Accelerated Failure Time Shared Frailty Models: Application to HIV/AIDS Patients on Anti-Retroviral Therapy in Delhi, India

Hızlandırılmış Arıza Zaman Paylaşımlı Zayıflık Modelleri: Hindistan, Delhi'de Antiretroviral Terapi Gören HIV/AIDS Hastalarına Uygulanması

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ABSTRACT Objective: The present paper demonstrates the applications of Accelerated Failure Time (AFT) model with gamma and inverse Gaussian frailty distributions to estimate the effect of prognostic factors on the survival of HIV/AIDS patients undergoing Antiretroviral Therapy (ART) in Delhi, India. **Material and Methods:** The results of both these models have been compared to without frailty model. Akaike Information Criterion (AIC) and Bayesian Information criterion (BIC) have been used to select best model for HIV/AIDS data. **Results:** The prognostic factors sex, mode of transmission, baseline hemoglobin and weight are found to be statistically significant (P-value <0.05) for HIV/AIDS patients on ART. Gamma shared frailty model with lognormal as baseline distribution is found to be the best model for HIV/AIDS patients. The model also reflected there is strong evidence of high degree of heterogeneity in the HIV/AIDS patients. **Conclusion:** Therefore shared frailty model is an appropriate approach for analyzing the HIV/AIDS data than without frailty model.

Key Words: AIDS; ART; Gamma shared frailty model; inverse Gaussian shared frailty model

ÖZET Amaç: Mevcut makale Hindistan, Delhi'deki antiretroviral tedavi gören HIV/AIDS hastalarının sağkalımlarını etkileyen prognostik faktörleri tahmin etmek amacıyla gamma ve ters Gauss zayıflık dağılımlı hızlandırılmış başarısızlık zamanı (AFT) modelinin uygulanmasını göstermektedir. **Gereç ve Yöntemler:** Bu iki modelin sonuçları zayıflık modeli olmadan karşılaştırılmıştır. HIV/AIDS verileri için en iyi modeli seçmek için Akaike Bilgi Kriteri (AIC) ve Bayes Bilgi Kriteri (BIC) kullanılmıştır. **Bulgular:** Prognostik faktörler; cinsiyet, bulaşma biçimi, başlangıç hemoglobin ve ağırlık ART'deki HIV/AIDS hastalarında istatistiksel olarak anlamlı bulunmuştur (p<0,05). Temel dağılım olarak lognormalli Gamma paylaşımlı zayıflık modeli HIV/AIDS hastaları için en iyi model olarak bulunmuştur. Model ayrıca HIV/AIDS hastalarında yüksek derecede heterojenlik olduğunun güçlü kanıtını yansıtmaktadır. **Sonuç:** Bu nedenle HIV/AIDS verilerinin analizi için paylaşılan zayıflık modeli zayıflık modeli olmayan modelden daha uygun bir yaklaşımdır.

Anahtar Kelimeler: AIDS; ART; Gamma paylaşımlı zayıflık modeli; ters Gauss paylaşımlı zayıflık modeli

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CD4 cell counts are a very important type of white blood cells that orchestrates the immune response of the body. It is widely used as a clinical biomarker for HIV disease progression and eligibility criterion to start antiretroviral therapy of HIV/AIDS infected individuals. CD4 cell counts are a primary target of the human immune deficiency virus (HIV), because of its central role in controlling immune response. It is well known that higher CD4 cell count typically signifies healthier immune system. CD4 cell counts vary over time across the study population due to a variety of demographic, environmental, immunological and genetic factors that probably persist

