Exponentiated Parametric Survival Models for Primary Congenital Glaucoma Data.

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Abstract:

The Exponentiated Parametric Survival (EPS) models like Exponential, Weibull and Gamma are alternative analysis for Exponential, Weibull and Gamma models. The Exponentiated Exponential has specifications like Scale and Shape, which is same like that of Weibull or Gamma family. However, the Exponentiated Weibull has a scale and two shape parameters, whereas the exponentiated gamma has a scale and shape parameter. In this study we used three types of Exponentiated Parametric Survival models for the Primary Congenital Glaucoma data and the study concludes that the Weibull model has the lowest Akaike Information Criterion (AIC) score which demonstrates a good fit for the data analysis of Primary Congenital Glaucoma.

Key words: Exponentiated Survival Models, Weibull Distribution, Exponential Distribution, Gamma Distribution, Primary Congenital Glaucoma.

Introduction:

Despite the low rate of incidence, Primary Congenital Glaucoma (PCG) is a leading cause of childhood blindness in most of the developing countries. As part of the condition, intraocular pressure (IOP) builds up leading which deteriorates the condition, further the drainage of fluid in the eye often gets blocked leading to the spike in IOP, which ultimately impairs the optic nerve[21]. Congenital glaucoma expresses in the neonatal period or it manifests at a very young age of patient[22]. The anti-glaucoma medication for the treatment of PCG provides low response [23] and hence, it is usually followed by surgical intervention. The outcome of surgical intervention depends upon the gravity of the condition and the treatment needs long term follow-up. The survival rate of PCG is analyzed using different statistical survival models. The time to event data or survival data are generally used to study the time to an event, where the study subjects are observed for a period of time and often follows up beyond the time period. But, choosing the most appropriate model to fit with the data is always challenging and the commonly used survival analysis is Kaplan-Meier Curve, the long rank test and the Cox Proportional Hazard Models. Many researchers used both parametric and non-parametric survival models for such data, like the Cox Proportional Hazard models, which is neither precisely parametric nor non-parametric. The prametric models will always guide to stronger assumptions of data, however, the application of Exponentiated Parametric Models on the data of PCG is sparse. Hence this is a unique study which focuses on the application of different exponentiated parametric survival models, like Exponentiated Exponential, Exponentiated Weibull and Exponentiated Gamma.

Exponentiated Exponential Model (EEM):

Among the different skewed unimodal distributions, the two parameter exponentiated exponential distribution in EEM is a right skewed unimodal distribution of data. The density function and hazard function of the exponentiated exponential distribution is analogous to the density function and hazard function of the gamma or Weibull distribution. Hence, this can be very well adopted effectively to analyze time- to-event data rather than using gamma or Weibull distribution. EEM can very well be explained as a particular case of Gompertz-Verhulst distribution function (Ahuja & Nash, 1967)[1] , which is explored by (Gupta & Kundu, 1999).[2] The cumulative distribution function of EEM (Gupta & Kundu, 1999, 2000, 2001 and 2003) is defined as [3-5]

$F_{EE}(t, \alpha, \lambda) = \left[1 - e^{-\lambda t}\right]^{\alpha}$; $\alpha, \lambda, t > 0$ (1)

and density function is defined by

$f_{EE}(t, \alpha, \lambda) = \alpha\lambda \left[1 - e^{-\lambda t}\right]^{\alpha-1} e^{-\lambda t}$; $\alpha, \lambda, t > 0$ (2)

where α and λ are respectively shape and scale parameters. If α =1, it results in the exponential family and it also represents the Gamma and Weibull model (Gupta & Kundu, 2001).

Survival function of EEM is

$S_{EE}(t, \alpha, \lambda) = P(T>t) = 1- (1 - e^{-\lambda t})^{\alpha}$; $\alpha, \lambda, t > 0$ (3)

The hazard function of EEM is

$h_{EE}(t, \alpha, \lambda) = \frac{\alpha\lambda \left[1-e^{-\lambda t}\right]^{\alpha-1} e^{-\lambda t}}{1- (1-e^{-\lambda t})\alpha}$; $\alpha, \lambda, t > 0$ (4)

and cumulative hazard is

$H_{EE}(t, \alpha, \lambda) = - \log S(t)$; $\alpha, \lambda, t > 0$ (5)

Exponentiated Weibull Model (EWM):

The scale parameter and two shape parameters of EWM is illustrated by Mudholkar and Srivastava (1993),[6]. The Weibull family and the exponentiated exponential family are found to be particular cases of this family. In order to address the failure rate, the distribution has been compared with the two-parameter Weibull and gamma distributions. EWM distribution is defined in the following way, it has distribution function given by

