (3), for the first time and developed by other authors including Farewell (4), Kuk and Chen (5), Sy and Taylor (6), and Peng et al. (7); a review paper has also been presented by Tsodikov et al. (8) in this area. In this model it is assumed that patients in the population are divided into two groups. One (θ) those who are

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not exposed to the occurrence of the event (cure) and the probability of their survival is equal to one, and those (1 - θ) who are exposed to the occurrence of the event and the probability of their survival is obtained by one of the common functions of survival (S(t)). The survival function of all population is achieved using the following formula:

$S_P(t) = \theta + (1 - \theta) S(t)$ (1)

Commonly, to estimate the percent of the cured people logistic link function is applied for θ.

Second type of cure model, known as non-mixture cure model, promotion time cure model, or bounded hazard cumulative model was first presented by, Yakovlev and Tsodikov (9) and then developed by Chen et al. (10).

Promotion Time cure model: In this model, it is assumed that the survival function for the subject in the population is $S_P(t) = \exp[-\theta F(t)]$ in which θ is the percent of cured patients and F(t) is the cumulative distribution function. Chen et al. (10) used latent variable process in their article in which N has Poisson distribution with parameter of θ. This represents the average number of cancer cells that remained after primary treatment which could be formed detectable tumor later. While $Y_i i = 1,2,3,\ldots,N$, has F(t) distribution and is considered to be independent from N. Thus, the T random variable which is defined as $T = \{\min Y_i, 1 \geq i \leq N\}$ has survival function of $S_P(t) = \exp[-\theta F(t)]$, and when N = 0, with the probability of exp(-θ), the survival time will be $T = \infty$.

In recent years, different distributions have been considered for the latent variable of N. For example, if the latent variable distribution is considered to be Bernoulli, mixture cure model is achieved. Also it should be noted that many other researchers have presented time promotion cure model including Cooner et al. (11) using Bernoulli, binomial and geometric, Borges et al. (12) using generalized power series, Rodrigues et al. (13) using COM-Poisson, Cancho et al. (14) using negative binomial, Rahimzadeh et al. (15) using hypergeometric generalized negative binomial, and Baghestani, et al. (16) using generalized Poisson lindely distributions.

It is worth to be mentioned that latent variable distribution can be each of discrete distribution which has probability density function at zero in order to clarify the rate of cure proportion. In analyzing long-term survival data, as well as high percent of people who are censored at the end of the study, there are two problems including over dispersion and right skewness resulting in the fact that the distributions with higher number of parameters which have a higher rate of flexibility are taken into consideration.

The model presented in this article has considered generalized Poisson-inverse Gaussian for distribution of latent variable. In order to estimate the parameters of model with Bayesian approach, prior distribution has been taken for the parameters of the model, and by applying Markov Chain Monte Carlo approaches from the posterior distributions, the model parameters are estimated. In order to select the best model based on deviance information criteria (DIC), the model with the least DIC is chosen.

Promotion time cure model with generalized inverse Gaussian distribution

In Poisson distribution, mean and variance are equal, and because of this they are not suitable in fitting to discrete data which has over dispersion. Therefore, discrete distributions have been presented to clarify this over dispersion which is mostly a mixture of Poisson distribution with continuous distribution. It means that if X has Poisson distribution with probability density function of $f(x|\lambda) = \frac{e^{-\lambda}\lambda^x}{x!}$, x = 0,1,…and λ > 0, and λ has continuous probability density function g(λ), for non-negative values; the marginal function of X is acquired using the following formula: $P(X = x) = \int_0^\infty \frac{\exp(-\lambda)\lambda^x}{x!} g(\lambda) d\lambda$ (2)

However, if λ has gamma distribution the marginal distribution of X will have negative binomial distribution (17). Whereas, if λ has generalized inverse Gaussian distribution, the marginal distribution of X will have generalized Poisson-inverse Gaussian (GPIG) which called Siche distribution (18). Generalized inverse Gaussian probability density function can be converted to gamma distribution or inverse Gaussian distribution under special circumstances (19).

Generalized Poisson-inverse Gaussian distribution includes Poisson distribution,

Poisson-inverse Gaussian distribution, discrete positive stable and degenerate distribution at zero, under special conditions. It also has three separate parameters for clarifying indicators like mean, variance, over dispersion and skewness. Therefore, it has more flexibility in comparison with Poisson distribution. Commonly, in count data in which we are faced with over dispersion and skewness, this type of distribution can be a good replacement for Poisson distribution.

