

AN EXTENSION OF MULTISTATE HAZARDS MODELS FOR TRANSITIONS AND REVERSE TRANSITIONS

ABU HENA M. MAHBUB-UL LATIF

Institute of Statistical Research and Training

and

M. ATAHARUL ISLAM

Department of Statistics

University of Dhaka, Dhaka-1000, Bangladesh.

SUMMARY

The multistate hazards model, where more than one intercommunicating states are taken into consideration to explain the transition from one state to another over time, provide more realistic interpretations of the data from a prospective study. A multistate hazard model for transition and reverse transition for longitudinal data is illustrated in this paper. Simple test procedures for the parameters and the different transition probabilities of the proposed model is also calculated. This proposed model is flexible enough to include unequal number of covariates in different transitions and provide us more realistic interpretations of the data. The potential risk factors at the transitions and reverse transitions, can be identified from this model, where the results can be compared in relative terms. As an example the proposed model is applied to the longitudinal data from Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (*BIRDEM*). The results based on proposed models, revealed some important features of the patients in terms of their status regarding the disease which could not be obtained by using the existing models.

Key Words and Phrases: Hazards Model, Reverse Transition, Diabetes Mellitus.

1. INTRODUCTION

In longitudinal studies, information about different subjects are collected at different time points as the subjects are observed in relation to an event of interest for a specified period of time. The data collected from this type of studies involved repeated observations that deals with change in the status under consideration. The use of traditional statistical models where the models are based on only one transient state is not adequate for analyzing such data. Hence we need to employ multistate analysis where more than one intercommunicating states can be taken into consideration to explain the transitions from one state to another over time.

In the class of multistate hazards model Lagakos (1976) proposed a stochastic model by allowing censored observation in the analysis. To define this model, two health and one death state with only one way forward transition between states are allowed. Other noteworthy highlights in Lagakos's model are, this model assumed that the observed survival times are exponentially distributed and the information about the occurrence of an auxiliary event is used in the analysis of this model. As an extension of the model developed by Lagakos (1976), Beck (1979) proposed a stochastic model for survival data analysis that incorporates covariates. No direct reverse transition between two health states are allowed in this model. The provision of using different covariates in different transitions makes this model more general than Chiang's (1980) illness-death process. Beck's model is only flexible for time independent covariates.

To include time dependent covariate in the multistate framework, Kay (1982) proposed an extension of Cox's (1972) proportional hazards model. The defined likelihood function in this model is similar to that of Cox's model except the definition of risk set. This model includes several health state but reverse transition is not considered. In 1994 Islam proposed an extension of Kay's (1982) model which incorporates reverse and repeated transition. Since non-constant hazard rates are assumed in these two models, the estimation procedure becomes complicated for a large number of nuisance parameters. In 1984 Klein et al. proposed another multistate hazard model which is applicable for only one time dependent covariate based on a hierarchical approach. Anderson et al. (1993) discussed the multistate hazards model in counting process framework.

In this study, the model proposed by Beck (1979) is extended for transitions and reverse transitions and is applied to the diabetes mellitus data from Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (*BIRDEM*), to show the utility of such models in real life situations. This model is also used to predict future disease status for an individual by using their given information about different covariates. Diabetes is such a disease that the disease status of an individual having diabetes mellitus is frequently changed over time. These changes may be attributed to several factors. On the basis of information about these changes over time with corresponding covariates for each individual, in this study we use a multistate analysis to identify the important factors which may influence the transitions from one

state to another state of the disease. We can also examine and compare the characteristics of individuals that influence transitions and reverse transitions. In constructing this model, we try to overcome the limitations of the existing models which are inadequate to cover the changes in respect of diabetes mellitus.

2. AN EXTENSION OF BECK'S APPROACH

In the previous section it has been noted that one of the limitations of Beck's model is that it can not be used for reverse or repeated transitions. To include reverse transitions in the model, Beck's suggestion to allow new states in the model has been adopted in this study. To construct such model it is assumed that the survival times are exponentially distributed.