$G_{\alpha}(z) = (1 - \exp\{-(\lambda z)^{\gamma}\})^{\alpha}$, $z > 0$, $\alpha, \lambda, \gamma > 0$ (6)

And therefore, its probability density function (pdf) is of the form

$$g_\alpha(z) = \alpha\gamma\lambda^\gamma z^{\gamma-1} (1 - \exp\{-(\lambda z)^\gamma\})^{\alpha-1} \exp\{-(\lambda z)^\gamma\},\ z>0. \quad (7)$$

The corresponding survival function is

$$S_\alpha(z) = 1 - (1 - exp\{-(\lambda z)^\gamma\})^\alpha \quad (8)$$

and the failure rate is

$$r_\alpha(z) = \frac{\alpha\gamma\,\lambda^\gamma\,z^{\gamma-1}\exp\{-(\lambda z)^\gamma\}\left(1-exp\{-(\lambda z)^\gamma\})^{\alpha-1}\right)}{(1-(1-exp\{-(\lambda z)^\gamma\})^\alpha)} \quad (9)$$

Here (α, γ) denote the shape parameters and λ is the scale parameter. For γ =1, it represents the exponentiated exponential (EE) family, and for α =1, it represents the Weibull family. Thus, EWM is a generalization of the exponentiated exponential family as well as the Weibull family.

Exponentiated Gamma Model (EGM):

Gupta et al. (1998)[7] put forward the exponentiated gamma (EG) distribution, which is flexible enough to fit in both monotonic and non-monotonic failure rates. The EG distribution has the distribution function:

$$F(x; \theta, \lambda) = \left[1 - e^{-\lambda x}(\lambda x + 1)\right]^\theta,\ \theta, \lambda, x > 0 \quad (10)$$

Therefore, EG distribution has the density function:

$$f(x; \theta, \lambda) = \theta\lambda^2 x e^{-\lambda x}\left[1 - e^{-\lambda x}(\lambda x + 1)\right]^{\theta-1},\ \theta, \lambda, x > 0 \quad (11)$$

the survival function

$$R(x; \theta, \lambda) = 1 - \left[1 - e^{-\lambda x}(\lambda x + 1)\right]^\theta,\quad \theta, \lambda, x > 0 \quad (12)$$

And the hazard function

$$h(x; \theta, \lambda) = \frac{\theta\lambda 2xe{-}\lambda x\left[1-e^{-\lambda x}(\lambda x+1)\right]\theta{-}1}{1-\left[1-e^{-\lambda x}(\lambda x+1)\right]\theta},\quad \theta, \lambda, x > 0 \quad (13)$$

here θ, and λ are the shape and scale parameters, respectively.

PPCG is an uncommon condition, which is an inherited developmental defect in the trabecular meshwork and anterior chamber angle of the eye that demonstrates itself in the neonatal or infantile period of the patient with elevated intraocular pressure, corneal enlargement with edema, and optic nerve cupping (Alkemade P, 1969; Broughton WL, et al. 1981).[8,9] PCG is a significant and leading eye disease, which fits with the survival model for PCG data. This will facilitate a best model to predict the significant factor for the failures of PCG survival. Exponentiated Exponential, Exponentiated Weibull and Exponentiated Gamma models were applied to the data and comparisons were made to find the best model.

Methods:

The study is retrospective in nature, consisting of 85 patients (148 eyes), who were diagnosed with PCG and undergone surgical interventions during the period from January 1991 to December 2011 at King Fahd Hospital of the University, Kingdom of Saudi Arabia. The data pertaining to the study was generated from the medical records and the data related with secondary forms of congenital glaucoma were excluded. The data consists of age at the time of presentation, sex of patient, corneal diameter, corneal transparency, and the latest follow–up information. The number of surgical interventions and the method of intervention, status of control, and the period of follow–up were obtained.

The protocol for diagnosis and its treatment was based on the existence of corneal edema with the Decemet's membrane pulled apart, increased corneal diameter, elevated IOP and the presence of glaucomatous cupping, where visualization was feasible. The clinical examinations of the patients were conducted initially in the outpatient department for neonates, while they are awake and on feeding. But, the elder children underwent their clinical examination either with general anesthesia or on sedation using chloralhydrate (100 mg per Kg for the first 10 Kg, and 50 mg for each additional Kg). While the corneal diameters were measured under general anesthesia, by calipers applied to horizontal corneoscleral limbus, whereas IOP was measured using applanation tonometer (Perkin's tonometer). After making the diagnosis of PCG, all patients were put on medical therapy, consisting of Timolol 0.25% BID, with Diamox 5 – 10 mg per Kg every 6 hours, as indicated.

