Estimation of Survival Time of HIV/ AIDS Patients While Reducing the Number of Predictors using a Partial Correlation/ Association Technique

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A number of techniques have been developed for variable reduction in the survival analysis. However, none of those techniques take into consideration the correlation among the predictors. This paper focuses on the reducing the number of predictors using the concept of partial correlation/ association and then estimating the survival time of HIV/ AIDS patients while. Partial correlation is preferred over pairwise correlation & multiple correlation as pairwise correlation takes into account only the linear relationship between two predictors at a time and multiple correlation may give misleading results if one variable is numerically related to other variable and both the variables again are taken simultaneously to find the association/ correlation. This can be avoided by controlling the confounding variable using partial correlation coefficient. Partial correlation is used to assess the correlation between a continuous predictor and a categorical predictor when the controlling variable is also categorical. ANCOVA is used to determine the association between two categorical predictors when the controlling variable is also categorical. AFT models are used to estimate survival times with/ without reduction in the number of predictors. It is observed that the estimated survival times are not affected by the reduction of predictors from 11 to 4. Also, the estimates obtained by the new proposed technique are found to be more efficient than the existing methods.

Keywords: AIDS; AFT; ANCOVA; HIV.

Presently, Human Immuno deficiency virus (HIV) has been assumed to have a measure of an international epidemic[1, 2] and it's notably most striking in Asia[3]. Worldwide about 36 Million persons have been estimated to be infected with HIV. It has also resulted in death of 1.2 million people globally[4]. Of all HIV infected people, 90% live in developing countries[1]. India has third largest HIV epidemic in the world. In India, 2.5 million individuals were estimated to have been living with HIV infection till 2014[4]. All the above mentioned figures designate the enormous measure of HIV and as a result validate a crucial requirement to conduct a depth research of the calamity of various prognostic factors to which the HIV patients are left unprotected to.

Anti-retroviral therapy (ART) plays a crucial role in treating the patients infected with HIV/AIDS. It has the capability to reduce mortality as well as morbidity rates among HIV patients, and as a result help in improving the life quality of patients. This treatment (ART) has been available

freely for patients since 2004 in India. At ART clinics, HIV patients have access to nutritional advice, testing and counselling (HTC) by experts. They are needed to go through a CD4 count test half yearly[5]. Moreover, the government is also rolling out several campaigns to aware people about their appointments to increase the overall attendance[6].

With the use of ART and vast improvements in preventive facilities , HIV epidemic in India has slowed down considerably with a 19% reduction in new HIV infections (130,000 in 2013), and a reduction of 38% in deaths contributed by AIDS between 2005 and 2013[4]. By the end of 2013, more than 700,000 people were receiving ART which is a great achievement in itself considering that it is the second largest number of people on treatment in any single country.

To check the intensity of HIV virus in the AIDS patients, one of the most important predictors is the CD4 cell counts. A healthy person is estimated to have 1200 CD4 cells per mm3 in blood. CD4 cells are deteriorated as immune system is attacked by HIV virus.

Center for Disease Control (CDC) recommended initiating Anti-retroviral therapy (ART) when the CD4 cells goes down 200 cells per . and Various observational studies and Two randomized controlled trials (RCTs) showed that initiation of ART at CD4 < 350 cells/mm3 results in significantly reduction of disease progression, mortality and the incidence of opportunistic diseases, especially TB and non-AIDS-defining conditions[6].

Various studies have been proposed to estimate the survival and effects of underlying covariates on the survival among HIV patients by using Cox PH model (Ghate *et al*., 2011[7]; Rai *et al*., 2013[8]; Kee *et al*., 2009[9]; Jerene *et al*., 2006) [10]. Markus Abigo Erango. (2017) predicted and compared the survival time of HIV/AIDS patients in three hospitals in Ethiopia. Three parametric accelerated failure time distributions: lognormal, log logistic and Weibull are used to analyze, predict and compare survival probabilities of the patients. The results indicated that the empirical hazard rates of the three data sets reveal maximal peaks[11]. Jaya Chakravarty *et al.* (2013) analyzed the factors affecting the survival of patients under routine programme conditions in an ART centre in India five years after its initiation. She found