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throughout the course of HIV infection.[1] This variability can lead to increasing differences in immune systems, exposure to infection and also in the composition of the study populations. Patients with lower CD4 counts have lesser chance of survival. In survival analysis we ignore this heterogeneity and implicitly assume that all the patients under study have same risk of death if they have same values of covariates. By ignoring the presence of unobserved heterogeneity will produce incorrect estimates of parameter in survival analysis. These differences of risk in the population can be modeled by taking into account the unobserved heterogeneity or using a frailty model. A frailty is an unobservable random effect shared by subjects within a subgroup, or in simply a frailty is an unobserved random proportionality factor that modifies the hazard function of an individual or related individual. It is recognized that individuals in the same family are more similar than the individuals in different families because they share similar genes and similar environment. Here we have used a shared frailty model to study the cluster variation (based on the ranges of CD4 cell counts) effect on the survival of HIV/AIDS patients, which cannot be explained by the covariates itself. The shared frailty model is a mixture model because the common risk in each cluster (the frailty) is assumed to be random. The model assumes that all the event times in a cluster are independent given the frailty variables. In other words, it is a conditional independence model where the frailty is common to all individuals in a cluster and therefore responsible for creating dependence between event times. This is the reason a shared frailty model can be expressed as a mixed (random effects) model in survival analysis with group variation (frailty) and individual variation described by the hazard function.[2] Thus frailty or random effect models try to account for correlations within groups. It is worth pointing out that applying the general Cox proportional hazard model or the accelerated failure time model directly to a cluster data set without considering the possible correlations in each cluster may lead to incorrect conclusions.[3]

Vaupel et al. introduced the term frailty in order to account for unobserved heterogeneity, random effects and association in univariate survival model.[4] Clayton discussed the application of the model to multivariate survival data (without using the notion "frailty") in his seminal paper on chronic diseases incidence in families.[5] Frailty models are extension of Cox proportional hazard model, in this model the hazard rate will not just be a function of covariates but also a function of frailties.[6] Shared frailty model is extensively studied by many authors.[7-9]

Zare and Moradi applied parametric shared frailty models to waiting time to first pregnancy and found that height, age at marriage and menstruation regularity to be important predictors of waiting time to pregnancy.[10] Mahmood et al. used a shared frailty model to identify important factors associated with length of birth intervals of Bangladeshi women.[11] Govindarajulu et al. has applied the methodology to choose between frailty and no- frailty models in assessing genetic variability and found sex and birth year as significant covariates.[12] Dias et al. used a Cox proportional hazard model with frailty to identify independent predictors of hospital mortality in HIV associated hospitalizations in Portugal.[13] Kong et al. applied a parametric frailty model to examine the relationship between explanatory variables and the survival outcomes that are subject to arbitrary censoring, while accounting for the correlation within clusters for HPV infection data.[14]

Although there are several studies to estimate the effect of prognostic factors on the survival of HIV/AIDS patients, but none has considered the longitudinal CD4 cell counts as cluster variable to the best of our knowledge, and this is the first investigation about the factors influencing survival of HIV/AIDS patients on ART by using Accelerated Failure Time (AFT) shared frailty model.

In order to study the effect of ART on improvement in the longevity and quality of life, it is imperative to consider the ranges of CD4 cell counts as cluster variable i.e (cluster 1; <200 cells/mm^3, cluster 2; 201-350 cells/mm^3, cluster 3;

351-500 cells/mm^3, and cluster 4; >500 cells/mm^3). A Gamma shared frailty and an inverse Gaussian shared frailty model with baseline distributions as exponential, weibull, log normal and log-logistic have been applied to estimate the effect of prognostic factors on the survival of HIV/AIDS patients on ART. The results of both these models have been compared to without frailty model. In order to compare the performance of these models we have used Akaike Information Criterion (AIC) and Bayesian Information criterion (BIC).

The remainder of this paper is organized as follows. In section 2, AFT shared frailty models are discussed, and in section 3 we have applied these models to HIV/AIDS data set. Finally the results and discussions are presented in section 4.

MATERIAL AND METHODS

AFT MODEL WITH SHARED FRAILTY FOR HIV/AIDS PATIENTS

The AFT shared frailty model is an appropriate choice for multivariate clustered survival time data, especially when observations within a cluster share a common unobservable frailty. It explicitly takes into account the possible correlation among failure times.