2.1 THE MODEL

The blood glucose level (*BGL*) is a measure of glucose concentration in blood which is usually used to establish the diagnostic status of diabetes mellitus. In this study we only consider non-insulin dependent diabetes mellitus (*NIDDM*). The *NIDDM* can be classified in terms of impaired glucose tolerance (*IGT*) and diabetes mellitus (*DM*), where *IGT* denotes borderline diabetes and *DM* denotes confirmed diabetes. Those who use insulin are treated as insulin dependent diabetes mellitus (*IDDM*) in this study. In this study, it is assumed that initially all the individuals were *IGT* at the time of registration at *BIRDEM*. The disease status of diabetes mellitus is not changed frequently. Usually a patient visit, *BIRDEM* when some problem arise. That is, for a specific visit if the disease indicator is changed then the exact transition time and the time of patient's visit do not differ substantially. In this study, the patient's follow-up times are considered as their exact transition/survival times. Moreover, in this type of multistate frame Anderson, Hansen and Keiding (1991) showed that the transition probabilities are not changed significantly under this assumption when it is not correct.

For the proposed model we consider four states of which one is absorbing "death" state and others are transient "health" states and can defined in respect of diabetes mellitus as follows:

- s_1 : State for the patient having $BGL \leq 11.1$ mmol/litre, i. e. for *IGT*,
- s_2 : State for the patient having $BGL > 11.1$ mmol/litre, i. e. *DM*,
- s_3 : Controlled *DM* (*CDM*) state i. e. having *BGL* level same as state s_1 ,
- s_4 : State for the patient who use insulin, i. e. *IDDM*.

Among the patients who were in state s_1 at the time of entering into the study is selected for our analysis. We used all the available information from these patients till the end of study period to estimate different parameters and to obtain different useful probabilities by using the proposed model. For computational simplicity, we consider the patient's information upto the first order reverse transition and we exclude the information after that transition for an application of this model.

To construct the proposed model we also assume that the patients who enter a new state can not return to the previous state. And under this assumption we consider the following transitions

- (i) $s_1 \longrightarrow s_2$
- (ii) $s_1 \longrightarrow s_2 \longrightarrow s_3$
- (iii) $s_1 \longrightarrow s_4$
- (iv) $s_1 \longrightarrow s_2 \longrightarrow s_4$
- (v) $s_1 \longrightarrow s_2 \longrightarrow s_3 \longrightarrow s_4$.

Here the transition $s_1 \longrightarrow s_2 \longrightarrow s_3$ gives the first order reverse transition. At the end of the study the patients who were observed in state s_4 are considered to be in the state of failure and remaining observations are considered to be censored in the context of such transition.

A flow diagram of the proposed model with associated hazard functions is demonstrated below:

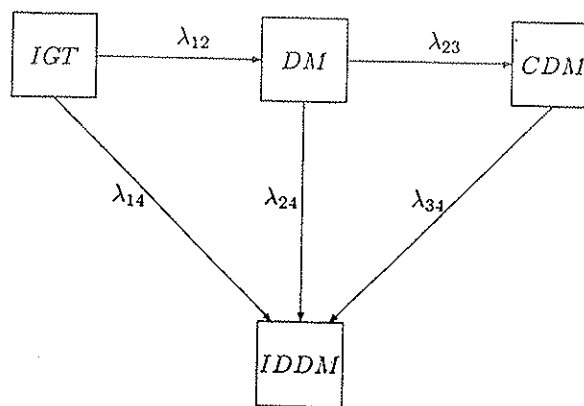


Figure 1

A Flow Diagram for Displaying the Transitions among States of Diabetes Mellitus.