poor survival in the first half year of therapy mainly in patients with severe immunosuppression. Thus, she emphasized the requirement for early enrolment into the programme[12]. Performance of Cox Proportional Hazard Model and the Accelerated Failure Time Model was compared by Derek Ngbandor Nawumbeni *et al.* (2014) using HIV/TB Co-infection Survival data. They concluded that the Accelerated Failure Time model has better predictive power as compared to the Cox model[13]. Emeka E. Orisakwe *et al.*, (2012) determined whether knowledge of HIV and the attitude of patients referred for HCT correlated with a willingness to test for HIV[14]. Colins Kingoum Nubed (2016) assessed the KAPs of senior secondary school students in Fako Division, Cameroon, on HIV/AIDS. This cross-sectional study was conducted on 464 students between 13 to 25 years of age. Participants were selected by systematic quota random sampling from secondary schools in Fako, from April to June 2014[15]. Hanhui Ye *et al.*, (2016) conducted an analysis to analyze the correlation between AIDS restriction and metabolic pathway gene expression. They showed that HIV-1 postentry cellular viral from AIDS restriction genes can be coexpressed in human transcriptome microarray datasets[16]. Grover and Swain (2013) tried to estimate the survival time of HIV/ AIDS patients who underwent Antiretroviral Therapy in Delhi. They used Non- Parametric Maximum Likelihood Estimation method (NPMLE) for interval censored data and KM survival time for left, right and mid-point imputation to estimate the survival of these patients[17]. Richard Hafner et. al (1999) studied the linear relationship between Mycobacterium avium complex (MAC) infection of blood and bone marrow in human immunodeficiency virus—infected patients before and during treatment[18]. Sergio Rueda (2016) conducted a systematic review and series of meta-analyses on the association between HIV related stigma and health among people living with HIV. They conducted a structured search on 6 electronic databases for journal articles reporting associations between HIV-related stigma and health related outcomes published between 1996 and 2013[19]. Ravi *et al* (2018) determined highly positively correlated predictors and reduced the number of predictors using pairwise correlation / association and then estimated the survival time patients on

ART[20]. Grover G *et al*. (2018) examined the effect of reduction of predictors affecting the survival of patients using a multiple correlation/technique. They observed that the estimated survival times are not affected by the reduction of predictors from 11 to 4[21].

In this paper, we have proposed a partial correlation/association screening procedure for reducing the number of predictors to be included in the model without affecting the estimated survival time and also resulting in lower Standard error. So, this research paper aims at
• Estimating the survival time of patients on ART by taking all the prognostic factors by using AFTM;
• Determining the significantly partially correlated/ associated predictors in the model by using suitable technique;
• Determining the effect of partially correlated predictors on the survival time of HIV/AIDS patients under ART;
• Estimating the survival times of HIV/AIDS patients on ART in the presence of reduced number of predictors
• Compare the two models (One having all the available prognostic factors and other with the reduced number of prognostic factors) on the basis of their AIC values.
• Comparing the proposed method with the methods discussed in[20] and[21] and existing variable reduction methods[22], [23].

Table 1. Log- Likelihood to compare different AFT models

Distribution	Log-Likelihood	Degrees of Freedom
Exponential	-1086.9	18
Weibull	-798.3	18
Log- Normal	-918	18
Logistic	-662.7	18
Log- logistic	-836	18

We have used SPSS and R software to fit the models and to compute the associations/ correlations among predictors.

METHODS AND MATERIALS

Methods Used

Assuming that number of HIV/AIDS patients under ART as and survival time of patient as with survival function . Then assuming a linear relationship between and predictors, we have

$$\log(T_i) = \beta_0 + \beta_1 x_{1i} + \beta_2 x_{2i} + \ldots \ldots + \beta_p x_{pi} + \sigma \varepsilon_i$$

...(1)

Where
ßo is the intercept
ßi are the coefficients of "p"explanatory variables for ith patient.
σ is the scale parameter

ei is a random variable used to model the deviation of values of loge (Ti) from the linear part of model.

