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MULTI-STATE MODELS AND DIABETIC RETINOPATHY

GUILLERMO MARSHALL AND RICHARD H. JONES

Department of Preventive Medicine and Biometrics, School of Medicine, Box B-119, University of Colorado Health Sciences Center, Denver, CO 80262, U.S.A.

SUMMARY

This paper discusses the application of a multi-state model to diabetic retinopathy under the assumption that a continuous time Markov process determines the transition times between disease stages. The multi-state model consists of three transient states that represent the early stages of retinopathy, and one final absorbing state that represent the irreversible stage of retinopathy. By using a model with covariables, we explore the effects of factors that influence the onset, progression, and regression of diabetic retinopathy among subjects with insulin-dependent diabetes mellitus. We can also introduce time-dependent covariables in the model by assuming that the covariables remain constant between two observations. We can also obtain survival-type curves from each stage of the disease and for any combination of patient risk factors.

INTRODUCTION

The classification of early diabetic retinopathy on a scale from grade I to grade VI according to the modified Airlie House classification[1,2] suggests that multi-state modelling might offer an innovative methodology to analyse the natural course of this disease and may be the most appropriate methodology for finding the factors that influence this disease process. Such analysis will likely not only assess more accurately the effects of the risk factors in the disease process, but will also allow the prediction of transition times between disease stages.

Previous studies[3–6] have used contingency tables and logistic regression models to find patient risk factors associated with progression of diabetic retinopathy. Only one previous study[7] has modelled the effects of risk factors consistently with the longitudinal nature of the disease process using proportional hazard models. No previous study, however, has modelled diabetic complications using a multi-state model that allows progression and regression transitions among the different stages of diabetic retinopathy.

A multi-state Markov model without covariates has had successful applications to the stages of cancer,[8] the stages of HIV infection,[9] and the stages of diabetic retinopathy[10] among chronic diseases. In all of these cases the major problem is the type of data collected from the respective longitudinal medical studies. Ideally, researchers would like to observe every transition time in a patient's disease process. In general, however, one can only collect observations on stage of the process at the time of the patients' irregular clinical visits.

Marshall[11] and Marshall and Jones [12] proposed the extension of this model in various directions. One such direction is the inclusion of covariates in the model. By introducing covariates into the models, one can not only describe the natural course of the disease, but also find the factors associated with progression and regression between disease stages. Marshall and Jones[13] have developed a computer program called MARKOV to fit a general k-state Markov model.

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THE DATA

The subjects were 277 patients who had type I diabetes for at least five years, a mean age of 18 years and ranged in age from 14 to 29 years when initially seen at the Eye-Kidney Clinic of the Barbara Davis Center for Childhood Diabetes at the University of Colorado Health Sciences Center. The Eye-Kidney Clinic is open to all patients 14 years of age or older, and who have had type I diabetes for at least three years.

The average duration of insulin dependent diabetes mellitus for this populations is approximately 10 years, ranging from three to 28 years. The gender distribution is uniform. In data collection for this study, all subjects were seen longitudinally at least twice with visits at an average of one year apart for a mean follow-up of three years. A total of 882 patient visits occurred during the study period.

At each visit, a retinal specialist graded retinal findings using a modified Airlie House classification[1,2] in which: grade I indicates no retinopathy; grade II indicates microaneurysms only; grades III and IV indicate intermediate stages of background retinopathy, and grades V and VI indicate preproliferative and proliferative retinopathy, respectively. The worse eye grade for each visit was used to define the subject's state at the time of the visit.

THE MULTI-STATE MARKOV MODEL

The four-state Markov model that we consider for the analysis of these data includes three transient disease states: grade I; grades II–III, and grades IV–V of early retinopathy ($j = 1, 2\ 3$), and one absorbing state 4 representing retinopathy or grade VI. In this model the transient states are ordered according to j, and instantaneous transition, represented by the intensities, λ, can occur from state j to the adjoining states $j - 1$ or $j + 1$ as shown in Figure 1. No direct transitions are allowed from an early stage of retinopathy to the absorbing state (except from the state IV–V), and if transitions like this occurred, the model assumes that unobserved transitions have occurred before the final transition. Alternatively, we might have considered a six-state Markov model using the six grades of retinopathy. However, in addition to the attractiveness of a model with a reduced number of paramaters, the four-state model can reduce substantially the false transitions due to misclassification.