Let t_{ji} , $j = 1, 2, 3$ be the exact time that the i th individual $i = 1, 2, \dots, n$ spends in the state s_j . Now corresponding to different transitions let us define hazard rates which are function of covariates but independent of time are given below:

$$\left. \begin{aligned} \lambda_{12i} &= \lambda_{120} e^{z_{12i} \beta_{12}} \\ \lambda_{14i} &= \lambda_{140} e^{z_{14i} \beta_{14}} \\ \lambda_{23i} &= \lambda_{230} e^{z_{23i} \beta_{23}} \\ \lambda_{24i} &= \lambda_{240} e^{z_{24i} \beta_{24}} \\ \lambda_{34i} &= \lambda_{340} e^{z_{34i} \beta_{34}} \end{aligned} \right\} \quad (2.1)$$

where λ_{120} , λ_{230} , λ_{140} , λ_{240} , and λ_{340} are the arbitrary baseline hazard functions, and β_{12} , β_{23} , β_{14} , β_{24} and β_{34} are the unknown vector of parameters corresponding to the covariates z_{12} , z_{23} , z_{14} , z_{24} and z_{34} , respectively.

2.2. ESTIMATION OF PARAMETERS

Now to obtain the m. l. e. of the parameters set $\theta = (\lambda, \beta)'$, let us define the indicator variable e_{jki} , for $j = 1, 2, 3$ and $k = 1, 2, 3, 4$ as

$$e_{jki} = \begin{cases} 1, & \text{if } i\text{th individual enters } s_k \text{ from } s_j, \\ 0, & \text{otherwise.} \end{cases}$$

In this case the vector λ and β takes the following form

$$\lambda = (\lambda_{120}, \lambda_{140}, \lambda_{230}, \lambda_{240}, \lambda_{340})', \quad \beta = (\beta_{12}, \beta_{14}, \beta_{23}, \beta_{24}, \beta_{34})'$$

and θ be a vector of order $b = (b_{12} + b_{23} + b_{14} + b_{24} + b_{34} + l)$, where $b_{kk'}$ be number of covariates are used for the transition $s_k \rightarrow s_{k'}$ and l be the number of underlying hazard rates.

By using the expression of defined hazard rates (1), the log-likelihood function of the parameter vector θ for this model can be written in the following form

$$\begin{aligned} \log L(\theta) = & \sum_{i=1}^n [-d_{1i}t_{1i}(\lambda_{120} e^{z_{12i}\beta_{12}} + \lambda_{140} e^{z_{14i}\beta_{14}}) - d_{3i}t_{3i}\lambda_{340} e^{z_{34i}\beta_{34}} + d_{2i}(\log \lambda_{120} + z_{12i}\beta_{12}) \\ & - d_{2i}t_{2i}(\lambda_{230} e^{z_{23i}\beta_{23}} + \lambda_{240} e^{z_{24i}\beta_{24}}) + d_{3i}(\log \lambda_{230} + z_{23i}\beta_{23}) + d_{4i}(\log \lambda_{140} + z_{14i}\beta_{14}) \\ & + d_{5i}(\log \lambda_{240} + z_{24i}\beta_{24}) + d_{6i}(\log \lambda_{340} + z_{34i}\beta_{34})]. \end{aligned} \quad (2.2)$$

where

$$\lambda_{1.i} = (\lambda_{12i} + \lambda_{14i}), \quad \lambda_{2.i} = (\lambda_{23i} + \lambda_{24i}), \quad \lambda_{3.i} = \lambda_{34i}$$

$$d_{1i} = e_{11i} + e_{12i} + e_{23i} + e_{14i} + e_{24i} + e_{34i}, \quad d_{2i} = e_{12i} + e_{23i} + e_{24i} + e_{34i}, \quad d_{3i} = e_{23i} + e_{34i},$$

$$\text{and } d_{hi} = e_{h'4i}, \text{ for } h = 4, 5, 6 \text{ and } h' = 1, 2, 3.$$

To obtain the maximum likelihood estimator of $\theta = (\lambda, \beta)$ we use Newton-Raphson iterative procedure and for the initial estimate of θ , let us consider the regressors have no effect, i. e. $\beta^{(0)} = 0$. Then the crude estimate of the baseline hazard rates $\lambda^{(0)}$ can be obtained by assuming that the first recorded time in new state is the exact time of entry into that state. Hence we have for transition from state s_k to s_l

$$\lambda_{kl}^{(0)} = \frac{\text{number of transitions from state } s_k \text{ to } s_l}{\text{total time spent in state } s_k}.$$

One can also take these initial estimates by using the prior information about the parameters to be estimated.

