International Journal of Applied Data Science
Volume1, Issue 3, 2025

STATISTICAL ANALYSIS OF SURVIVAL TIMES BASED ON PROPORTIONAL GENERALIZED ODDS MODELS

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Article Info

Received: 22-03-2025 **Revised:13-04-2025** **Accepted:07-06-2025** **Published:10-07-2025**

Abstract: The Cox proportional hazards (PH) model is the most widely used regression model in the field of survival analysis. Unfortunately, the PH model cannot be used in reality since not all data sets meet the PH criteria. The proportional odds (PO) model (Pettitt 1982 and Bennett 1983a) and the generalized proportional odds (GPO) model (Dabrowska and Doksum, 1988), which are essentially extensions of the PH model, were offered as solutions to the issue. Nevertheless, there are instances that suggest that the PO or GPO paradigm is inappropriate. Consequently, a broader model has to be taken into account. The proportional generalized odds (PGO) model, which includes the PO and GPO models as specific examples, is presented in this study. The GPO model's underlying survival function and regression parameter estimation are examined. The model is applied to a collection of data.

Key words: Burr distribution; Frailty parameter; Maximum likelihood estimation; Censored data.

Introduction

The Cox proportional hazards (PH) model is a popular regression model where lifespan is subject to right censoring, as long as the data meets certain PH requirements (Cox 1972). Different regression models must be built to suit the data since it is usual for the PH conditions to be broken. The proportional odds (PO) model put out by Pettitt (1982) and Bennett (1983a, b) is one of them. Similar to the PH model, the PO model makes the assumption that the chances of a lifetime distribution are proportional to the odds of a baseline distribution rather than the hazard rates. It should be noted that the PO model is not a straightforward extension of the PH model. Pettitt (1984), Bickel (1986), Cheng et al. (1995), Cuzik (1988), Dabrowska and Doksum (1988), Shen (1995), Wu (1995), and Murphy et al. (1997) are a few of the studies on the PO model. The estimate of the underlying survival function is the primary focus of the majority of investigations. Furthermore, Dauxois and Kirmani (2003) established a technique for determining if the data meets the PO assumption for two independent samples with right-censored lifetimes.

A generalization of the PO model was suggested in addition to it. Dabrowska and Doksum (1988) established the generalized proportional odds (GPO) model for two-sample lifespan data and created a testing procedure for comparing two survival functions that meet the GPO criteria. Refer to Clayton and Cuzick (1986), Dabrowska et al. (1989), Banerjee et al. (2007), and their sources for more information.

Despite the GPO model's generality and flexibility in fitting data, there are still several situations in which its use is inappropriate (see Section 4). In order to do this, we suggest a more comprehensive model known as the proportional generalized odds (PGO) model. The GPO model implies a common frailty factor for two groups of survival periods under consideration, but the PGO model permits the two groups

to have separate frailty factors. This is the primary difference between the two models. The suggested PGO model matches the data, but the GPO model does not, as will be shown in Section 4. Bennett (1983a) and the present research vary primarily in two ways: (i) the current PGO model is more generic than the PO model; and (ii) regression models are included in the current analysis but not in Bennett (1983a).

The remainder of this essay is structured as follows: The PGO model is described and its relationship to other relevant models is discussed in Section 2. Semi-parametric estimation of the PGO model is covered in Section 3. The PGO model is used on a data set in Section 4.

set about recurring episodes of renal illness. Section 5 presents a few debates.

1. Proportional generalized odds model

Let $T \geq 0$ denote a lifetime and z a vector of covariates. Assume that the survival function $S(t) = P(T > t)$ of T is continuous. The ratio $[1 - S(t)]/S(t)$ is called odds, which measures the odds of "failure" against "survival" at time $t \geq 0$. Pettitt (1982) and Bennett (1983a, b) introduced the PO model as follows,

$$\frac{1 - S(t)}{S(t)} = \theta(z)\frac{1 - S_0(t)}{S_0(t)}, \quad \text{for all } t \geq 0,$$

in which S_0 is a baseline survival function. This model assumes that lifetime T is associated with its covariate z only through θ, which is independent of time t. This model actually assumes that the odds ratio (against a baseline) at any time t is a constant θ, free of t. This model has been applied to various data sets where the use of the PH model is not appropriate. As mentioned in Section 1, the PO model is a different model, not an extension of the PH model. In particular, if we let $\lambda(t)$ denote the hazard function corresponding to $S(t)$ then, under the PO model, the hazard ratio

$$\frac{\lambda(t)}{\lambda_0(t)} = [1 + (\theta(z) - 1)S_0(t)]^{-1},$$

which it is not a constant unless $\theta(z) = 1$.