It may be possible that two or more predictors are associated with a single predictor; we can replace these predictors with a single predictor with which they are associated. However, it may be possible that this correlation will give misleading results if one variable is numerically related to other variable and both the variables are taken simultaneously to find the association/ correlation. This bias can be avoided by controlling the confounding variable which is done by partial correlation. Partial correlation helps in measuring the strength of a relationship between two variables when controlling the effect of other variables. As a result, we can reduce the number of predictors included in the original model by excluding any spurious predictor which will lead in estimating the survival time of HIV/AIDS patients by AFTM.

Table 2. Akaike Information Criterion (AIC) values for AFT models

Distribution	Log-Likelihood	DF	C	AIC
Exponential	-1086.9	18	1	2210.4
Weibull	-798.3	18	2	1636.6
Log- Normal	-918	18	2	1876
Logistic	-662.7	18	2	1349.4
Log- Logistic	-836	18	2	1712

ANCOVA is used to test the association between two categorical predictors with the controlling variable being also categorical predictor.

To test the independence among two categorical predictors while the controlling predictor is also categorical, ANCOVA is used and then on the basis of p- value, we rejected or accepted null hypothesis that these variables are partially independent or not.

Model Comparison

Akaike's Information Criteria (AIC) is used to compare the different models where AIC is given by :-

$$AIC = -2k + 2\ln(\hat{L}) \qquad ...(2)$$

where k be the number of estimated parameters in the model and be the maximum value of the likelihood function for the model. The model with smaller value of AIC can be considered as a better model compared to other models under consideration.

Data Sources and Results

Data of 767 HIV/AIDS patients undergoing ART in Dr. Ram Manohar Lohia Hospital, New Delhi, India, during the period of January 2004 to December 2014 were collected in this retrospective follow-up study and an Accelerated Failure time model, taking all the possible predictors, is fitted. Different AFT models are fitted to determine the best fitted model. Logistic model is found to be the best model. Results are shown in Table 1 and 2 below:-

Two statistical criterion (likelihood ratio test and AIC) are used to compare these models. Gamma model nested exponential model, the Weibull model and the log-normal model (Table 1).

It is observed that the AIC for logistic model in the presence of all predictors is least among all the fitted models. Also, LR test showed that the logistic model fits best as compared to other models (Table1). Also, Cox-Snell residual fits good to the Logistic Accelerated Failure Time model (Figure 1).So, we fit the survival data using Logistic AFT model and results are shown in the table 3 below:-

From the results of the table 3, males are supposed to have longer survival time than females and Eunuchs as the time ratio for both of these genders are less than 1 (0.495 for females and 0.333 for eunuchs). Similarly, patients living
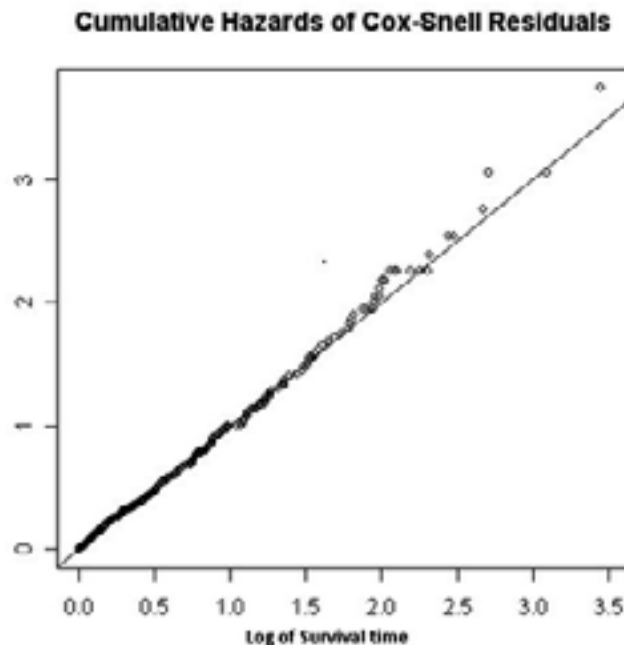

Fig. 1. Cox-Snell residual plot for Logistic AFT model

in North India are expected to have shorter survival time than the patients living in Central and East India as their time ratios are greater than 1. Again, patients who were smokers or were alcoholic are observed to have shorter survival time than the ones who never smoked or non- alcoholic in their lives. Unmarried patients are expected to have shorter survival patients than the married patients. Patients who have bacterial infection are observed to have shorter survival time than the patients who have viral infection where those having fungal infection

have longer survival time than the ones who have viral infection. Patients living in rural areas are expected to have shorter survival time than the ones who live in urban areas.