This 3-parameter distribution which is also known as Sichel distribution was first presented by Sichel in 1982, this distribution acts better than negative binomial distribution and Poisson-inverse Gaussian distribution when we are dealing with fitting to discrete data with high level of dispersion (20).

Methods

In an article, presented by Zhu and Joe, regarding fitting to count data with long series (21), the probability generating function has been presented as follow:

$G_X(x, a, b, c) = \exp\{b[(1-c)^a - (1-cx)^a]\}$

$0 < a \leq 1$, $b > 0$ and $\leq c \leq 1$ (3)

Mean, variance, over dispersion, and skewness of this distribution are given by:

$\mu = abc/(1-c)^{1-a}$,

$\sigma^2 = abc(1-ac)/(1-c)^{2-a}$,

$D = {\sigma^2}/{\mu} = c(1-a)/(1-c) + 1$,

$\gamma = E(X - E(X))^3/\sigma^3 =$

$abc(1-c)^{a-3}[1 + c - 3ac + a^2c^2]/\sigma^3$ (4)

In case c=1, generalized Poisson-inverse Gaussian distribution turns into a stable discrete function which has an unlimited average and do not have variance and skewness. If $a = \frac{1}{2}$ it reduces to Poisson-inverse Gaussian distribution and for $c \neq 1$ and $a = 1$ it reduces to Poisson distribution with bc parameter. If $0 < a < 1$ and $0 \leq c < 1$, this distribution will have over dispersion, in a way that the rate of over dispersion is affected by the parameters a and c. The rate of over dispersion increases when c increases or a decreases (21).

Without considering the bounded value of 0 and 1 for the parameter c, analyzing skewness according to the value of parameter b and c indicates that, when $c < 0.87$, the rate of skewness decreases when parameter of a increases. However, this pattern is completely different when $c > 0.9$. Totally, the amount of skewness of this distribution is more than inverse Gaussian Poisson distribution (21).

In the form was introduced by Zhu and Joe the distribution of Sichel does not have any simple form (21). Although in the promotion time cure model, Tsodikov et al. (8), indicated that survival function for all the population is acquired on the basis of first activation scheme of Cooner (11), can be given by:

$S_P = P(N=0) + \sum_{n=1}^{\infty} P(Z_1 > t, \ldots, Z_n > t)P(N = n) =$

$+ \sum_{n=0}^{\infty} S(t)_n P(N = n) = G_N(S_{(t)})$ (5)

Whereas $G_N(.)$ is the probability generating function of random latent variable of N, and it is obvious that we do not need density function to form promotion time cure model. If the probability generating function has closed form, inference for the model parameters will be possible; it does not matter using Bayesian method, or maximum likelihood. Therefore, survival function and density function for population is acquired by the following formula:

$S_p(t) = \exp\{b[(1-c)^a - (1-ct)^a]\}$, $0 < a \leq 1$, $b > 0$ and $0 < c \leq 1$

$f_p(t) = ab\big(1 - cS(t)\big)^{a-1}\exp\{b[(1-c)^a -$

$(1 - cS(t))^a]\}$ (6)

Regarding the range of each parameter, exponential link, logistic link or complementary log-log link can be applied in order to specify the effect of covariates on the parameters. In this way, for the parameters a and c whose amount is between 0 and 1 logistic link function or complementary log-log link, and for the parameter b which accepts the values more than 0 exponential link can be applied.

The proportion of cured in this model is obtained using, $G_X(0) = \exp\{-b[1-(1-c)^a]\}$.

Regarding the fact that Weibull distribution is one of the most common distribution for fitting to survival data, it is considered the distribution function S(t). In this case, the survival data is as follow:

$S(t|\gamma) = \exp\big(-e^{\lambda}x^{\alpha}\big)$, $\alpha > 0$ and $-\infty < \lambda < +\infty$ (7)

If $\alpha > 1$, the hazard function is increasing and if $\alpha < 1$, it is decreasing.

Parameter Estimation: The likelihood function for the cure model is as follows:

$$L(\beta, a, \alpha, \lambda | D_{obs}) = \prod_{i=1}^{n} f_p(t_i)^{\sigma_i} \times S_p(t_i)^{1-\sigma_i} = \prod_{i=1}^{n} h_p(t_i)^{\sigma_i} \times S_p(t_i) \quad (8)$$

If n is the number of participants in this study, and Y_i and C_i are survival time and being censored respectively for the ith, the observed time for this person is $T_i = \min \{Y_i, C_i\}$.