AFT models have been received much attention in recent years. Klein et al. considered a lognormal regression model with shared lognormal frailty to account for dependence between the observed survival times.[15] Pan proposed the AFT frailty model by assuming a frailty structure on the error term, which is called the AFT gamma frailty model.[16] Xu and Zhang developed a stable estimation procedure for semi parametric gamma frailty AFT model.[17] Lambert et.al. used parametric AFT models with frailty effect to kidney transplant survival data.[18]

Suppose Y_{ij}(=log T_{ij}) be the logarithm of the survival time of the jth HIV/AIDS patient in the ith cluster, (j=1, 2,…n_i, and i= 1,2…m), and X_{ij} be the vector of covariates associated with this individual. Then the shared AFT frailty model is given by

$$Y_{ij} = \log(T_{ij}) = \mu + X'_{ij}\beta + U_i + \sigma \in_{ij} \qquad (1)$$

where β is the vector of unknown regression coefficients μ is the intercept parameter, σ is the scale parameter, the $\in_{ij}$'s are independent identically distributed random errors, and the U_i's are the cluster specific random effects which are assumed to be i.i.d random variable with density function $f(u_i)$. Here we have assumed that the shared frailty (random) effect U_i following gamma and inverse Gaussian distribution with mean zero and variance θ, as defined in the density function in equation (2) and (3) respectively.

$$f(u) = \frac{u^{\frac{1-\theta}{\theta}} \exp\left(\frac{-u}{\theta}\right)}{\theta^{\frac{1}{\theta}}\sqrt{\left(\frac{1}{\theta}\right)}} \qquad u > 0 \qquad (2)$$

$$f(u) = \left(\frac{1}{2\Pi\theta u^3}\right)^{\frac{1}{2}} \exp\left(\frac{-(u-1)^2}{2\theta\Pi}\right) \qquad u > 0, \theta > 0 \qquad (3)$$

Where θ >0, indicates presence of heterogeneity. So the large values of θ reflect a greater degree of heterogeneity among groups and a stronger association within groups. The choice of gamma and inverse Gaussian distribution as frailty distributions are its mathematical convenience. In these models, frailty could be considered as an unobserved covariate that is additive on the log failure time scale and describe some reduced or increased event times for different clusters. All observations within a cluster share a common unobserved random effect.

Now the conditional survivor function and hazard function for the jth individual of ith cluster has the form

$$S_{ij}(t/u_i) = S_0\left(\frac{\log t_{ij} - \mu - X'_{ij}\beta}{\sigma}\right.$$

$$h_{ij}(t/u_i) = \frac{1}{\sigma t_{ij}} h_0\left(\frac{\log t_{ij} - \mu - X'_{ij}\beta - U_i}{\sigma}\right/U_i)$$

Where $S_0(.)$ and $h_0(.)$ is the survivor and hazard function of $\in_{ij}$ respectively, and β is a vector of fixed effects associated with a vector of covari-

ates X_{ij} measured on the j^{th} individual in the i^{th} cluster.

From equation (1), we have $\in_{ij} = \frac{\log t_{ij} - \mu - X'_{ij}\beta - U_i}{\sigma}$,

Then the conditional survivor function and hazard function can be written as

$$S_{ij}(t/u_i) = S_0(\in_{ij}/U_i) \quad (4)$$

$$h_{ij}(t/u_i) = \frac{1}{\sigma t_{ij}} h_0(\in_{ij}/U_i) \quad (5)$$

Here we have considered the error term $\in_{ij}$ follows exponential, Weibull, lognormal and log-logistic distributions.

MAXIMUM LIKELIHOOD ESTIMATION

Let m denote the number of clusters and n_i denote the sample size within the i^{th} cluster, if the censoring is assumed to be independent of survival, then the conditional likelihood (conditional on the random effects) for the observed data is given by

$$L_c = \prod_{i=1}^{m}\prod_{j=1}^{n_i}\left[\frac{1}{\sigma t_{ij}} h_0(\in_{ij}/u_i)\right]^{\delta_{ij}} S_0(\in_{ij}/u_i) \quad (6)$$