Then, in the first step, we have tried to determine the predictors which are jointly associated/ correlated with each other. We have used MANOVA to test the joint independence among two or more continuous and two or more categorical predictors and Log- linear models are used to test the joint independence among

Table 3. Results ofLogistic AFTM model for HIV/ AIDS patients

Predictors		Std. Error	TR	95% C.I
Age	-0.0118	0.00804	0.98827	(1.30, 3.98)
Male			1	
Female	-0.7025	0.34583	0.49536	(-0.027 ,0.003)
Eunuch	-1.0992	0.00000	0.333142	(-1.099, 0.065)
North India			1	
Central India	6.8151	0.00000	1.513	(6.815, 7.086)
East India	0.1864	0.77448	1.204925	(-1.331 ,1.704)
Smoking- Yes			1	
Smoking- No	0.1252	0.22841	1.133381	(-0.322, 0.572)
ALCOHOL- Yes			1	
ALCOHOL- No	0.1433	0.16252	1.154103	(-0.175,0.461)
DRUGS- Never			1	
DRUGS- Past	5.8478	0.18161	1.474	(5.491, 6.203)
DRUGS- Yes	0.7756	1.0675	0.571879	(-1.295,2.847)
Opportunistic Infection- Viral			1	
Opportunistic Infection- Bacterial	-0.6424	0.14163	0.526036	(-0.919,-0.365)
Opportunistic Infection- Fungal	0.6009	0.26871	1.823728	(0.074,1.127)
Urban			1	
Rural	-0.5271	0.18308	0.59031	(-0.885,-0.168)
Government Employee			1	
Non- Working	0.5102	0.35621	1.665702	(-0.187,1.208)
Agricultural Labor	0.1055	0.18550	1.111221	(-0.258,0.469)
Regular Employee	0.529	0.21158	1.697212	(0.114,0.943)
Business Man	-0.5673	0.32049	0.56704	(-1.195,0.060)
Un Married			1	
Married	0.3221	0.54588	1.379957	(-0.747 ,1.391)
Spouse- Positive			1	

Table 4. Result of the tests of the joint dependence among significantly associated/ correlated pairs of predictors

Predictor	Jointly dependent predictors	Model used	p- value
Age	Sex, Alcohol, Occupation and Spouse	MANOVA	0.015
Sex	Opportunistic infection, Marital Status and Spouse	Log- linear	0.000
Smoking	Alcohol, living Status, Occupation and Opportunistic infection	Log- linear	0.000
Drugs	Occupation and Spouse	Log- linear	0.000

Table 5. Significant values of Correlation and p- values for partial correlation/ association