Assuming that the underlying process is a Markov process, we represent this model using the transition intensity matrix $\mathbf{\Lambda}$ as

$$\mathbf{\Lambda} = \begin{pmatrix} -\lambda_{12} & \lambda_{12} & 0 & 0 \\ \lambda_{21} & -(\lambda_{21} + \lambda_{23}) & \lambda_{23} & 0 \\ 0 & \lambda_{32} & -(\lambda_{32} + \lambda_{34}) & \lambda_{34} \\ 0 & 0 & 0 & 0 \end{pmatrix}, \tag{1}$$

or the transition probability matrix $\mathbf{P}(t)$. We establish the relation between the transition probability matrix $\mathbf{P}(t)$ and the transition intensity matrix $\mathbf{\Lambda}$ with the Kolmogorov forward differential equations

$$\frac{\partial \mathbf{P}(t)}{\partial t} = \mathbf{P}(t)\mathbf{\Lambda}, \tag{2}$$

where the element (i, j) of the matrix $\mathbf{P}(t)$ represents the probability of a transition from the state i to the state j in a time interval t, denoted as $p_{ij}(t)$. We can express the solution to this system of

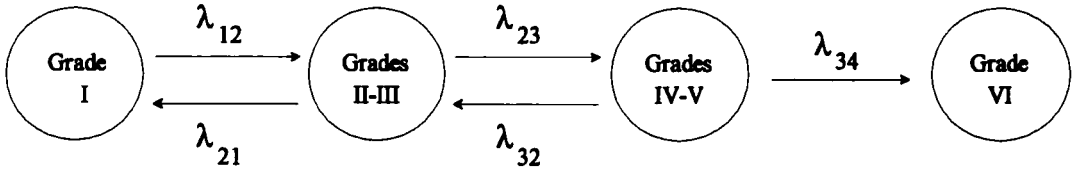

Figure 1. The multi-state Markov model for diabetic retinopathy with 4 states defined by the eye findings according to the Airlie House classification

differential equation as

$$\mathbf{P}(t) = \mathbf{A}\,\mathrm{diag}\{e^{\rho_1 t}, e^{\rho_2 t}, \ldots, e^{\rho_k t}\}\mathbf{A}^{-1}, \tag{3}$$

where $\mathbf{A}$ is the square matrix containing in column i the eigenvector associated with the eigenvalue ρ_i of the transition intensity matrix $\mathbf{\Lambda}$. For a more detailed discussion about Markov processes, see Cox and Miller.[14]

We can extend the model by introducing covariables as a proportional factor in the baseline transition intensities λ's. We represent the regression for the element (i, j) of the transition intensity matrix $\mathbf{\Lambda}$ as

$$\lambda_{ij}(\mathbf{z}) = \lambda_{ij} e^{\beta_{ij}\mathbf{z}}, \tag{4}$$

where β_{ij} is the vector of regression coefficients associated with the vector of covariables $\mathbf{z}$ for the transition between the states i and j. Note that model (4) for the transition intensity $\lambda_{ij}(\mathbf{z})$ resembles the proportional hazard model with constant hazard function. We can use the resulting transition intensity matrix $\mathbf{\Lambda}(\mathbf{z})$ for a subject with vector of covariates $\mathbf{z}$ in equations (2) and (3) to compute the transition probability matrix $\mathbf{P}(t|\mathbf{z})$. The elements $p_{ij}(t|\mathbf{z})$'s of this transition probability matrix constitute the contribution of each observation to the likelihood function.

MODEL SELECTION

We must consider two types of model selection procedures in the context of this multi-state Markov model. The first, more classical in statistical analysis, is the selection of covariates associated significantly with the progression and regression of the process. Given the large number of parameters associated with each covariate in model (4), it seems reasonable to consider a forward selection procedure. The second, more specific to this Markov model, relates to the selection of the most parsimonious representation of the association between each covariate and the disease process.

Consider the case of a model with a single covariate. In the context of this four-state model for diabetic retinopathy, there are three natural models for representing the effect of the covariate in the progression and regression of the disease process. The first, named the saturated model, is defined as the model in which the effect of the covariate differs in each of the five disease transitions (Figure 1). In this model we have a total of 10 parameters, five baseline transition intensities, and five different regression coefficients. The second model, named the progression and regression (PR) model, is defined as the model in which the effect of the covariate is the same for all progression transitions, and the same for all regression transitions. More formally, we formulate this model by assuming that the null hypothesis H_0': $\beta_{j,j+1} = \beta_p$, $j = 1, 2, 3$ and $\beta_{j,j-1} = \beta_r, j = 2, 3$ is true. Under this hypothesis the number of parameters associated with each covariable reduces from five to only two. We can write the proportional intensity model (4) under

this hypothesis as

$$\lambda_{ij}(\mathbf{z}) = \begin{cases} \lambda_{ij} e^{\beta_p z} & j = i + 1 \\ \lambda_{ij} e^{\beta_r z} & j = i - 1 \end{cases}. \tag{5}$$

Finally, the third model, called the progression minus regression (PMR) model, is defined as the model in which the effect of the covariate is the same for all progression transitions and the same, but with a sign change, for all regression transitions. Formally, we can formulate the hypothesis as H_0'': $\beta_p = -\beta_r = \beta$, provided that H_0' is true, and therefore model (4) reduces to

$$\lambda_{ij}(\mathbf{z}) = \begin{cases} \lambda_{ij} e^{\beta' z} & j = i + 1 \\ \lambda_{ij} e^{-\beta' z} & j = i - 1 \end{cases}. \tag{6}$$

Assuming that this hypothesis is true, we reduce by four the number of parameters associated with this covariate with respect to model (4) and by one parameter with respect to model (5). This reduction becomes extremely important when we include more variables in the model. In addition to the reduction in the number of parameters, if the null hypotheses H_0' and (or) H_0'' are true we can expect, according to our experience, to have a more robust estimation and substantially more power to assess the effect of the covariate in the disease process, and less chance that we overfit the model.

