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Statistics

COMPARISON OF COX PROPORTIONAL HAZARD MODEL AND ACCELERATED FAILURE TIME (AFT) MODELS: AN APPLICATION TO UNDER-FIVE MORTALITY IN UTTAR PRADESH

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ABSTRACT The statistical field of survival analysis focuses on the examination of time-to-event data. The proportional hazards (PH) model is the most widely used in multivariate survival analysis to examine the effects of various factors on survival time. The statistics, however, do not always support the PH models assumption of constant hazards. The power of the associated statistical tests is reduced when the PH assumption is broken, which leads to incorrect interpretation of the estimation results. The accelerated failure time (AFT) models, on the other hand, do not, like the PH model, assume constant hazards in the survival data. Additionally, the AFT models can be employed in place of the PH model if the constant hazards assumption violated. This study set out to examine how well the PH model and the AFT models performed when it came to identifying the proximate variables influencing under – five mortality from National Family Health Survey data in Uttar Pradesh. Three AFT models that were based on the Weibull, exponential, and log-normal distributions were the only ones discussed in this article. The research employing a graphical technique and a statistical test revealed that the NFHS-5 data set has non-proportional hazards. The log-normal AFT model was the most acceptable model among the ones studied, according to the Akaike information criterion (AIC).

KEYWORDS : Proportional hazards (PH), Accelerated failure time (AFT), National family health survey and Akaike information criterion (AIC)

Introduction

Statistics is fast developed as a powerful omnipresent discipline. It is being used in every perceivable area to derive reasonable answers to tough questions. Besides innumerable other practical applications, the subject of Statistics also finds several applications in the field of Medicine. One of the most notable ones is in explaining the risk for certain diseases, by means of establishing links between certain behaviors and those diseases, say, cancer or heart disease [1]. The branch of Statistics which aims to fulfill this purpose is called Survival Analysis, also referred to as "time to event analysis". It is defined as a set of methods for analyzing data where the outcome variable is the time until the occurrence of an event of interest [2]. It aims to estimate the three survival functions, namely, survivorship, density, and hazard functions, denoted by S(t), f(t) and h(t), respectively [3].Here, the survival function S(t) gives the probability of surviving beyond time t, and is the complement of the cumulative distribution function, F(t), i.e., S(t) = 1 – F(t), and the hazard function h(t) gives the instantaneous potential per unit time for the event to occur, given that the individual has survived up to time t [4]. Survival Analysis provides a range of parametric (such as exponential, Weibull, Gompertz, Lognormal, Log-Logistic, Gamma, etc.), non-parametric (such as Kaplan &Meier (K-M), log rank test, life table), as well as semi-parametric (Cox Proportional Hazards (CPH)) methods for the estimation and modelling of these survival functions [4].

One of the oldest and most straightforward non-parametric methods for analyzingtime-to-event data is to compute the life table, which was proposed by Berkson and Gage [5] for studying cancer survival. Another important non-parametric survival analysis method for estimating the survival probability was obtained by Kaplan and Meier [6]. The Kaplan-Meier estimator, also known as the product limit estimator, is essentially, the non-parametric maximum likelihood estimate of the survival function when the model is a non-parametric survival model. Apart from these, the log-rank test [7,8] is another non-parametric method used to compare the survival probabilities across different groups.

If the underlying probability distribution of the baseline hazard function in the Cox Proportional Hazards model becomes known, then it can be identified as a parametric Proportional Hazards model. In that case, the maximum likelihood estimates and inferences based on the parametric Proportional Hazards model are expected to be more precise and useful statistically.

The parametric AFT model assumes that the survival and hazard functions follow a certain probability distribution, the parameters of which can be estimated. These estimates are more precise as compared to those obtained through the non-parametric or the semi-parametric survival analysis models. A major advantage of the AFT model over the Proportional Hazards model is that the interpretation of the results becomes easier, since the effect of the covariates is expressed in terms of the mean survival time instead of the hazard rate. Therefore, the application of AFT survival models, such as the Weibull AFT model, Logistic AFT model, Log-normal AFTmodel, Log-logistic AFT model, Generalized gamma AFT model and Exponential AFT model in order to obtain smooth hazard rates and cumulative hazard functions of the covariates/risk factors and to extrapolate the survival functions, is quite common [9,10].