A more general model was introduced by Dabrowska and Doksum (1988) as follows. First, they extended the odds to generalized odds defined as

$$r\frac{1 - S^{1/r}(t)}{S^{1/r}(t)}.$$

Obviously, it reduces to the usual odds when $r = 1$. Then they proposed the following GPO model

$$\frac{1 - S_2^{1/r}(t)}{S_2^{1/r}(t)} = \theta\frac{1 - S_1^{1/r}(t)}{S_1^{1/r}(t)},$$

where S_1 and S_2 are, respectively, survival functions of two independent samples, and r is a (frailty) parameter. Since it is shown that the generalized odds converge to the *cumulative hazard* $-\log S(t)$ as $r \to \infty$, the GPO model becomes the PH model as $r \to \infty$. That is, the GPO model covers the PH and PO models as special cases. Studies of the GPO model focus on testing for the hypothesis of equality of S_1 and S_2 when they satisfy the GPO condition, and the model has been studied extensively in the past two decades. Recently, we tried to apply the model to a data but found that the data does not satisfy the GPO

assumption. For this reason, we extend the GPO model by allowing different r for different sample. In particular, we propose the following *proportional generalized* odds (PGO) model,

$$\frac{1-S^{1/r}(t)}{S^{1/r}(t)}=\theta\frac{1-S_0(t)}{S_0(t)},\qquad \text{for all } t\geq 0, \tag{2.1}$$

where S_0 denotes a baseline survival function, $r>0$ and $\theta>0$ are parameters. To compare it with the GPO model, let us consider two independent samples. Let S_i denote the survival function of sample i, $i=1, 2$. Then it is seen that

$$\frac{1-S_1^{1/r_1}(t)}{S_1^{1/r_1}(t)}=\frac{\theta_1}{\theta_2}\frac{1-S_2^{1/r_2}(t)}{S_2^{1/r_2}(t)},\quad \text{for all } t\geq 0. \tag{2.2}$$

So the PGO model is a generalization of the GPO model. It can be verified that Burr distribution (Burr, 1942) with different scale parameters (See Section 3 below) satisfies the PGO condition but not the PO condition.

In addition to the natural extension, the PGO model can also be obtained from an engineering point of view. Let $X_1, \cdots, X_n, \cdots$ be a random sample of observations with distribution function F and survival function $S=1-F$, and let N be a random variable having a geometric distribution with probability of "success" $\theta \in (0, 1)$. Then Kirmani and Gupta (2001) showed that the distribution of lifetime $Y=\min$

$$\theta\frac{1-S_Y(t)}{S_Y(t)}=\frac{1-S(t)}{S(t)},\quad \text{for all } t\geq 0,$$

and the distribution of the lifetime $Z=\max_{1\leq i\leq N} X_i$ of a "parallel" system satisfies the PO equation

$$\theta\frac{1-S(t)}{S(t)}=\frac{1-S_Z(t)}{S_Z(t)},\quad \text{for all } t\geq 0.$$

These two equations provide a physical support to the PO model. In a similar manner, the following is for the PGO model in (2.1).

Proposition 1 Suppose that N follows a negative binomial distribution with parameters (r,θ). Then, for all $t\geq 0$,

$$\theta\frac{1-S_Y^{1/r}(t)}{S_Y^{1/r}(t)}=\frac{1-S(t)}{S(t)}, \tag{2.3}$$

$$\frac{F_Z^{1/r}(t)}{1-F_Z^{1/r}(t)}=\theta\frac{F(t)}{1-F(t)}. \tag{2.4}$$

Proof For any t, the survival function

$$
\begin{aligned}
S_Y(t) &= P\left(\min_{1\le i\le N} X_i > t\right) \\
&= \sum_{n=r}^{\infty} P\left(\min_{1\le i\le n} X_i > t\right)\cdot P(N=n) \\
&= \sum_{n=r}^{\infty} S^n(t)\cdot\binom{n-1}{r-1}\theta^r(1-\theta)^{n-r} \\
&= \theta^r S^r(t)\sum_{n=r}^{\infty}\binom{n-1}{r-1}\left[(1-\theta)S(t)\right]^{n-r} \\
&= \frac{\theta^r S^r(t)}{[1-(1-\theta)S(t)]^r}\sum_{n=r}^{\infty}\binom{n-1}{r-1}\left[1-(1-\theta)S(t)\right]^r\left[(1-\theta)S(t)\right]^{n-r} \\
&= \frac{\theta^r S^r(t)}{[1-(1-\theta)S(t)]^r}.
\end{aligned}
$$