Our preferred treatment for PCG was trabeculotomy to address the marked corneal edema preventing visualization of the iridocorneal angle structure in most cases and trabeculectomy in case of failure to spot the Schlemm's canal. Other surgeries conducted were goniotomy, combined trabeculotomy and trabeculectomy, and cyclophotocoagulation with conventional method. A patient who complies with the postoperative follow-up for a minimum period of 3 months was included in the study. The surgery was considered successful only if IOP decreased to <21 mm Hg and if the corneal diameter and cup-disc ratio became constant with or without medical topical treatment. As per the objective of this study, Exponentiated parametric survival models were used to know the best model for PCG data. SAS package has been used to fit the models.

Results:

A total number of 148 eyes with PCG were included into the study. The demographic information of the patients (age, gender, IOP, and follow-up) illustrates that the majority of children were less than 1 month of age (n=40; 47.1%). The median age at the time of reporting was 60 days, ranging from 1day to 8 years. More than half of the children were females (n=45; 53%) and 63 (74.1%) patients were presented with PCG on both eyes. The mean corneal diameter was observed as 12.6 ± 1.1 mm with a range of 10-15 mm. Trabeculotomy was the most common surgical procedure done in 88 (59.5%) eyes and trabeculectomy was carried out in 37 (25.0%) eyes and a combination of both the surgical interventions were carried out in 55 (37.2%) eyes. The mean follow-up was 49.6 ± 46.2 months, ranging from 3 - 216 months with a median period of 36 months.

After constructing different types of exponentiated parametric survival models, the Exponential, Weibull and Gamma models were compared to their AIC (Table 1) to determine the best fit model. The exponentiated Weibull model illustrates the lowest AIC which is 1209.66, demonstrating a better overall fit than the other models with parameters 2.2583 (1.9288). Figure 1 shows that the survival curve of all three models indicates that survival curve of these models were similar, but the data distribution in Weibull exponentiated model stands apart from the other two models, which is illustrated in the figure 2, the probability density function.

Table 1: The parameter estimates and Akaike Informational Criterion (AIC) of different models

Models	Parameter	Optimization Results				
		Estimate	S.E	-2LL	AIC	Median Survival Time
Exponentiated Exponential	lambda	0.01664	0.0021	-605.33	1210.66	50 Months
	alpha	1.04711	0.1207			
Exponentiated Weibull	lambda	0.03852	0.0431	-604.83	1209.66	39 Months
	alpha	2.25834	1.9286			
	beta	0.64126	0.2837			
Exponentiated Gamma	lambda	0.02202	0.0026	-605.37	1210.74	50 Months
	alpha	0.50682	0.0569			