Where δ_{ij} takes value 0, if j^{th} HIV/AIDS patient's survival time in the i^{th} cluster is censored, and takes value 1, otherwise. Integrating out the unobserved frailties Ui, the marginal likelihood function for all clusters can be expressed as

$$L_m = \prod_{i=1}^{m}\int\prod_{j=1}^{n_i}\left[\frac{1}{\sigma t_{ij}} h_0(\in_{ij}/u_i)\right]^{\delta_{ij}} S_0(\in_{ij}/u_i)\ f(u_i)\ du_i \quad (7)$$

Now the estimates of parameters can be obtained by maximizing the likelihood function (7) with respect to σ, β and θ. Since the integration involved in equation (7) is analytically intractable, MCMC or Laplace approximation to the integral can be used to evaluate the exact log-likelihood numerically.

Results obtained from AFT shared frailty models can be summarized in the exponentiated form as time ratio (i.e TR(=exp(β)) unlike Cox model hazard ratio. Thus TR>1, indicates prolonged survival time and TR<1, associated with a decrease in survival time.

MODEL COMPARISON

In order to compare gamma shared frailty and inverse Gaussian shared frailty model with different baseline distributions, we have used Akaike Information Criterion (AIC)[19] and Bayesian Information Criterion (BIC). The AIC provides an attractive basis for model selection and is defined as

AIC= -2*Log-likelihood +2(p+k)

where p is the number of covariates in the model, k=1 for exponential and k=2 for weibull and lognormal models. The model with smaller AIC is termed as better model. The AIC penalizes the number of parameters less strongly than the BIC[20] and it is defined as

BIC= -2*Log-likelihood + p.log(n)

where p represents the number of covariates in the model and n represents the number data points. The main advantage of the BIC approximation is that it includes the BIC penalty for the number of parameters being estimated. The model with smallest BIC values is chosen as the best model.

APPLICATIONS TO HIV/AIDS DATA

We have considered 1259 adult (>18 years age) HIV/AIDS patients who were undergoing Antiretroviral Therapy in the ART centre of Dr. Ram Manohar Lohia Hospital, New Delhi, India, during the period April 2004 to November 2009, and were followed up through the ART routine register records till December 2010. The event of interest was time to death. Out of 1259 patients 198 patients died by the end of the study. The baseline information such as age, sex, last available CD4 count, mode of transmission (MOT), weight and hemoglobin were collected. These variables were entered into the model as categorical variables - Sex (male/female), MOT (sexual/Blood+IDU/Unknown) and continuous variables- Age, Hemoglobin and Weight. The category 'sexual' of the covariate MOT included both Homosexual and Heterosexual transmissions. The ranges CD4 cell counts used as cluster variable i.e (<200 cells/mm^3, 201-350 cells/mm^3, 351-500

cells/mm^3, and >500 cells/mm^3) and the clusters having 21.4%, 32.0%, 24.8% and 21.8% patients respectively. Patients who were alive at the end of the study period, were treated as right censored. The "survival" and "frailtypack" package of R software version 3.0.2 has been used to perform the statistical analyses. In all cases, $p < 0.05$ is defined as the statistical significant.

The descriptive statistics are given in Table 1. Out of 1259 patients, 67.6% were males and 32.4% were females. The predominant mode of HIV transmission was sexual route, which includes both homo and hetro sexual transmission, 64% were sexually transmitted patients, 9.7% patents were transmitted by blood and injecting drug use, for remaining 26.3% patients mode of transmission was not known. The mean age at diagnosis was 34.24(± 8.24) years whereas the mean weight at the time of enrolment was 50.10 (±10.5) kg. In order to investigate the effect of covariates on the time to death of HIV/AIDS patients on ART, we first did a univariate analysis by fitting separate model for each covariate. Covariates that were found to be significant in the univariate analysis were included in multivariable analysis. We performed multivariable survival analysis by assuming exponential, weibull, lognormal and loglogistic distributions for baseline hazard functions; and the gamma and inverse Gaussian frailty distributions.

TABLE 1: Descriptive characteristic of HIV/AIDS patients on ART.