Thus, we have

$$
\frac{S_Y^{1/r}(t)}{1-S_Y^{1/r}(t)} = \frac{\theta S(t)}{1-(1-\theta)S(t)-\theta S(t)} = \theta\frac{S(t)}{1-S(t)}.
$$

Likewise, the distribution function

$$
F_Z(t) = \sum_{n=r}^{\infty} F^n(t)\cdot\binom{n-1}{r-1}\theta^r(1-\theta)^{n-r} = \frac{\theta^r F^r(t)}{[1-(1-\theta)F(t)]^r},
$$

and thus

$$
\frac{F_Z^{1/r}(t)}{1-F_Z^{1/r}(t)} = \frac{\theta F(t)}{1-(1-\theta)F(t)-\theta F(t)} = \theta\frac{F(t)}{1-F(t)},
$$

for any *t*.

2. Estimation

A nonnegative random variable X is said to follow a Burr distribution (Burr, 1942), denoted as $X \sim$ Bur(α, σ, r), if it has the survival function

$$
S(x) = \left(1+\frac{x^\alpha}{\sigma}\right)^{-r}, \qquad x \ge 0,
$$

where the shape parameter α, the scale parameter σ and the frailty parameter r are all positive. Bur(*1, 1, r*) is called the standard Burr distribution.

Proposition 2 below shows that Burr distribution satisfies the PGO condition. Since it is straightforward, we state it without proof.

Proposition 2 Suppose $X_i \sim$ Bur(α, σ_i, r_i), i = 1, 2. Then, for all $t \ge 0$,

$$\frac{1-S_2^{\frac{1}{r_2}}(t)}{S_2^{\frac{1}{r_2}}(t)} = \theta \frac{1-S_1^{\frac{1}{r_1}}(t)}{S_1^{\frac{1}{r_1}}(t)},$$

where $\theta = \sigma_1/\sigma_2 > 0$.

It is easy to verify that PGO equation (2.2) is invariant under positive increasing transformations. That is, if X_1 and X_2 satisfy (2.2), then so do $h(X_1)$ and $h(X_2)$ for any increasing function h. Proposition 3 below tells that any two random variables satisfying (2.2) may be regarded as increasing transformations of two Burr random variables with a common shape parameter.

Proposition 3 Suppose X_2 and X_1 satisfy the PGO model

$$\frac{1-S_2^{\frac{1}{r_2}}(t)}{S_2^{\frac{1}{r_2}}(t)} = \theta \frac{1-S_1^{\frac{1}{r_1}}(t)}{S_1^{\frac{1}{r_1}}(t)}, \qquad \text{for } \theta > 0 \text{ and all } t \geq 0.$$

$$h(t) = \frac{1-S_2^{\frac{1}{r_2}}(t)}{S_2^{\frac{1}{r_2}}(t)}$$

gives rise to $h(X_2) \sim \text{Bur}(1, 1, r_2)$ and $h(X_1) \sim \text{Bur}(1, \theta, r_1)$.

Proof Note that $S_2(X_2)$ has the standard uniform distribution, we have, for any $t \geq 0$,

$$P(h(X_2) > t) = P\left(\frac{1-S_2^{\frac{1}{r_2}}(X_2)}{S_2^{\frac{1}{r_2}}(X_2)} > t\right) = P\left(S_2(X_2) \leq (1+t)^{-r_2}\right) = (1+t)^{-r_2}.$$

That is, $h(X_2) \sim \text{Bur}(1, 1, r_2)$, the standard Burr distribution. And in a similar manner it also holds that, for any $t \geq 0$,

$$\begin{aligned} P(h(X_1) > t) &= P\left(\frac{1-S_2^{\frac{1}{r_2}}(X_1)}{S_2^{\frac{1}{r_2}}(X_1)} > t\right) \\ &= P\left(\frac{1-S_1^{\frac{1}{r_1}}(X_1)}{S_1^{\frac{1}{r_1}}(X_1)} > \frac{t}{\theta}\right) \\ &= P\left(S_1(X_1) \leq \left(1+\frac{t}{\theta}\right)^{-r_1}\right) \\ &= \left(1+\frac{t}{\theta}\right)^{-r_1}. \end{aligned}$$

That is, $h(X_1) \sim \text{Bur}(1, \theta, r_1)$.