Although the application of AFT models is recommended in the analysis of lifetime data and medical research, the review of available literature has indicated that its application is comparatively more common in the field of industrial research [11, 12]. Though the AFT models have been studied extensively by various authors, limited literature on comparative studies between different survival models such as the semi-parametric Cox Proportional Hazards model and the parametric AFT models is available, especially in the area of clinical research. These few studies have used simulation methods to perform comparison on a small sample with several censored observations, which is frequently the case in clinical research [13]. One such study has shown that the AFT models fit better to the influenza data than the Proportional Hazards model [12]. However, most of the real life applications, such as those in the areas of demography and public health, call for the analysis of large samples. In such scenarios, a conclusive comparative evaluation of these two models remains largely unexplored. Therefore, the main purpose of this paper is to explore this untraversed territory in comparing the performance of the Cox Proportional Hazards model and the various AFT models.

Material & Methods

We have used National Family Health Survey (NFHS-5) data which was conducted in year 2019-21. In analysis we have included Under-five children of state Uttar Pradesh. Total live births were reported 36374 in Uttar Pradesh in last five year.

Data analysis

In this study survival analysis was carried out to model time to surviving under-five deaths. The Kaplan-Meier approach was used to describe the survival functions of the under-five deaths and the Log-rank test was used to compare the survival curves among groups. The time to surviving under-five deaths was modelled by using the following models viz: Cox proportional hazard model and Accelerate failure time (AFT) models (Weibull, Log-normal and exponential AFT models).

The Kaplan Meier Product limit method

In Kaplan Meier product limit method, survival probabilities can be obtained as:

$$S = \Pi_{k}^{j=1}\left(\frac{n_j - d_j}{n_j}\right), k \le n, \;\; t_j \le t < t_{j+1}$$

Where, d_j= the number of failure in t_j,n_j is the number of incident cases at risk in t_j , k is the number of sequential observations , n is the total number of incident cases .

The log rank test

The log rank test is a hypothesis test to compare the survival distribution of two samples. It is appropriate to use when the data are right skewed and censored

Hypothesis: H_0: No difference between survival curves

H_1 : There is difference between survival curves the log rank statistics for two groups is Cox Proportional hazard (ph) model

The basic tool used for analysis in the Cox proportional hazards model is the hazard function. The model developed by Cox (1972) to express the relationship between the hazard function and a set of covariates for the i[th] individual is given as:

$$h_i(t|X) = h_0(t)\exp(\beta' X_i)$$

or

$$h_i(t|X) = h_0(t)\exp\left(\sum_{j=1}^{p}\beta_j X_{ji}\right); \quad j = 1,2,\dots,p; \quad i = 1,2,\dots,n$$

Where,

t is the survival time or the time elapsed since the beginning of the study,

$\beta=(\beta_1,\beta_2,\dots,\beta_p)'$ is a vector of p unknown regression coefficients/parameters that are to be estimated and are assumed to be the same for all individuals participating in the study,

$X_i=(x_{1i},x_{2i},\dots,x_{pi})$ is a vector of p measured characteristic/covariates for the i[th] individual at time t,

h_0 (t) is an unspecified baseline hazard function at time t. The hazard function for the i[th] individual is referred to as the baseline hazard function, if X_i , the vector of covariates is taken as a zero vector. Thus, it is simply the hazard function in the absence of covariates or when the values of all the parameters of the covariates are replaced by zero, and h_i (t|X) is the hazard function at time t dependent on the vector of covariates.

Dividing both sides of the above equation by h_0 (t), a model of the following form is obtained, which explains where the term 'proportional' comes from:

$$\frac{h_i(t|X)}{h_0(t)} = \frac{h_0(t)\exp\left(\sum_{j=1}^{p}\beta_j X_{ji}\right)}{h_0(t)} = \exp\left(\sum_{j=1}^{p}\beta_j X_{ji}\right); \quad j = 1,2,\dots,p; \quad i = 1,2,\dots,n$$

This gives us a function that remains constant over time, known as the hazards ratio. The impact of the covariates/explanatory variables on the hazards ratio is described by the exponentiated linear regression part on the right-hand side of the above equation. Hazard ratios can be used in the comparison of survival times of two or more distinct population groups.

Accelerated failure time (AFT) model

The AFT model describes the relationship between survival probabilities and a set of covariates. for a group with covariates (X_1 ,X_2 …………………..X_p), the AFT model is written mathematically as

$S(t \mid x)=S_0(t \mid \eta(x))$

Where S_0 (t) is the baseline survival function and η is an acceleration factor i.e. a ratio of survival times corresponding to any fixed values of S (t)

The acceleration factor is given according to the formula

$\eta(x)= e(\alpha_1 x_1+\alpha_2 x_2+\dots\dots+\alpha_p x_p$

According to the relationship of survival function and hazard function the hazard function for an individual with covariateX_1, X_2 ………………X_p is given by

$$h(t|x) = \left[\frac{1}{\eta(x)}\right] h_0[(t|\eta(x)]$$

Under an accelerated failure time model the covariate effect are assumed to be constant and multiplicative on the time scale that is the covariate impacts on survival by a constant factor (acceleration factor). The corresponding log- linear form of the AFT model with respect to time is given by

$\log T_i = \mu+\alpha_1 X_{1i}+\alpha_{21} X_{2i}+\dots\dots+\alpha_{p1} X_{pi}+\sigma_i$

Where μ is intercept σ is scale parameter and is a random variable,$€_I$ assumed to have a particular distribution.