Variables	Category (Code)	N=1259	Percent
Sex	Male (0)	851	67.6
	Female (1)	408	32.4
MOT	Sexual (1)	806	64.0
	Blood+ IDU (2)	122	9.7
	Unknown(3)	331	26.3
CD4+ cell counts	<200 (1)	236	21.4
	201-350 (2)	352	32.0
	351-500 (3)	273	24.8
	>500 (4)	240	21.8
Status	Alive (0)	1061	84.3
	Death (1)	198	15.7
Hemoglobin	10.97±1.87 Mean± SD		
Weight	50.10±10.5 Mean± SD		
Age (in years)	34.24±8.24 Mean± SD		

TABLE 2: AIC and BIC values of the parametric AFT shared frailty models.

Baseline distributions	Frailty distributions	AIC	BIC
Exponential	Gamma	1260.926	1300.957
	Inverse Gaussian	1261.312	1301.344
Weibull	Gamma	1262.819	1307.855
	Inverse Gaussian	1263.207	1308.242
Lognormal	Gamma	**1191.105**	**1236.141**
	Inverse Gaussian	**1194.307**	**1237.454**
Log-logistic	Gamma	1248.60	1338.66
	Inverse Gaussian	1243.007	1336.120

The AIC and BIC values of the different parametric AFT models with gamma and inverse Gaussian shared frailty models are shown in Table 2. The AIC and BIC values of lognormal baseline distribution with gamma frailty model are found to be minimum among all other considered models, indicating that it is the most efficient model to describe the HIV/AIDS dataset using various parametric frailty models.

Table results of only gamma and inverse Gaussian shared frailty model with lognormal baseline distribution has been given in Table 3, which was found to be best model for HIV/AIDS patient data. The estimated values, standard error, time ratio, estimated parameters of baseline distributions and frailty variance (σ^2) are presented in the table 3. The lognormal with gamma shared model shows that the prognostic factors sex, MOT, baseline hemoglobin and weight are statistically significant (P-value <0.05) for HIV/AIDS patients on ART, whereas age is not found to be a significant factor for HIV/AIDS patients. Female patients had longer survival by a factor of 3.04 than their male counterpart (TR>1). An increase in survival time is associated with per unit increase in hemoglobin. Patients with sexual mode of transmission are found to have lesser survival than those with Blood + IDU mode of transmission (TR<1). An increase in weight (in kg) leads to increase in life expectancy.

TABLE 3: AFT Model with Shared Frailty for HIV/AIDS patients on ART.

	Lognormal (No frailty)			Lognormal (Gamma)			Lognormal (Inverse Gaussian)		
Parameters	β	**TR**	**Std.error**	β	**TR**	**Std.error**	β	**TR**	**Std.error**
Age	-0.017	0.983	0.014	-0.002	0.998	0.011	-0.002	0.998	0.011
Sex	1.842	6.309	0.322***	1.112	3.040	0.245***	1.113	3.040	0.245***
MOT									
Sexual	Ref	1		Ref	1		Ref	1	
Blood+IDU	-0.509	0.601	0.352	-0.722	0.486	0.276***	-0.724	0.485	0.276***
Unknown	1.418	4.128	0.431**	1.379	3.971	0.340***	1.378	3.967	0.340***
Hemoglobin	0.400	1.491	0.069***	0.225	1.252	0.051***	0.225	1.252	0.050***
Weight	0.097	1.101	0.015***	0.054	1.055	0.011***	0.054	1.055	0.011***
Intercept	-2.219				2.324			1.488	
λ	2.69				0.206			0.332	
γ	0.446				0.680			0.680	
Frailty (σ^2)	_				2.06***			4.32***	
Kendall's τ					0.507			0.089	

TR: Time Ratio, λ= Scale, γ=Shape, *indicates significance at the 5% level, ** at 1% level and *** at 0.1% level.

The estimates obtained by *inverse* Gaussian shared frailty model are very close to the results obtained by the gamma shared frailty models, indicating robustness of the analysis with respect to the choice of the baseline hazard function. The value of shape parameter in the lognormal-gamma shared frailty model is (γ=0.680), which is less than unity indicating that the shape of hazard function is unimodal.