Figure 1: Survival Curve

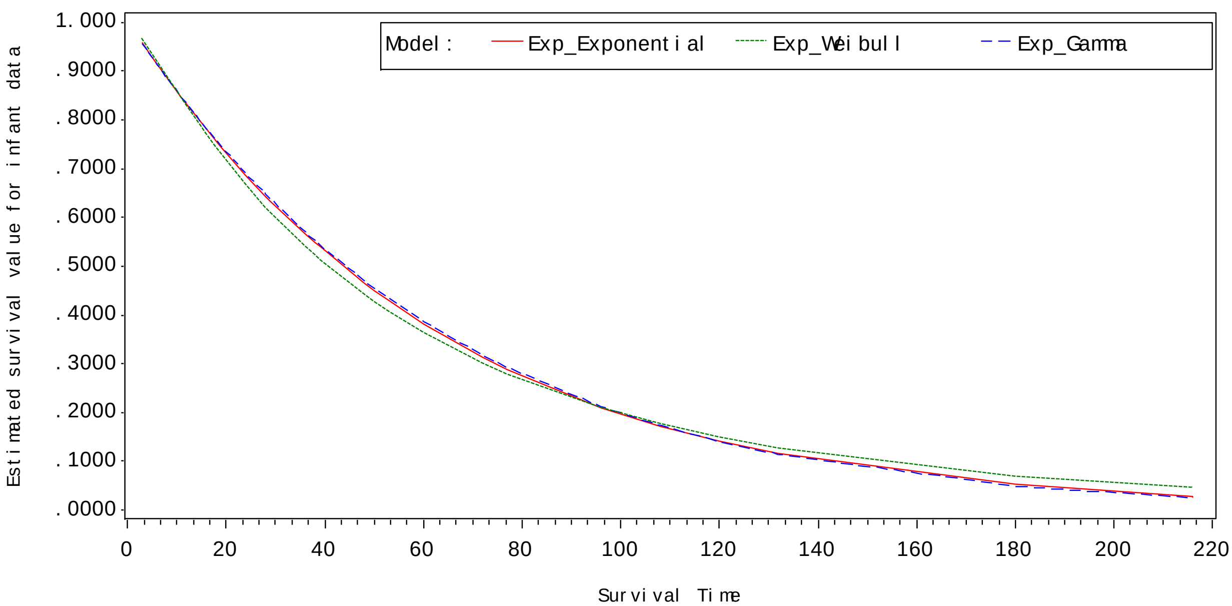
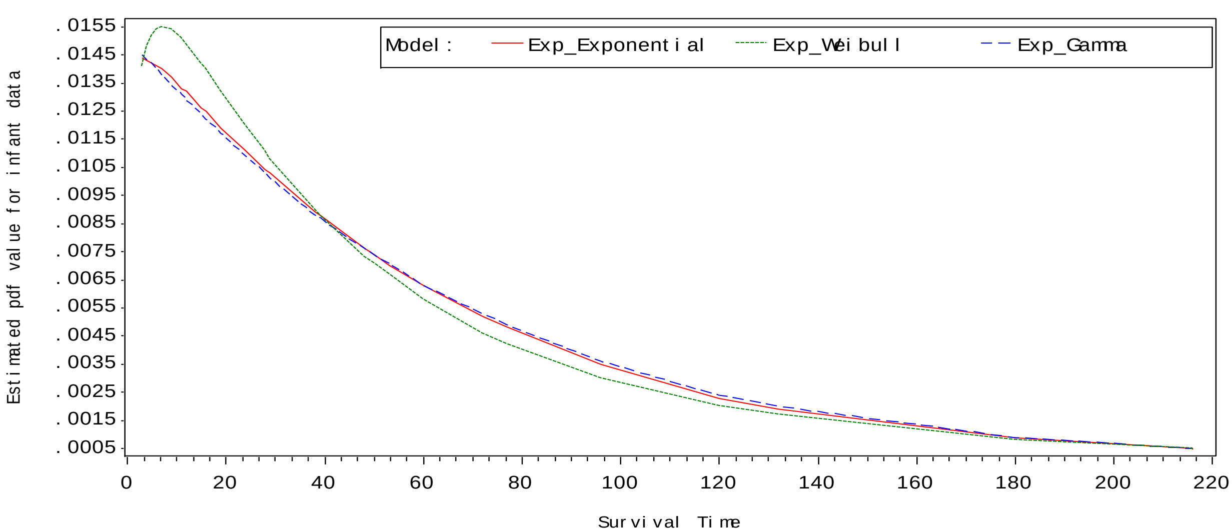


Figure 2: Probability density function curve



Discussion:

There are few studies looking into the survival analysis of PCG, but those studies were focusing on any one of the surgical managements, the trabeculectomy or trabeculotomy.[10-12] Research exploring survival analysis of these two management procedures and its combination are uncommon.[13,14] The available studies of PCG survival analysis looked into either one of the surgical procedures using any one of the analytical methods, the univariate or multivariate analysis.[10,11] Most of the studies use univariate analysis, but only a few studies used multivariate analysis.[15-17] This study is unique by identifying best survival model for this PCG data.

Many studies were available for the application of exponentiated exponential model like the research put forward by Venkatesan et al, 2011, who observed that the EEM model to be very much suitable for the spinal TB data in comparison to an Exponential and Weibull models.[18] However,, R.D.Gupta, 2001 also conclude that EE has a better fit compare to Weibull or Gamma, but he came forward with another conclusion for another data set, pointing out that Weibull model is much more suitable than EE or Gamma.[19] Yet another study from M.Pal et al, 2006 derives that the exponential Weibul distribution is a better fit than the exponentiated exponential model.[20] This study also conforms with the findings of other studies, illustrating that the exponentiated Weibull model had the lowest AIC, which is 1209.66, indicating a better overall fit than the other models with parameters 2.2583 (1.9288). AIC for other two models were too close to the Exponentiated Weibull model and hence, it is not guaranteed that the Weibull Exponentiated model will always behave better than the Exponentiated Exponential and Exponentiated Gamma. This is because the AIC values for those models were almost close to each other. However, the Exponentiated Weibul Model (EWM) might work better than Exponentiated Exponential or Exponentiated Gamma. Therefore, further studies with larger sample size is warranted to conform this finding.

Conclusion:

Survival rates were measured by exponentiated exponential, exponentiated Weibull and exponentiated gamma, which were visualized through graphs. On a comparison with the exponentiated parametric survival models, exponentiated Weibull is found to be a better fit in accordance with the AIC value for the PCG data.

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