Weibull AFT model

Suppose the survival time T has W (γ;λ) distribution with scale parameter and shape parameter under AFT model, the hazard function for the i[th] individual is

$$h_i(t) = \frac{1}{[\eta_{i(x)}]\gamma}\lambda\gamma(t)^{r-1}$$

Where η_i= exp($\alpha_1 x_1+\alpha_2 x_2+\dots\dots+\alpha_p$ p) for individual i with p explanatory

The AFT representation of hazard function of the Weibull model is given by

$$S_i(t) = \exp[-\exp\{\frac{-\mu-\alpha_1 x_{1i}-\dots\dots-\alpha_p x_{pi}}{\sigma}\} t^{1/\sigma}]^{-1}$$

The hazard function for the i[th] individual is given by

$$h(t) = \frac{1}{\sigma t}[1+ t^{\frac{1}{\sigma}}\exp(-\mu - \alpha_1 X_{1i} - \dots\dots - \alpha_1 X_{pi}]^{-1}$$

The Log – normal AFT model

If the survival times are assumed to have a log – normal distribution the baseline survival function are given by

$$S_0(t) = 1 - \phi\left[\frac{\log t-\mu}{\sigma}\right]$$

$$h_0(t) = 1 - \frac{\phi\left[\frac{\log t}{\sigma}\right]}{[1-\phi\left[\frac{\log t}{\sigma}\right]]\sigma t}$$

Where μ intercept is σ is scale parameter and is a random variable;ϕ(x) is the cumulative density function of the standard normal distribution. The survival function for the i[th] individual is

$$S_i(t) = S_0(t|\eta_i) = 1 - \phi\left(\frac{\log t-\alpha^t x_i}{\sigma}\right)$$

Where, η_i= exp($\alpha_1 x_1+\alpha_2 x_2+\dots\dots+\alpha_p$ p) Therefore the log survival time for the ithindividual has normal ($\mu+\alpha^t x^i$,) . The log - normal distribution has the AFT property.

Results:The survival time at which the cumulative survival function is equal to 0.5. This is summarized in Figure 1.The common testing technique known as the Log-rank test, which makes use of the chi-square statistic, is used to explain how to determine whether or not K-M curves for two or more groups are statistically significant. When two K-M curves are statistically equal, it signifies that there is no evidence to suggest that the underlying population survival curves (probabilities) are different based on testing process that compares the two curves generally. There appears to be a statistical difference between the survival probabilities, as seen in Table 1.

Figure 1

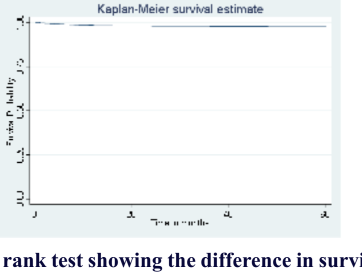

Table 1: Log rank test showing the difference in survival function between the groups.

Socio-economic factors	Observed	Expected	2 (p-value)
Mother's educational status			
No education	285	208.86	52.62***
Primary	97	90.66	

Secondary	227	265.74	
Higher	59	102.75	
Family size			
<=5	328	232.31	60.56***
>5	340	435.6	
Wealth status			
Poor/poorer	436	364.24	49.71***
Middle	111	121.54	
Rich/richest	121	182.22	
Environmental factors			
Source of sanitation facility			9.75**
Unimproved access	415	450.29	
Improved access	214	178.71	
Use of cooking fuel			
Solid fuel	204	258.46	19.52***
Clean fuel	425	370.54	
Maternal factors			
Mother's age at first birth			
<20	253	198.5	21.41***
20-24	336	377.69	
>=25	79	91.81	
Use of contraception			
Never used	351	254.14	59.76***
Ever used	317	413.86	
Total children ever born			
<=2	212	341.44	123.41***
3-4.	305	244.95	
>=5	151	81.61	
Place of delivery			
Home	173	112.71	39.0***
Health facility	486	546.29	
Anaemia level			
Severe or moderate anaemic	211	193.71	5.62*
Mild anaemic	173	160.37	
Non anaemic	262	291.92	
TT Status			
Yes	31	17.47	11.11**
No	286	299.53	
ANC visits			
No	38	17.45	27.93***
1-3.	168	166.46	
4+	111	133.09	
Birth order			
First birth order	166	216.64	35.54***
Second & third order	318	322.47	
Fourth & more birth order	184	128.89	
Size of baby			
Large	88	107.38	32.04***
Average	441	463.75	
Small	107	64.87	