In this formula, for the indicator function of δ_i when $\delta_i=1$ we will have $T_i=Y_i$, and if $\delta i=0$, then $T_i=C_i$. Therefore, for the ith person, Observations Matrix is $D_{obs} = \{T_i, \delta_i , X_i \}$ is achieved, in which X_i is the matrix of covariates.

In this paper it is assumed that N_i and Z_i,I = 1, …, n are independent from each other and Z_i s have generalized Poisson-inverse Gaussian distribution. In a way that $0 < a \leq 1$, $b > 0$ and $0 < c \leq 1$ are the distribution parameters. If $N_i = n_i$ the required time for the formation of diagnosable tumor will be independent from each other and will have Weibull distribution mentioned in 7. Therefore, the likelihood function is:

$$L(\alpha, \theta, \beta, \tau, \nu | D_{obs}) = \prod_{i=1}^{n} S_p(t)^{1-\delta_i} \times f_p(t)^{\delta_i} = \left\{\exp\{b[(1-c)^a - (1-cS(t))^a]\}\right\}^{1-\delta_i} \times \left\{ab\left(1-cS(t)\right)^{a-1}\exp\{b[(1-c)^a - (1-cS(t))^a]\}\right\}^{\delta_i} \quad (9)$$

These model parameters have been considered as non-informative priors distribution in a way that the probability of likelihood for estimating Bayesian parameters have a more dominant effect on posterior distributions. Without affecting the issue adversely, it can be assumed that the prior distributions are independent. For the regression coefficients, uniform non-informative distribution with $\pi(\beta) \propto 1$, for the parameters of Weibull distribution λ and α, based on their domain, normal distribution and gamma distribution have been used respectively and for the parameter a, uniform distribution of U(0,1) have been applied.

Therefore, complete conditional distribution for the model parameters of cure model with generalized Poisson-inverse Gaussian distribution is acquired.

$$p(\beta_k | D_{obs}, \beta_{(-k)}), \propto L(\beta,\alpha,\lambda,a|D_{obs}) \times \pi(\beta_k)$$
$$p(\alpha | D_{obs}, \beta,\lambda,a) \propto L(\beta,\alpha,\lambda,a|D_{obs}) \times \pi(\alpha)$$
$$p(\lambda | D_{obs}, \beta,\alpha,a) \propto L(\beta,\alpha,\lambda,a|D_{obs}) \times \pi(\lambda) \quad (10)$$
$$p(a | D_{obs}, \beta,\alpha,\lambda) \propto L(\beta,\alpha,\lambda,a|D_{obs}) \times \pi(a)$$

In the Posterior distributions $\beta_{(-k)}$ is the rest of B_k where the kth component has been omitted, and $\pi(B_k)$, $\pi(\tau)$, $\pi(\lambda)$ and $\pi(a)$ are the prior distributions used in model.

Due to the high level and complexity of the posterior distributions, it is not possible to calculate the posterior distribution of parameters of model using analytical approach. Therefore, Markov-chain Monte-Carlo method (MCMC) approaches are applied to interference about the parameters of model. To do so, by consecutive sampling from the complete conditional distributions of parameters, using Metropolis Hastings algorithm, Markov chain is formed; whose approximate distribution is an acceptable approximation of posterior parameters of the model (22). In this paper, the effect of covariates will be considered on the parameter b and c.

In order to compare the presented model with the Poisson and Poisson-inverse Gaussian models, the deviance information criterion (DIC) was applied which has been presented by Spiegelhalter et. al (23). This criterion includes both fitting and complexity, and does not have the problems related to non-informative prior, and is defined as $DIC = \overline{D(\theta)} + P_D$, in which $\overline{D(\theta)}$ is considered to be the mean of posterior deviation and indicates the amount of fitting, and P_D is equal to the number of effective parameters which shows the complexity of the model, and is equal to the difference between the mean of posterior deviation and the amount of deviation in mean point of the posterior parameters of the model, and is defined as $P_D = \overline{D(\theta)} - (\bar{\theta})$. According to this criterion, the model which has the least value of DIC is selected as the best model. This criterion can be used for every sample size and can be easily calculated in Monte Carlo Markov chain ways.

Results

In this article a set of data related to skin cancer was used containing 205 participants who have undergone the surgery in order to remove the infected mass during 1962–77 and the patients were followed up to 1977. These data are available in timereg set, in the software R (24-25), and have been studied by several

authors in order to fit different cured models with different distributions (12, 13, 26).

The survival time ranged from 10 days to 5565 days, which means from 0.027 to 25.15 years with the average of 5.9 and deviation of 3.1.