The results of both the models indicates that there exist significant heterogeneity (σ^2) in the population in terms of their CD4 cell count, even though each patients share the same value of the covariate. For comparison purpose we have also applied the lognormal AFT model without frailty. These results are shown in the same table 3, the factors that are found to be significant in frailty model are also found to be significant in without frailty model. The variability (heterogeneity) in the population of clusters (in terms of ranges of CD4 cell counts) estimated by lognormal with gamma shared frailty is 2.06. The Kendall's tau (τ) is higher for higher values of (σ^2) which measures the association within the clusters. The estimated τ=0.507 shows that there is strong dependence within the clusters for lognormal gamma frailty model. From the Cox-Snell residual plot in Figure 1, we can ascertain that all the AFT models are fitted well to the data. However, the plot is more close to the line in case of lognormal model; supporting the claim that lognormal model is the best fit.

DISCUSSION

This paper focuses on Accelerated failure time shared parametric frailty models, which implies parametric specification of the baseline hazard and the distribution of the frailty. Here we have considered four clusters based on the ranges of CD4 cell counts of HIV/AIDS patients on ART for potential dependence in the random quantities corresponding to each failure time which is induced by frailty. Gamma shared frailty and an inverse Gaussian shared frailty model with baseline distribution as exponential, weibull and log normal have been applied to estimate the effect of prognostic factors on the survival of HIV/AIDS patients on ART. The results of both of these models have also been compared to without frailty model.

The prognostic factors viz. sex, MOT, baseline hemoglobin and baseline weight are found to be statistically significant (P< 0.05) by both gamma and inverse Gaussian shared parametric AFT Model. Most of the previous studies have suggested that the age is a significant prognostic

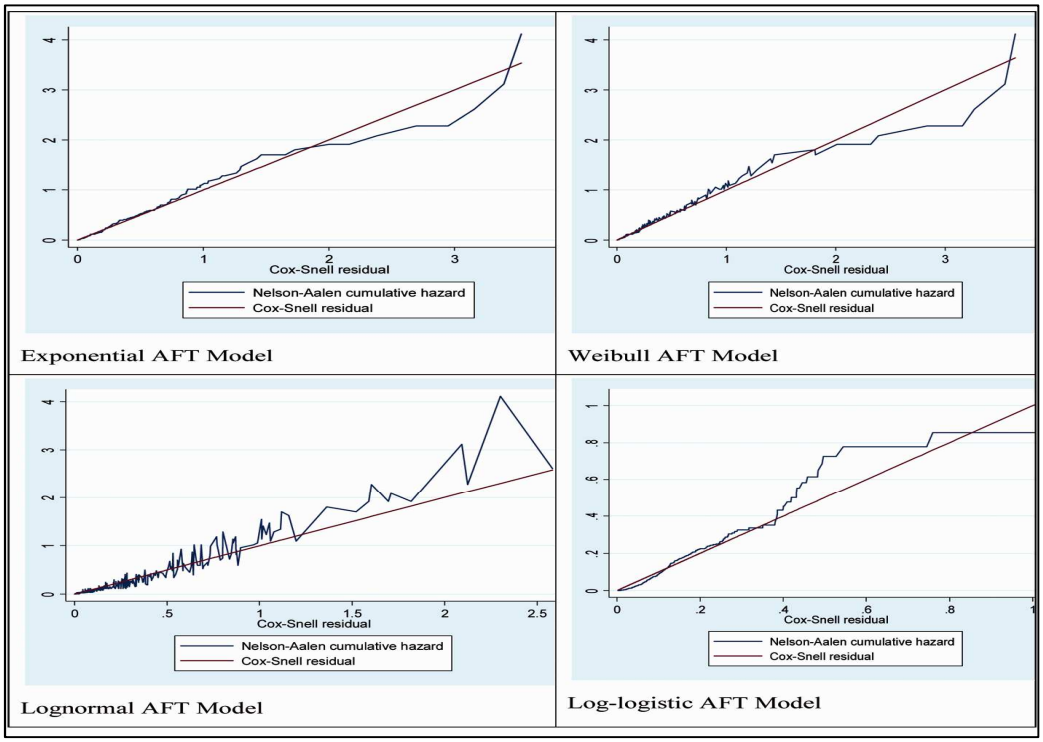

FIGURE 1: Cumulative hazard plot of Cox-Snell residual for AFT models.