(*p-vaule>0.05 non significant, **p-value<0.05, ***p-vaule<0.001)

Checking PH assumption by the goodness of fit (GOF) testing approach

The GOF testing method is particularly appealing since it offers statistical tests to determine whether non-PH is present. As a result, the choice of the PH assumption is more objective than the technique using log cumulative hazard plots, which was covered in the previous subsection. A GOF test based on the Schoenfeld residual is one of the most often used GOF testing techniques .The fundamental evidence of the test is that there is no association between the Schoenfeld residuals and the survival time if the PH assumption for a covariate is not violated. In other words, it will examine the hypothesis □□:□ =0. (There is no correlation between the covariate and time). If the Ho hypothesis is not accepted, the PH assumption cannot be held for the covariate. Table 2 demonstrates that the tests for each variable consist of at least one significant covariate at a 5% level for all transformation variants. Consequently, there are is no relationship between a particular transformation form and the covariate. To put it another way, this covariate does not support the PH premise. Moreover, all surviving time was taken into account in the Global tests. Transformation forms provide compelling non-PH evidence (p-value = 0.00).

Table 2: The goodness of fit test based schoenfeld residual for the background characteristics

Background characteristics	HR	SE	p-value
Mother's educational status	0.88	0.06	0.071
Family size	0.39	0.05	0.000
Wealth status	1.05	0.10	0.605
Source of sanitation facility	1.04	0.14	0.745
Use of cooking fuel	1.22	0.19	0.192
Mother's age at first birth	0.94	0.10	0.516
Use of contraception	0.48	0.06	0.000
Total children ever born	1.36	0.18	0.019
Place of delivery	0.89	0.13	0.439
Anaemia level	0.98	0.04	0.634
TT Status	0.72	0.15	0.126
ANC visits	0.84	0.09	0.091
Birth order	1.30	0.18	0.066
Size of baby	1.43	0.18	0.006
Global test	2	df	p-value
	21.93	14.00	0.04

Fitting the PH model and the AFT models

The PH assumption is violated in the NFHS data, as has previously been demonstrated in earlier subsections. As an alternative to the PH model, the AFT models, which make no assumptions about PH, are utilized. In this study, the regression coefficients are estimated using the partial likelihood and MLE approaches.

PH model and AFT model coefficients, respectively. The estimation of bothcomputation Withthe STATA package "survival" performs models for NFHS data in UttarPradesh. The parameters estimation and its corresponding p-values of PH model, Weibull AFT model, exponential AFT model, and log-normal AFT model are given in table 3.

Table 3 shows the estimation results and the p-values of PH model and AFT models in order to assess the effects of each parameter on the survival time. In PH model eight parameters are significant and six parameters are insignificant at 5% level that is the parameters of the wealth status, source of sanitation facility, mother's age at first birth, total children ever born, place of delivery, anemia level and TT status . However wealth status, source of sanitation facility, mother's age at first birth, total children ever born, place of delivery, anemia level and TT status insignificant at 5 % level for Weibull AFT model exponential AFT model and for log normal AFT model .

Table 3: Results Of Fitting The Proportional Hazard Model Accelerated Fitted Models

Socio-economic factors	Cox PH		Exponential AFT		Weibull AFT		Lognormal AFT	
	HR	p-value	Coef.	p-value	Coef.	p-value	Coef.	p-value
Mother's educational status								
No education	1.76	0.04	-0.56	0.04	-0.99	0.04	-0.93	0.04
Primary	1.43	0.24	-0.39	0.20	-0.65	0.21	-0.60	0.24
Secondary	1.55	0.09	-0.48	0.06	-0.79	0.07	-0.73	0.08
Higher ®								
Family size								
<=5	2.68	<0.001	-0.95	0.00	-1.72	<0.001	-1.65	<0.001
>5 ®								