Controlling variable	Variables	Correlation coefficient or p- value
Spouse	Age, Sex	-0.109
Spouse	Age. Alcohol	0.045
Spouse	Age, Occupation	0.141
Spouse	Sex, Alcohol	0.502
Spouse	Sex, Occupation	-0.152
Spouse	Alcohol, Occupation	0.93
Marital Status	Sex, Opportunistic Infections	*0.000*
Sex	Age, Alcohol	-0.019
Sex	Age, Occupation	0.135
Sex	Age, Spouse	-0.170
Sex	Alcohol, Occupation	0.56
Sex	Alcohol, Spouse	0.51
Sex	Spouse, Occupation	-0.059
Alcohol	Age, Occupation	0.157
Alcohol	Age, Spouse	-0.216
Alcohol	Age, Sex	0.68
Alcohol	Spouse, Occupation	-0.11
Alcohol	Sex, Occupation	0.53
Alcohol	Spouse, Sex	0.35
Occupation	Age, Spouse	-0.209
Occupation	Age, Sex	-0.158
Occupation	Age, Alcohol	0.62
Occupation	Spouse, Sex	0.69
Occupation	Spouse, Alcohol	-0.147
Occupation	Sex, alcohol	0.510
Spouse	Sex, Opportunistic Infections	*0.000*
Opportunistic Infections	Sex, Spouse	*0.000*
Opportunistic Infections	Sex, Marital Status	*0.51*
Spouse	Sex, Marital Status	*0.000*
Marital Status	Sex, Spouse	*0.000*
Opportunistic Infections	Sex, Spouse	*0.000*
Opportunistic Infections	Marital Status, Spouse	*0.66*
Spouse	Marital Status, Opportunistic Infections	*0.810*
Marital Status	Spouse, Opportunistic Infections	*0.207*
Occupation	Smoking, Living Status	*0.000*
Occupation	Smoking, Alcohol Status	*0.000*
Occupation	Smoking, Opportunistic Infections	*0.004*
Alcohol	Smoking, Opportunistic Infections	*0.000*
Alcohol	Smoking, Occupations	*0.000*
Alcohol	Smoking, Living status	0.610
Opportunistic Infections	Smoking, Living status	*0.000*
Opportunistic Infections	Smoking, Alcohol	0.06
Opportunistic Infections	Smoking, Living Status	0.243
Opportunistic Infections	Smoking, Occupations	*0.000*
Living Status	Smoking, Occupations	0.083
Living Status	Smoking, Opportunistic Infections	*0.000*
Living Status	Smoking, Alcohol	0.753
Living Status	Alcohol, Opportunistic Infections	*0.000*
Living Status	Alcohol, Occupations	*0.040*
Occupation	Living Status, Opportunistic Infections	*0.000*
Spouse	Drugs, Occupations	0.159

categorical predictors only. Predictors which are found to be jointly significantly correlated/ associated are listed below in the Table 4 below:-

Since p-value for each group is less than 0.05, alternative hypothesis can be accepted and can be concluded that these predictors are jointly dependent. After this partial correlation/ association between each possible pair are determined using suitable methods. The results are shown in the Table 5 below. The italic values are p- values and bold values are the significant values of correlation

(Correlation coefficient > .50 and p- values less than 0.05).

Using this procedure, 4 predictors are selected. In the next step, survival times are estimated using AFTM with only these selected predictors. Again, for this model, Logistic model is found to be the best AFT model by LR test and AIC values. Again, Cox-Snell residual was plotted and it fits well as shown in figure 2. Results are presented below in Table 6:-

Table 6. Results of modified Logistic AFTM model for HIV/ AIDS patients

Predictors	β	Std. Error	TR	95% C.I
Age	-0.00818	0.00796	0.9918568	-0.0242,0.008
DRUGS- Never			1	
DRUGS- Past	6.26359	0.16436	0.0980558	
DRUGS- Yes	0.96137	1.05338	0.6152831	-1.240,3.163
Male			1	
Female	-1.76615	0.1548	0.1709898	-2.0695,-1.462
Eunuch	-1.62039	0.0125	0.1978218	-1.620,0.624
Smoking- Yes			1	
Smoking- No	0.3776	0.19208	1.4587837	-0.077,0.832
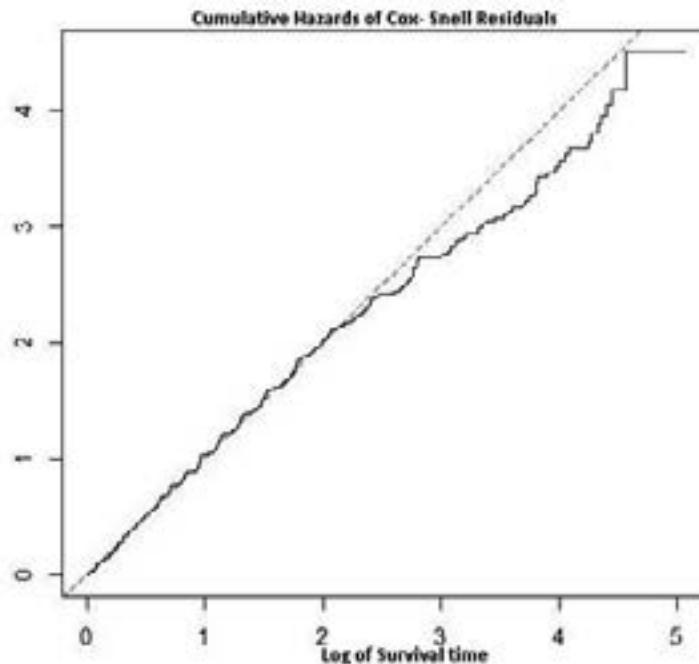
Fig. 2. Cox-Snell residual plot for Logistic AFT model