factor.[21,22] As age increases the survival time of HIV/AIDS patient decreases. Old age is associated with high risk of disease progression but in our analysis age is not found to be a significant prognostic factor. Also females are observed to have better survival than their male counterpart. As reported previously female had higher life expectancies than male.[23-26]

Another important result of our study is that patients with sexual (hetro or homo) mode of transmission have worst survival than patients with blood and intravenous drug user mode of transmission. However, Remafedi et al.[27] have shown that there are no significant differences between deceased and other subjects in relation to mode of transmission. Baseline hemoglobin is found to be a significant factor for HIV/AIDS patients, and thus it can be used as a simple and practical tool for initial risk assessment in the absence of CD4 cell count and viral load, as is identified in earlier studies by Johannessen et al. in Tanzania and Mocroft et al. in Europe.[28,29] Patient's weight is positively associated with survival, this is corroborating to the findings of other studies that patients improved clinically with regard to weight and hemoglobin.[21,23]

Nevertheless, in all cases the estimates of the frailty variance for all the models reflects that there is strong evidence of high degree of heterogeneity in the HIV/AIDS patients. The Kendall's tau also supports the strong association within the clusters. Therefore shared frailty model is an appropriate approach for analyzing the HIV/AIDS data than without frailty model. This is consistent to the findings of previous studies.[12,30]

From the AIC and BIC values we can conclude that the gamma shared frailty model with lognormal as baseline distribution is the best model for HIV/AIDS patients data. Hence, a survival model needs to be chosen arbitrarily to fit event times, the baseline hazard function as well as the frailty distribution should be compared and the most appropriate model should be selected for appropriate inference. Mixture of methods involving both quantitative and qualitative approaches could be employed for further understanding of the unmeasured variables. It will be very much helpful for treatment provider to fo-

cus on important prognostic factors for which interventions could be developed or existing ones enhanced to improve patient management and care.

There are some limitations to our study; first, we have assumed that only positive association within the cluster, which is not always possible. Second, the unobserved risk factors to be same within a cluster, which is not reasonable. The study uses data of only one ART centre, so the finding of our study may be generalized at national level with utmost care. This can be further analyzed by using a correlated frailty model.