We now discuss the PGO regression model. Assume that in model (2.1) survival function S is affected by covariates $\boldsymbol{z}$ only through θ. Specifically, model (2.1) becomes

$$\frac{1-S^{1/r}(t)}{S^{1/r}(t)} = \theta(z) \frac{1-S_0(t)}{S_0(t)}, \qquad \text{for all } t \geq 0,$$

where $\theta(z) = \exp\{\boldsymbol{\beta}'\boldsymbol{z}\}$,

$$\boldsymbol{z} = \begin{pmatrix} z_1 \\ \vdots \\ z_p \end{pmatrix}, \qquad \boldsymbol{\beta} = \begin{pmatrix} \beta_1 \\ \vdots \\ \beta_{p.} \end{pmatrix}$$

Let $T_1 \sim S_1$ and $T_2 \sim S_2$ be two independent lifetimes satisfying the PGO model

$$\frac{1-S_i^{\frac{1}{r_i}}(t)}{S_i^{\frac{1}{r_i}}(t)} = \theta(z)\frac{1-S_0(t)}{S_0(t)}, \qquad \text{for some } r_i > 0 \text{ and } i = 1, 2. \tag{3.1}$$

Apparently it is a semi-parametric model. We now use the likelihood principle to estimate the baseline S_0, parameters β and r_i, and survival functions $S_i(t; z)$, i = 1, 2, based on censored data. This can be considered as a two-sample problem with covariates. The same method can be used for three or more samples. Define

$$Y_i = [1 - S_0(T_i)]/S_0(T_i), \quad i = 1, 2.$$

Then, by Proposition 3, Y_i follows a Burr distribution with survival function

$$Q_i(y; z) = \frac{1}{\left(1+\theta(z)y\right)^{r_i}}, \quad y \geq 0. \tag{3.2}$$

Since both samples share the same baseline S_0, we combine two samples into one in order to construct a pooled estimate of S_0. For simplicity let to denote the distinct observed lifetimes from the combined sample, of which some are from sample 1 and the others are from sample 2. Further, we let t^c_j, j = 1, 2, . . . denote censored lifetimes from the combined sample. In addition, we use $y^o_{(i)}$ and y^c_j, respectively, to denote the corresponding transformed values of $t^o_{(i)}$ and t^c_j, . Note that although it is not clearly labeled (for simplicity purpose), it is clear to us as for which sample an observation belongs to. Still for simplicity, we are going to use r for both r_1 and r_2, Q for both Q_1 and Q_2 and the density function of Q

$$q(t; z) = \frac{r\theta(z)}{\left(1+\theta(z)y\right)^{r+1}}$$

for q_1 and q_2, the density functions of Q_1 and Q_2. With these notations, the likelihood function in terms of Y takes the form of

$$\mathcal{L}(\boldsymbol{\theta}, r_1, r_2; \boldsymbol{y}) = \prod_i \left\{ \prod_{l\in\mathcal{O}_i} \left[q\left(y^o_{(i)}; z_{(l)}\right) \frac{\mathrm{d}y^o_{(i)}}{\mathrm{d}t^o_{(i)}} \right] \right\} \cdot \prod_j \left[\prod_{l\in\mathcal{C}_j} Q\left(y^c_j; z_{(l)}\right) \right], \tag{3.3}$$

where O_i is the set of subscripts of observed lifetimes tied at $t_{(i)}$, C_j is that of right-censored lifetimes in $[t_{(j)}, t_{(j+1)})$, and the derivative is Jacobian due to the transformation. Notice that y's as a function of S_0 are also unknown parameters. To obtain the likelihood estimates of all parameters, following two approximations are used, which are similar to Bennett (1983a). First we replace the derivative by its approximation $\frac{y_{(j)} - y_{(j+1)}}{t_{(j)} - t_{(j+1)}}$; second, we replace $Q(y^c_j, z)$ by $Q(y'_{(j)}, z)$ where $y'_{(j)}$ is the largest observed lifetime before y^c_j from the same sample. Then the above likelihood function is approximated by

$$\prod_i \left\{ \prod_{l \in \mathcal{O}_i} \left[\frac{r\theta(z_k)}{\left(1+y^o_{(i)}\theta(z_k)\right)^{r+1}} \frac{y^o_{(i)} - y^o_{(i-1)}}{t^o_{(i)} - t^o_{(i-1)}} \right] \right\} \cdot \prod_j \left[\prod_{l \in \mathcal{C}_j} \frac{1}{\left(1+y^l_{(j)}\theta(z_l)\right)^r} \right]. \qquad (3.4)$$

Once the likelihood (3.4) is maximized with respect to parameters β, r_1, r_2, and $y^o_{(i)}$ $i = 1$, 2, . . . , k, the baseline survival function $S_0(t)$ can be estimated by

$$S_0(t_{(i)}) = \frac{1}{1+y^o_{(i)}}, \qquad i = 1, 2, \cdots, k.$$

3. An application

This section applies the proposed PGO model to a data set about kidney patients recurrent times.