To infer about the parameter $\theta = (\lambda, \beta)$ we use simple Wald's test and likelihood ratio test procedure in this study. For instance, to test the significance of the covariate set we consider the null hypothesis $H_0: \beta = 0$, the test statistic

$$\chi^2 = -2 \log \left[\frac{L(\tilde{\theta})}{L(\hat{\theta})} \right]. \quad (2.3)$$

where $L(\tilde{\theta})$ be the likelihood function under null hypothesis and is obtained by using the m. l. e. of underlying hazards rates λ and parameters corresponding to the covariates $\beta = 0$ in the likelihood function, and $L(\hat{\theta})$ is

the likelihood function with the m. l. e. of full parameter set $\theta = (\lambda, \beta)$. This χ^2 follows chi-square distribution with 5 d.f.

2.3. ESTIMATION OF TRANSITION AND SURVIVAL PROBABILITIES

On the basis of the proposed model, we can easily obtain different transition and survival probabilities for a given covariate set which may help us for the prediction of the future disease status. The transition and survival probabilities for this model can be estimated from the following expressions:

The probability that the i th individual will not change his disease state s_1 during the interval $[0, t]$ is given as

$$\begin{aligned} P_{11i}(t) &= \Pr \{ \text{ith individual is in state } s_1 \text{ at time } 0 \text{ will} \\ &\quad \text{remain at state } s_1 \text{ at time } t \} \\ &= e^{-\lambda_{1,i} t}. \end{aligned} \quad (2.4)$$

An individual's probability for the transition from state s_1 to s_2 during the interval $[0, t]$ can be obtained from the following expression

$$\begin{aligned} P_{12i}(t) &= \Pr \{ \text{the } i\text{th individual is in state } s_1 \text{ at time } 0 \text{ will} \\ &\quad \text{be in state } s_2 \text{ at time } t \} \\ &= \frac{\lambda_{12i}}{(\lambda_{1,i} - \lambda_{2,i})} [e^{-\lambda_{2,i} t} - e^{-\lambda_{1,i} t}]. \end{aligned} \quad (2.5)$$

Similarly

$$\begin{aligned} P_{23i}(t) &= \Pr \{ \text{the } i\text{th individual is in state } s_1 \text{ at time } 0 \text{ will be in} \\ &\quad \text{state } s_2 \text{ at time } x \text{ and in } s_3 \text{ at time } t, \quad t > x \} \\ &= \frac{\lambda_{12i} \lambda_{23i}}{(\lambda_{1,i} - \lambda_{2,i})} \left[\frac{(e^{-\lambda_{3,i} t} - e^{-\lambda_{2,i} t})}{(\lambda_{2,i} - \lambda_{3,i})} - \frac{(e^{-\lambda_{3,i} t} - e^{-\lambda_{1,i} t})}{(\lambda_{1,i} - \lambda_{3,i})} \right]. \end{aligned} \quad (2.6)$$

Then we can easily obtain the survival probabilities of the i th patient at time t as

$$S_i(t) = P_{11i}(t) + P_{12i}(t) + P_{23i}(t) \quad (2.7)$$

i. e. $S_i(t)$ indicates the probability that i th individual will remain in the transient states during the interval $[0, t]$.