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REFERENCES

1. Mair C, Hawes SE, Agne HD, Sow PS, N'doye I, Manhart LE, et al. Factors associated with CD4 lymphocyte counts in HIV-negative Senegalese individuals. Clin Exp Immunol 2008;151(3):432-40.
2. Wienke A, , Frailty models in survival analysis, Chapman & Hall/CRC, Boca, Raton, 2011.
3. Chen P, Zhang J, Zhang R. Estimation of the accelerated failure time frailty model under generalized gamma frailty. Computational Statistics and Data Analysis 2013;62:171-80.
4. Vaupel JW, Manton K, Stallard E. The impact of heterogeneity in individual frailty on the dynamics of mortality. Demography 1979;16(3):439-54.
5. Clayton D. A model for association in bivariate life tables and its application in epidemiological studies of familial tendency in chronic disease incidence. Biometrika 1978;65(1): 141-51.
6. Cox DR. Regression models and life tables. Journal of Royal Statistical Society Series B (Methodological) 1972;34(2):187-220.
7. Hougaard P. Analysis of Multivariate Survival Data. 1st ed. New York: Springer; 2000. p.542.
8. Therneau TM, Grambsch PM. Modeling Survival Data: Extending Cox Model. 1st ed. New York: Springer; 2000. p.350.
9. Duchateau L, Janssen P. The Frailty Model. 1st ed. New York: Springer Verlag; 2008. p.316.
10. Zare N, Moradi F. Parametric frailty and shared frailty models applied to waiting time to first pregnancy. International Conference on Applied Mathematics and Pharmaceutical Sciences 2012;598-600.
11. Mahmood S, Zainaba B, Latif Mahbub AHM. Frailty modeling for clustered survival data: an application to birth interval in Bangladesh. Journal of Applied Statistics 2013;40(12): 2670-80.
12. Govindarajulu US, Lin H, Lunetta KL, D'Agostino RB Sr. Frailty models: applications to biomedical and genetic studies. Stat Med 2011;30(22):2754-64.
13. Dias SS, Andreozzi V, Martins MO, Torgal J. Predictors of mortality in HIV-associated hospitalizations in Portugal: a hierarchical survival model. BMC Health Serv Res 2009;9:125.
14. Kong X, Archer KJ, Moulton LH, Gray RH, Wang MC. Parametric frailty models for clustered data with arbitrary censoring: application to effect of male circumcision on HPV clearance. BMC Med Res Methodol 2010;10:40.
15. Klein JP, Pelz C, Zhang MJ. Modeling random effects for censored data by a multivariate normal regression model. Biometrics 1999;55(2):497-506.
16. Pan W. Using frailties in the accelerated failure time model. Lifetime Data Analysis 2001;7(1):55-64.
17. Xu L, Zhang J. An EM-like algorithm for the semi parametric accelerated failure time gamma frailty model. Computational Statistics and Data Analysis 2010;54(6):1467-74.
18. Lambert P, Collett D, Kimber A, Johnson R. Parametric accelerated failure time models with random effects and an application to kidney transplant survival. Stat Med 2004;23(20):3177-92.
19. Akaike H. A new look at the statistical model identification. IEEE Transactions on Automatic Control 1974;19(6):716-23.
20. Schwarz G. Estimating the dimension of a model. Ann Statist 1978;6(2):461-4.
21. Bachani D, Garg R, Rewari BB, Hegg L, Rajasekaran S, Deshpande A, et al. Two-year treatment outcomes of patients enrolled in India's national first-line antiretroviral therapy programme. Natl Med J India 2010;23(1):7-12.
22. Ghate M, Deshpande S, Tripathy S, Godbole S, Nene M, Thakar M, et al. Mortality in HIV infected individuals in Pune, India. Indian J Med Res 2011;133:414-20.
23. Grover G, Das R, Swain PK, Deka B. On the estimation of survival of HIV/AIDS patients on antiretroviral therapy using NPMLE method: an application to interval censored data. American Journal of Mathematics and Statistics 2013;3(4):213-9.
24. Antiretroviral Therapy Cohort Collaboration. Life expectance of individuals on combination antiretroviral therapy in high income countries: a collaborative analysis of 14 cohort studies. Lancet 2008;372(9635):293-9.
25. Farzadegan H, Hoover DR, Astemborski J, Lyles CM, Margolick JB, Markham RB, et al. Sex differences in HIV-1 viral load and progression to AIDS. Lancet 1998;352(9139):1510-4.
26. Donnelly CA, Bartley LM, Ghani AC, Le Fevre AM, Kwong GP, Cowling BJ, et al. Gender difference in HIV-1 RNA viral loads. HIV Med 2005;6(3):170-8.
27. Remafedi G, Lauer T. Survival trends in adolescents with human immunodeficiency virus infection. Arch Pediatr Adolesc Med 1995;149(10): 1093-8.
28. Johannessen A, Naman E, Ngowi BJ, Sandvik L, Matee MI, Aglen HE, et al. Predictors of mortality in HIV-infected patients starting antiretroviral therapy in a rural hospital in Tanzania. BMC Infect Dis 2008;8: 52.
29. Mocroft A, Kirk O, Barton SE, Dietrich M, Proenca R, Colebunders R, et al. Anaemia is an independent predictive marker for clinical prognosis in HIV-infected patients from across Europe. EuroSIDA study group. AIDS 1999;13(8):943-50.
30. Raman TT, Venkatesan P. Accelerated failure time frailty model in survival analysis. International Journal of Science and Technology 2012;2(2):65-9.