Wealth status								
Poor/poorer	0.89	0.57	0.09	0.68	0.19	0.60	0.24	0.50
Middle	0.92	0.71	0.05	0.81	0.12	0.74	0.18	0.62
Rich/richest ®								
Environmental factors								
Source of sanitation facility								
Unimproved access	1.04	0.78	-0.04	0.76	-0.07	0.77	-0.14	0.56
Improved access ®								
Use of cooking fuel								
Solid fuel	1.22	0.20	-0.22	0.16	-0.37	0.16	-0.41	0.13
Other	0.00	<0.001	10.21	<0.001	18.00	0.98	14.21	<0.001
Clean fuel ®								
Maternal factors								
Mother's age at first birth								
<20 ®								
20-24	0.79	0.09	0.17	0.21	0.37	0.12	0.40	0.09
>=25	1.02	0.90	-0.06	0.74	-0.07	0.83	0.08	0.82
Use of contraception								
Never used ®								
Ever used	0.50	<0.001	0.78	<0.001	1.27	<0.001	1.40	<0.001
Total children ever born								
<=2 ®								
3-4.	1.12	0.54	-0.08	0.66	-0.17	0.59	-0.15	0.65
>=5	1.69	0.05	-0.46	0.10	-0.89	0.07	-0.91	0.07
Place of delivery								
Home	1.12	0.45	-0.09	0.58	-0.19	0.49	-0.19	0.50
Health facility ®								
Anaemia level								
Severe\moderate anaemic	1.04	0.77	-0.11	0.43	-0.12	0.63	-0.15	0.55
Mild anaemic	1.07	0.66	-0.12	0.42	-0.15	0.57	-0.17	0.51
Non anaemic ®								
TT Status								
Yes	0.78	0.24	0.25	0.26	0.45	0.25	0.54	0.20
No ®								
ANC visits								
No ®								
1-3.	0.71	0.11	0.31	0.15	0.59	0.12	0.65	0.11
4+	0.64	0.05	0.42	0.06	0.77	0.05	0.80	0.05
Birth order								
First birth order ®								
2-3	1.15	0.46	-0.06	0.73	-0.19	0.56	-0.17	0.61
4+	1.83	0.03	-0.55	0.06	-1.03	0.04	-0.92	0.07
Size of baby								
Large ®								
Average	0.94	0.72	0.06	0.70	0.11	0.71	0.14	0.64
Small	1.92	<0.001	-0.70	<0.001	-1.18	<0.001	-1.23	<0.001

Table 4: Comparison Of The Proportional Hazard Models And The Accelerated Fitted Model Using AIC Criteria

Model	Log likelihood	AIC
Cox PH	-2658.73	5365.45
Exponential AFT	-1896.33	3842.67
Weibull AFT	-1829.37	3710.75
Lognormal AFT	-1819.09	3690.18

The full model used to derive the AIC values in table 3 means that all factors were taken into account. Table 4 shows that the PH model's AIC value is 5365.45 and doubles the AIC averages of all suggested AFT models. It demonstrates that the AFT models fit the data set far better than the PH model. Table 4 also shows that the log-normal AFT model has the lowest AIC value, which is another important point. In other words, out of all the models analyzed, the log-normal AFT model fits the data the best.

Discussion:

The PH model is frequently used in published studies rather than the AFT models in a variety of practical applications. Only a small number of studies, however, looked into the necessary PH assumption [14]. The model may be biased and unreliable if the PH assumption is violated [15]. As a result, dealing with the presence of non-PH in the data set can be dealt with in part by using AFT models. Moreover, Numerous studies [16, 17] and [18] have demonstrated that the AFT models are superior to the PH model for fitting the non-PH data set. This paper used two techniques to look for PH assumption violations in the NFHS data set. Specifically, the Schoenfeld residual based on the GOF test and Schoenfeld residual plots for checking PH assumption. The outcomes from both techniques revealed the presence of the non-PH in the set of data (figure 1 and table 1). This finding is comparable to [19] also demonstrated the inclusion of non-PH in the data set. In this study, the AFT and PH models' outputs were compared in order to examine the NFHS in Uttar Pradesh data this work employed the AIC value to compare these models. The estimated total amount of models (table 2) revealed that there were few discrepancies between the PH model and the AFT models when testing the significance of the covariates Weibull AFT model (AIC=3710.75), exponential AFT model (AIC= 3842.67), and log-normal AFT model (AIC= 3690.18) all have AIC values that are around twice as high as the AIC value of the PH model (AIC= 5365.45). This indicates that the AFT models perform significantly better in this situation than the PH model. The log-normal model is the one that fits the data the best among the other models that were taken into consideration, as shown by the AIC value. These findings are in line with those of earlier studies [5], [14], which found that the log-normal AFT model fit their data set the best.

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