The death transition probabilities are obtained by the following relationships

$$\left. \begin{aligned} Q_{14i}(t) &= \frac{\lambda_{14i}}{\lambda_{1,i}} [1 - e^{-\lambda_{1,i} t}], \\ Q_{24i}(t) &= \frac{\lambda_{12i} \lambda_{24i}}{\lambda_{1,i} \lambda_{2,i} (\lambda_{1,i} - \lambda_{2,i})} [\lambda_{1,i} (1 - e^{-\lambda_{2,i} t}) - \lambda_{2,i} (1 - e^{-\lambda_{1,i} t})], \\ Q_{34i}(t) &= \frac{\lambda_{12i} \lambda_{23i} \lambda_{34i}}{(\lambda_{1,i} - \lambda_{2,i})} \left[\frac{\lambda_{2,i} (1 - e^{-\lambda_{3,i} t}) - \lambda_{3,i} (1 - e^{-\lambda_{2,i} t})}{\lambda_{2,i} \lambda_{3,i} (\lambda_{2,i} - \lambda_{3,i})} \right. \\ &\quad \left. - \frac{\lambda_{1,i} (1 - e^{-\lambda_{3,i} t}) - \lambda_{3,i} (1 - e^{-\lambda_{1,i} t})}{\lambda_{1,i} \lambda_{3,i} (\lambda_{1,i} - \lambda_{3,i})} \right]. \end{aligned} \right\} \quad (2.8)$$

Now by using the m. l. e. of θ in these expressions i. e. in the equation (2.4) to (2.8), we obtain the estimate of the different transition and survival probabilities associated with the proposed model.

3. AN EXAMPLE OF THE MODEL

3.1. DESCRIPTION OF THE DATA

The data set collected by *BIRDEM* is used for this example which is illustrated in this section. *BIRDEM* has been providing services to diabetic patients since 1956 and is the only source of data on diabetes in Bangladesh. The information on all the patients who visit *BIRDEM* since the first diagnosis of the disease until the death or loss to follow-up of the patients are recorded over time. In *BIRDEM*, a comprehensive record sheet is maintained for each patient. This record sheet contains information regarding patient's demographic and socioeconomic characteristics, family history, diet, physical conditions, clinical features, different medical investigations, etc. After each patient arrives at *BIRDEM*, they are interviewed by social officer, dieticians and doctors in order to fill-up this record sheet. In addition a follow-up sheet also maintained for collecting information from patient's each visit to *BIRDEM* after registration.

3.2. ANALYSIS AND DISCUSSION

Though *BIRDEM* has a large collection of data on diabetes mellitus, but for this study we have selected only those individuals who were registered in *BIRDEM* between January, 1984 to December, 1984 and belong to state s_1 at the time of registration. A total of 4382 patients were registered in the year 1984 and we only found 406 patients in state s_1 . The frequency distribution of the selected patients (Table 1) shows that about 70 percent of them are male and median age at registration is 46. In this study the number of transitions completed by the patients in the entire study period is shown in the following table.

Table 1

Observed number of Transitions During 1984-94 for the patients
Registered at *BIRDEM* in 1984

Type of transition	Number of transitions	Percentages
$s_1 \rightarrow s_1$	124	19.9
$s_1 \rightarrow s_2$	221	35.47
$s_1 \rightarrow s_4$	60	9.63
$s_1 \rightarrow s_2 \rightarrow s_4$	13	2.09
$s_1 \rightarrow s_2 \rightarrow s_3$	159	25.52
$s_1 \rightarrow s_2 \rightarrow s_3 \rightarrow s_4$	46	7.38
Total	623	100

Table 1 shows that about 20 percent of the patients do not change their status from *IGT* and about 35 percent moved from *IGT* to Diabetes Mellitus (*DM*) during the follow-up period. Slightly more than 25 percent of the patients return to *IGT* from *DM* and transitions to insulin dependent state s_4 from all other states is not large enough.

By using the selected variables (age and sex), three models are considered in this analysis which are:

Model *A*: Age is the only covariate in the model,

Model *B*: Sex is the only covariate in the model,

Model *C*: Age and sex are included in the model.

The estimated value of hazard rate, covariate corresponding age and sex for the Model *A*, *B* and *C* are displayed in following table 2.