Patients who died from other causes or censored because of living at the end of study were considered censored (72%). The graph of survival function of Kaplan-Meier of these data is shown in figure 1. As it can be seen in this figure the survival function before reaching zero has become plateau which shows the existence of long-term survivors. In this data, There are two covariates including the ulceration status in two situations (absent = 0, n = 115 and present = 1, n = 90) and the thickness of tumor in millimeters (mean = 2.96, SD = 2.96).

In this paper, we have considered a model in which the fitting criterion (DIC) has the least value. In this regard, the effect of the covariates of tumor thickness is considered by using exponential link on parameter b, and the effect of covariates of ulceration status have been considered by logistic link on parameter c. The results have been shown in table 1.

The program used for fitting this model has been written in WinBugs software environment (27), for estimating the parameters of model according to the Bayesian approach with generalized Poison-inverse Gaussian distribution these prior have been considered.

$\lambda \sim N(0,0.1)$, $\alpha \sim G(0.1,0.1)$, $a \sim U(0,1)$

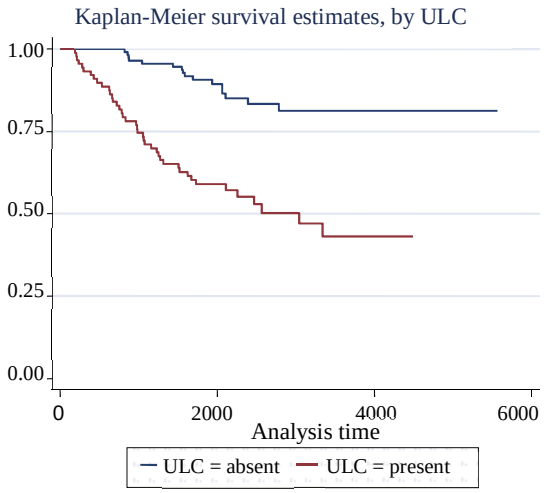

Figure 1. Kaplan-Meier curves stratified by ulceration (ULC) status

After sampling, in order to realize the convergence, Gelman-Roubin statistic has been applied in order to specify burn-ins duration, regarding the fact that this statistic is related to all parameters less than 1.07, 10000 samples seem appropriate for adapting period. In conclusion, the next 40000 samples have been considered as the samples obtained from posterior distribution of parameters. Moreover, to decrease the correlation, one sampling is done out of 10 times. The results of the fitting of these models (Poisson, Poisson-inverse Gaussian, and generalized Poisson-inverse Gaussian) are presented in the table 1.

Table 1. Posteriors summaries of the Poisson, Poisson-inverse Gaussian, and generalized Poisson-inverse Gaussian model

Model	Parameter	Mean	Standard Deviation	2.5 Percentile	97.5 Percentile
Poisson	α	-3.027	0.470	-3.962	-2.342
	λ	1.652	0.234	1.181	2.107
	Intercept	-1.705	0.487	-2.379	-0.6371
	ULC	1.25	0.312	0.672	1.892
Poisson-inverse Gaussian	α	2.195	0.349	1.571	2.919
	λ	-4.622	0.717	-6.318	-3.437
	Intercept	-0.785	0.470	-1.525	0.4138
	ULC	1.107	0.306	0.5328	1.712
	Thickness	1.163	0.448	0.4523	2.23
Generalized Poisson-inverse Gaussian	α	2.697	0.535	1.725	3.83
	λ	-5.526	1.064	-7.827	-3.617
	Intercept	-0.689	0.39	-1.4	0.126
	ULC	0.994	0.313	0.405	1.613
	Thickness	1.406	0.956	0.4052	2.521
	a	0.332	0.116	0.158	0.606

ULC: Ulceration

Time promotion cure model with generalized Poisson-inverse Gaussian distribution, with deviation criterion of 411.775, results in a better fitting rather than, Poisson and Poisson-inverse Gaussian distribution with deviation criterion of 426.243 and 414.673 (Table 2).

Table 2. Cure rate estimation based on the GPIG, PIG and P Model

Model	DIC	PD	$D(\bar{\theta})$	$\overline{D(\theta)}$
Cure model with GPIG distribution	411.775	5.076	406.699	401.623
Cure model with PIG distribution	414.673	4.426	410.247	405.822
Cure model with P distribution	426.243	4.856	421.387	416.531

GIPG: Generalized Poisson-inverse Gaussian; PIG: Poisson-inverse Gaussian; P: Poisson

Table 3 shows the estimations of cure rate for patients with tumor thickness equal to 0.320, 1.94, and 8.32 mm which correspond to the 5%, 50%, and 95% quintiles, respectively. It is seen that in the patients with present ulceration statues in comparison with the ones with absent ulceration statues, the cure rate is lower, considering fixed level of tumor thickness; moreover, it is obviously seen that the more the tumor thickness is the less the cure rate will be.