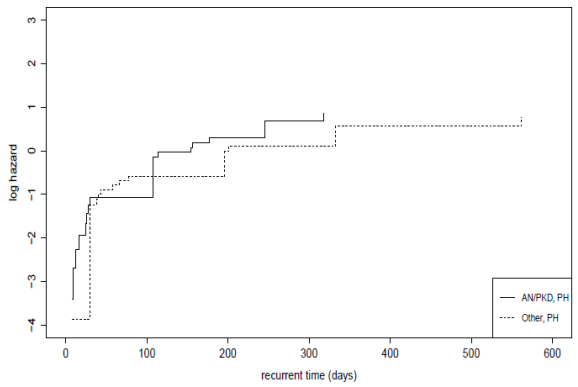
The data in Table 1 contains 38 kidney patients' second recurrent times to infection at point of insertion of the catheter for kidney patients using portable dialysis equipment, the risk variables are age, sex and type of disease coded as 0 = glomerulo nephritis (GN), 1 = acute nephritis (AN), 2 = polycystic kidney disease (PKD), 3 = other; in the event column, 1 denotes that time to infection was observed and 0 denotes that it was censored. The original data containing the first two consecutive recurrent times and sex had been studied by McGilchrist and Aisbett (1991) using a frailty model and by McGilchrist (1993) and Lam (1994) using the proportional hazards model. They all found that "sex" was not significant.

As an illustration we divide the data into two groups: AN and PKD in one group and GN and Other in another group. To see whether the Cox's PH model, the PO model or the GPO model is suitable for the data, we ignore covariates "age" and "sex" and then for each of the groups we obtained the estimate of the survival function using three different methods: Kaplan- Meier (KM) estimate, the PO model, and the GPO model. If, for example, the PO model fits the data, then there will be some $\theta > 0$ such that

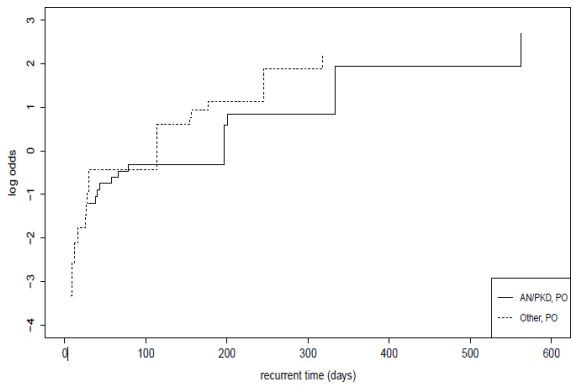
$$\frac{1-\hat{S}_2(t)}{\hat{S}_2(t)} = \theta \frac{1-\hat{S}_1(t)}{\hat{S}_1(t)}, \quad \text{for all } t \geq 0.$$

Table 1: Kidney patients' second recurrent times

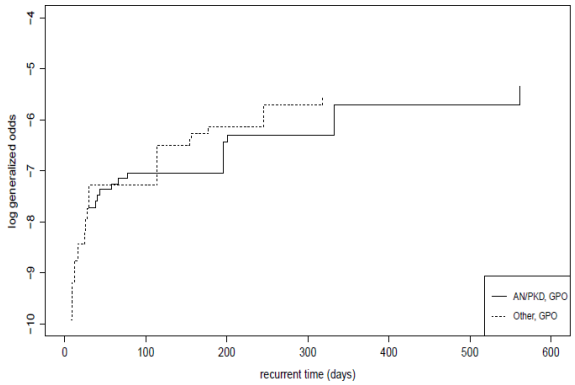
patient No.	recurrent time	event	sex	age	disease type
1	16	1	1	28	3
2	13	0	2	48	0
3	28	1	1	32	3
4	318	1	2	31.5	3
5	12	1	1	10	3
6	245	1	2	16.5	3
7	9	1	1	51	0
8	30	1	2	55.5	0
9	196	1	2	69	1
10	154	1	1	51.5	0
11	333	1	1	44	1
12	8	0	2	34	3
13	38	1	2	35	1
14	70	0	2	42	1
15	25	0	2	17	3
16	4	0	1	60	1
17	177	1	2	60	3
18	114	1	2	43.5	3
19	159	0	2	53	0
20	108	0	2	44	3
21	562	1	1	46.5	2
22	24	0	2	30	3
23	66	1	2	62.5	1
24	46	0	2	42.5	1
25	40	1	1	43	1
26	201	1	2	57.5	1
27	156	1	2	10	0
28	30	1	2	52	1
29	25	1	1	53	0
30	26	1	2	54	0
31	58	1	2	56	1
32	43	1	2	50.5	1
33	30	1	2	57	2
34	5	0	2	44.5	0
35	8	1	2	22	3
36	16	0	2	42	3
37	78	1	2	52	2
38	8	0	1	60	2