To compare the proposed method with the existing ones, variables are also selected using LASSO and elastic-net variable selection methods. LASSO method selected Six variables, viz, Age, Occupation, Opportunistic Infections, State, Sex and drugs whereas Elastic- net method selects Age, Alcohol status, Smoking Status, Spouse, and Occupation. Also, the standard errors of the coefficients of predictors in the models fitted by different methods are compared. It is observed that the standard error of the coefficients chosen by the proposed method is less than the standard error of the coefficients in the true model and with the standard errors of the coefficients chosen by LASSO and Elastic- net methods as shown in the Table 7 below:-

From table 8, it can be observed that AIC value is least for proposed method when compared with the AIC values for True, LASSO and Elastic-Net models and the methods discussed in[20] and [21].

CONCLUSION

Data of 767 patients diagnosed with HIV/ AIDS were collected in this analysis. The AFT modelling of the survival rates of patients

Table 7. Comparison of the Standard Error of the coefficients of the predictors selected using different variable selection methods

Predictors	S.E (True model)	S.E (Proposed Method)	S.E (LASSO Method)	S.E (Net- Elastic Method)	S.E (Pairwise Correlation technique)	S.E (Multiple Correlation technique)
Age	0.00804	0.00796	0.00799	0.00801	0.00796	0.00708
Male						
Female	0.34583	0.1548	0.32554			0.33493
Eunuch	0	0.0125	0			0
North India						
Central India	0		-0.001			
East India	0.77448		0.75256			
Smoking- Yes						
Smoking- No	0.22841	0.19208		0.20144		0.21578
ALCOHOL- Yes						
ALCOHOL- No	0.16252			0.12564		
DRUGS- Never						
DRUGS- Past	0.18161	0.16436	0.17512		0.16881	0.16728
DRUGS- Yes	1.0675	1.05338	1.06114		1.05695	1.03011
Opportunistic Infection- Viral						
Opportunistic Infection- Bacterial	0.14163		0.14256		0.14144	
Opportunistic Infection- Fungal	0.26871		0.16852		0.26792	
Urban						
Rural	0.18308				0.18111	
Government Employee						
Non- Working	0.35621		0.1725	0.25879	0.1747	0.16578
Agricultural Labor	0.1855		0.1810	0.1829	0.1829	0.17885
Regular Employee	0.21158		0.22147	0.22346	0.21123	0.20152
Business Man	0.32049		0.32247	0.31862	0.31784	0.30557
Un Married						
Married	0.54588					
Spouse- Positive						
Spouse- Negative	0.14234			0.13596		

Table 8. Comparison of proposed and existing variable selection methods on basis of AIC values

Model	No. of predictors	AIC
True	11	1349.4
Proposed Method	4	1295.2
LASSO method	6	1320.8
Net-Elastic method	5	1325.6
Pairwise Correlation technique	5	1316.4
Multiple Correlation technique	4	1313.2

from the prognostic factors selected Logistic as the best fitted model based on AIC. The Cox-Snell residual plot further confirmed the Logistic model as well fitted for evaluating the survival time of these 767 HIV/AIDS patients. Then, number of predictors have been tried to reduce by determining partial correlated/ associated variables/predictors using partial correlation/ ANCOVA. Using this technique, 4 predictors have been selected. It was disclosed that the model fitted with proposed technique is a good fit than the models fitted with all other methods. Therefore, from this study it can be concluded that it is not necessary to take all the predictors are not needed to take in the model to estimate the survival time of the patients as many prognostic factors may be partially correlated/ associated with each other and taking only one of them may satisfy the need of all of the remaining correlated/ associated predictors.

ACKNOWLEDMENT

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