Table 2
The Estimates of Different Parameters for Model *A*, *B*, and *C*
by Type of Transitions

Type of transition	Parameter	Model <i>A</i>	Model <i>B</i>	Model <i>C</i>
IGT to DM ($s_1 \rightarrow s_2$)	λ_{120}	.9987E-03†	.5251E-03†	.8977E-03†
	Age	-.1115E-01†	-	-.1126E-01†
	Sex	-	.2431	.1514
IGT to IDDM ($s_1 \rightarrow s_4$)	λ_{140}	.5455E-03†	.1598E-03†	.5522E-03†
	Age	-.2654E-01†	-	-.2655E-01†
	Sex	-	-.2775E-01	-.1800E-01
DM to CDM ($s_2 \rightarrow s_3$)	λ_{230}	.2498E-02†	.3101E-02†	.1921E-02†
	Age	.1640E-01†	-	.1126E-01†
	Sex	-	.6763†	.7524†
DM to IDDM ($s_2 \rightarrow s_4$)	λ_{240}	.3921E-04	.2163E-03	.3271E-04
	Age	.4917E-01 †	-	.4257E-01
	Sex	-	.8879	.7588
CDM to IDDM ($s_3 \rightarrow s_4$)	λ_{340}	.5177E-03	.5991E-03†	.4419E-03
	Age	.9620E-02	-	.7063E-02
	Sex	-	.3811	.1513
-2 Log Likelihood††		263†	74.62†	420.4†

† $p < 0.05$

††indicate the value of chi-square for testing the significance of covariate set

From Table 2, we observe that age has significant contribution in every transitions except *CDM* to *IDDM* in Model *A* and is negatively associated for both the transitions from *IGT* state. In case of underlying hazard function, we observe for both the transitions to *IDDM* from *DM* and *CDM* are non-significant. To test the significance of the covariate set $\beta = (\beta_{12}, \beta_{14}, \beta_{23}, \beta_{24}, \beta_{34})'$, we take the null hypothesis as

$$H_0 : \beta = 0.$$

For testing this null hypothesis, we use the likelihood ratio test procedure and the m. l. e. of λ is used to

obtain the value of conditional log-likelihood function. The table 2 indicates that age has significant effect for this model.

For Model *B*, table 2 also shows that, the variable sex has significant contribution only for the transition *DM* to *CDM*. The transition of the type *IGT* to *IDDM* does not appear to be significantly different for males and females. For all other types of transitions, males are more likely to move from one state to another. Like Model *A*, here the underlying hazard rate for all the transitions except *DM* to *IDDM* is significant. From Table 1 we observe that the number of transitions for *DM* to *IDDM* is only 2 percent of all the transitions. Like in Model *A*, by using the likelihood ratio test procedure, we get the covariate set is significant for model *B* also.

For Model *C* from Table 2, it is evident that except for the transition type *CDM* to *IDDM*, the variable age has significant contribution to all other transitions and these estimates are consistent as compared with that of Model *A*. It appears that sex is significantly associated with the transition of the type *DM* to *CDM*. This result is consistent with that of Model *B*. For Model *C* the underlying hazard rate is non-significant for transitions of the types *DM* to *IDDM* and *CDM* to *IDDM*. This result is consistent with that of Model *A*. In addition Model *B* shows the transition of the type *CDM* to *IDDM*, the underlying hazard rate is significant. Like other two models *A* and *B* the covariate set of model *A* is also significant.

For model *C* in addition to the above test, we try to reveal significant difference between the regression co-efficients of the the transitions to state s_4 from states s_1 and s_3 , by considering the following hypothesis

$$H_0 : \beta_{14} = \beta_{34}$$

Here we also used the likelihood ratio test procedure and value of test statistic $-2 \ln LR=4$ ($p>0.05$), indicates that the hypothesis may be accepted.

4. CONCLUSION

The analysis of repeated observations arising from longitudinal data deals with change in the status under consideration. For instance, an individual who is normal now, may develop mild state of disease during the next three months, and then he or she can move to severe state of the disease or may be cured in next six months. In this situation, use of traditional statistical models, where the models are based on only one transient state, can not adequately address these problems. Hence, we need to employ multistate analysis where more than one intercommunicating states can be taken into consideration to explain the transition from one state to another over time. In this study Beck's (1979) model has been extended in this regard that can cover the transitions, reverse transitions and repeated transitions.