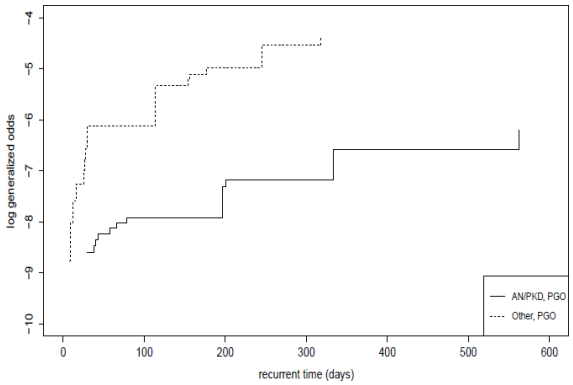
(a)Log hazard, PH model



(b) Log odds, PO model



(c) Log generalized odds, GPO model



(d) Log generalized odds, PGO model

Figure 1: Log odds and log generalized odds

For the PH model, replace the numerator $1-S(t)$ in the above equation with its density function $f(t)$. In other words, when taking log on both sides of the above equation, the two log(odds) curves (vs. time t) should be parallel if the model works. However, as is seen in Figure 1, the two log(hazard) curves based on the estimated hazard functions are not parallel (Fig 1(a)); the two log(odds) curves based on PO or GPO are not parallel either (Fig 1(b), 1(c)). By contrast,

the two curves based on the PGO model are nearly parallel (Fig 1(d)). This is evidence that the PGO model is more appropriate to fit this data than the other three models. In addition, goodness-of-fit tests for the hypothesis that the two groups (AN and PKD vs. GN and Other) satisfy the PO model using Neyman's smooth test and Kolmogorov-Smirnov test (see Kraus, 2009) have p-values of 0.014 and 0.094, respectively. This confirms our observation in Figure

1. By the way, if the data is divided into four groups, AN, PKD, GN, and Other, then the PH assumption is satisfied (p-value=0.503); however, when the data is divided into two groups as

described above, besides Figure 1(a), we performed a test and the result shows that the PH assumption is not satisfied (p-value=0.01329), which is consistent with Figure 1(a).

We fit the PGO model to this data using likelihood (3.4). The genetic algorithm was employed for the computation. The maximum likelihood estimates of parameters r1, r2, and the coefficients of "age" and "sex" are, respectively, $e^{5.5}$, $e^{7.7}$, 0.006 and -1.29. A likelihood ratio test was performed for "age" and "sex" and found that none of them is significant (p-value=0.82 for "age" and 0.17 for "sex").

4. Discussions

A model that generalizes the current PH, PO, and GPO models is proposed in this study. The suggested paradigm is supported by the example in Section 4. Even if the suggested PGO model is more adaptable than the current models, a way to confirm whether a piece of data fits the PGO criteria still has to be developed. We consider it to be a "must" duty rather than an easy one. The partial probability estimation of the model parameters is one of the most remarkable aspects of the PH model. Regretfully, we are unable to build a comparable estimator for the suggested PGO model. Therefore, we do not explore the large sample aspects of our maximum likelihood estimators. Furthermore, unlike the PH model, estimates of the baseline survival function and other parameters are achieved in a single step due to the absence of a partial probability function. More computation and computing time are required for this one-step calculation. After the Newton-Raphson method failed to converge for our data in Section 4, we utilized the genetic algorithm, which proved to be quite effective. Simulation studies are often required to examine the performance of a suggested model in the absence of theoretical findings. Unfortunately, technological issues prevented simulations from being performed in this article; nevertheless, we have planned to carry out a comprehensive simulation investigation in the future. In summary, this work represents a preliminary investigation of the topic; more research is required to make the suggested model practical.

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