Table 3. Cure rate estimation in GPIG, PIG and P Model

Thickness	0.32	1.94	8.32
Model	ULC (absent, present)	ULC (absent, present)	ULC (absent, present)
GPIG	0.874, 0.694	0.738, 0.441	0.612, 0.265
PIG	0.849, 0,593	0.665,0.372	0.637, 0.236
P	0.816, 0.518	0.799, 0.456	0.635, 0.205

GPIG: Generalized Poisson-inverse Gaussian; PIG: Poisson-inverse Gaussian; P: Poisson; ULC: Ulceration

Discussion

The application of ordinary survival analysis in analyzing the survival data is remarkable. However, in these models the primary presumption is the occurrence of the event by increasing the time of follow-up. However, for analyzing the survival data in which a certain percent of people are censored at the end of the study, the need to newer models like cure model is felt. One of the advantages of these models, besides estimating the cure rate of patients, is they are reduced to prevalent survival models when there are no cured patients. It should also be noted that the results achieved from these models are reliable in case the duration of study is long enough. One of the most well-known and easiest approaches for recognizing the cured patients is by drawing Kaplan-Meier graph. If this graph turns into a plateau before reaching zero, the existence of cured people is probable.

Using the distributions, which are converted to simpler distributions in special occasions, can be applied as a criterion for comparing other models. Time promotion cure model with generalized Poisson-inverse Gaussian distribution turns into time promotion cure model with Poisson-inverse Gaussian distribution if the $a = \frac{1}{2}$ (28). The results obtained from fitting the generalized Poisson-inverse Gaussian distribution indicates that the credible interval for this parameter includes value 0.5, therefore there is not a big difference in DIC in estimation of these two models. Besides, generalized Poisson-inverse Gaussian distribution turns into Poisson distribution with bc parameter if parameter a=1. Whereas the estimations achieved for this parameter indicates the inequity of this parameter with 1, and that is why Poisson model has a weak fit to data.

We have not considered any of the covariate to parameter a in fitting model, and the effect of ULC statues to parameter c with logistic link, and the effect of thickness on parameter b have been considered with exponential link. In different data, the effects of covariates on other parameters can be estimated. We have presented a model that has a better fitting to the data (smaller DIC).

In order to draw a better comparison between the promotion time cured models with generalized Poisson inverse Gaussian, Poisson inverse Gaussian with Poisson distribution, we consider the effects of covariates on the common parameters that exist in all three models. In this case, in the cure model with generalized Poisson inverse Gaussian distribution we will have two extra parameters (a, c) ranging from 0 to 1 and non-informative prior U (0,1) has been applied for both parameters. In the cure model with Poisson inverse Gaussian distribution we will

have one extra parameter (c) and non-informative prior U (0,1) has been applied for that. In both models, negative amount of P_D is obtained that indicates in Bayesian models the improper prior use of parameters, and thus the DIC increases and gets closer to the DIC of Poisson distribution. In addition, the estimation of the model parameters, except the constant does not undergo notable changes, but any change in constant causes a total change in estimating the cure rate, and this indicates that adding extra parameters does not help much in a better fitting, but linking covariate to extra parameter causes a higher rate of flexibility.

On discrete data analysis when there is over-dispersion, negative binomial distribution is the most common alternative, and in cure models its priority over Poisson models is proved by Cancho et al. (14). Thus, this model is applied here for data fitting (DIC = 416.269). Although this value was lower than that in Poisson distribution, it was higher than that in both generalized Poisson-inverse Gaussian model and Poisson-inverse Gaussian model. In several studies, it has been shown that Poisson inverse Gaussian distribution has a higher probability on extreme values and larger kurtosis compared to negative binomial distribution (18).

In this paper, the model which was applied for data fitting was based on the Conner first activation scheme. Although random activating scheme and last activating scheme can be applied, in other papers Conner first activation scheme had more accurate fitting which was the reason we selected the generalized Poisson-inverse Gaussian based on Conner first activation scheme (29).

In this paper we used the distribution that the probability distribution does not have close form but probability generating function had closed form. It is worthy because we can use more complicated distribution that is obtained by compounding different distribution without worry about the probability distribution that have close form.

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