As an application of such extension, the problems associated with the changes in the status of diabetes mellitus has been used. For studying this type of data properly, it is necessary to define some states of the

disease according to different stages of that disease. For an individual the transitions between these states over time is regarded as a random variable and give some important information about disease progression. For utilizing the information about different transitions between states of disease in the analysis of the lifetime data, the concept of multistate hazards model is introduced. In addition, the influence of covariates on transitions may also be included in the construction of multistate hazards model.

This study is based on 406 patients who were *IGT* at the time of registration in *BIRDEM*. To keep the analysis simple, two covariates (age and sex) have been used for the application of this model. In this study, in the presence of covariates, three models *A*, *B* and *C* are defined. From the analysis of these models, it is observed that though the parameter sets corresponding to covariates are significant, but individually all the parameters are not significant. The covariate age, gives consistent result for both Model *A* and *C*, we found age as significant for all other transitions in these two models except the transition from controlled *DM* state to insulin dependent state. For both these models we found age is negatively associated only for any transition from *IGT*.

Similarly for sex, we found except for the transition to remission state, the variable sex has non-significant contribution to all other transitions for both the models *B* and *C*.

On the other hand, for underlying hazard rates λ_{120} , λ_{140} and λ_{230} are found significant in all the three models and λ_{340} is significant only for model *C*. In this situation our observation is that the less number of observed transition from controlled *DM* state to insulin dependent state may have influenced the estimation of β and λ in the opposite direction. For testing the equality of β_{14} and β_{34} , the likelihood ratio test procedure gives evidence that this equality may exist in the population.

It is noteworthy that we can obtain a wide range of information through applications of the proposed models. The proposed models use the longitudinal history regarding the disease status in its natural order of occurrences of events. Hence the proposed models can be utilized to obtain more realistic information regarding the factors influencing in the change of the status of a disease. The proposed models have a serious limitation as well. They give better estimate but at the cost of complexity in programming the equations from which solutions are obtained. However, in this world of modern computer facilities, we can take this challenge confidently.

ACKNOWLEDGEMENT

The authors of this paper would like to thanks Professor A. K. Azad Khan, Secretary General, *BIRDEM* for his kind permission to use the data employed in this study. The authors are indebted to Dr. Abu Sayeed, Senior Research Officer, Research Division, *BIRDEM* for his suggestions at different phases of this study.

REFERENCES

- Andersen, P. K., Borgan, O., Gill, R. D. and Keiding, N. (1993). *Statistical Models based on Counting Process*. Springer-Varlag New York Inc.
- Andersen, P. K., Hansen, L. S. and Keiding, N. (1991). Assessing the Influence of reversible disease indicators on survival. *Statistics in Medicine*. 10, 1061-1067.
- Beck, G. L. (1979). Stochastic survival models with competing risks and covariates. *Biometrics*. 35, 427-38.
- Chiang, C. L. (1980). *An introduction to stochastic processes and their applications*. Robert E. Krieger publishing co. New York.
- Chiang, Y. (1989). An illness-death Process with time dependent covariates. *Biometrics*. 45, 669-681.
- Cox, D. R. (1972). Regression models and life tables (with discussion). *Journal of the Royal Statistical Society, series B*. 34, 187-202.
- Islam, M. A. (1994). Multistate survival models for transitions and reverse transitions : An application to contraceptive use data. *Journal of the Royal Statistical Society, series A*. 157, 441-55.
- Kay, R. (1982). The analysis of transition times in multistate stochastic process using proportional hazard models. *Communications in Statistics Theory and Methods*. 11, 1743-56.
- Klein, J. P., Klotz, J. H. and M. R. Grever (1984). A biological marker model for predicting disease transitions. *Biometrics*. 40, 927-36.
- Lagakos, S. W. (1976). A stochastic model for censored survival data in the presence of an auxilliary variable. *Biometrics*. 32, 551-9.