We can use the likelihood ratio and the Wald tests to test these two hypotheses. The first is more convenient for covariate selection, while the Wald test is more convenient for testing H_0' and H_0'', since we need only fit the saturated model.

ESTIMATION OF PARAMETERS

The major distinction of this multi-state Markov model with respect to other related techniques is its ability to analyse unobserved transition times based on the observation of the process at arbitrary times. Typical information collected at each visit from the patient includes the grade of diabetic retinopathy and other disease-related measurements. If i and j represent the observed states of the process at times s and t, respectively, then the contribution of this observed transition to the likelihood function is $p_{i,j}(t - s; \mathbf{z})$, that is, the element (i, j) of the transition probability matrix (3) evaluated at time $t - s$ and with covariate $\mathbf{z}$.

The total contribution of an individual to the likelihood function is the result of the product of the contribution from each observed transition. The full likelihood function is the product of all individual contributions. The model can be adapted to handle time-dependent covariables by replacing the time-invariate covariate contribution, $p_{i,j}(t - s; \mathbf{z})$, with $p_{i,j}(t - s; \mathbf{z}(s))$ by assuming that the time-dependent covariate remains constant between the two consecutive times s and t. Note that the times s and t are more often arbitrary times and they do not necessarily represent the actual transition times of the underlying disease process. Furthermore, given the form in which the data is collected, we must assume that more than one transition may possibly occur between these two observed times.

Maximum likelihood estimates for λ and β can be obtained by maximizing the likelihood function with respect to these parameters, and asymptotic estimates of the standard errors of the estimates can be obtained by inverting the empirical information matrix. Quasi-Newton algorithms can be used to find the maximum likelihood estimates using only an analytical expression for the likelihood function and using finite differences to obtain numerical approximations of the derivatives. Given the high cost of the evaluation of the likelihood function in this case, this algorithm can be significantly accelerated by using an analytic expression for the first derivatives. In both situations the second derivative is updated at each iteration by using

Cholesky or QR factorization. A complete discussion of these methods can be found in Dennis and Schnabel.[15]

SURVIVAL CURVES

This type of data can also be analysed using more traditional techniques found in survival analysis. If we denote T as the random variable representing the time free of state 4 (grade VI) retinopathy, we can use Cox's regression model to find factors associated with the distribution of T. The problem with using this model and other classical survival analysis models is the high percentage, 98 per cent in this case, of right censoring in the data. On the other hand, an important amount of data representing transitions between intermediate stages of the disease process is collected during the study period. This data contains valuable information about the disease process and can be used to find the various factors that are associated with the progression and regression of the various stages of the disease.

The multi-state model can be seen as a natural generalization of classical survival analysis models. Instead of having one transient and one absorbing state that characterize survival analysis, the multi-state model allows multiple transient states and the same absorbing final state. This characteristic can make this model an approach significantly more efficient in analysing highly censored data. This is particularly true when most of the transition data are observed between intermediate states, such as in diabetic retinopathy

The functional relationship between the survival function and the transition probability matrix can be obtained by the equation

$$S_i(t|\mathbf{z}) = 1 - p_{i4}(t; \mathbf{z}),$$

where $S_i(t|\mathbf{z})$ is the survival function from the state i for a subject with covariables $\mathbf{z}$, and where $p_{ik}(t; \mathbf{z})$ is the element (i, k) of the transition probability matrix $\mathbf{P}(t; \mathbf{z})$ Although the transition intensities are time-invariant, the associated hazard function is

$$h_i(t; \mathbf{z}) = \frac{-(\mathrm{d}S_i(t|\mathbf{z})/\mathrm{d}t)}{S_i(t|\mathbf{z})} = \frac{\sum_{j=1}^{4} p_{ij}(t; \mathbf{z})\lambda_{j4}(\mathbf{z})}{1 - p_{i4}(t; \mathbf{z})} = \frac{p_{i3}(t; \mathbf{z})}{1 - p_{i4}(t; \mathbf{z})}\lambda_{34}(\mathbf{z}).$$

since $\lambda_{14}(\mathbf{z}) = \lambda_{24}(\mathbf{z}) = \lambda_{44}(\mathbf{z}) = 0$, and where the expression in the numerator is direct consequence of the Kolmogorov forward differential equation (2).

RESULTS

At the beginning of the study, the patients were distributed among the four stages of diabetic retinopathy as 42 per cent, 53 per cent, 5 per cent and 0 per cent, respectively. By definition in this study, stage 4 started with no subjects. The distribution at the end of the study period was 26 per cent, 53 per cent, 19 per cent, and 2 per cent, respectively. Note that these probabilities distributions do not correspond to a fixed period of time for each subject, so they are not valid information for estimating transition probabilities.

A single-covariate Markov model was used to assess the individual effects of factors associated with diabetic retinopathy using a custom-designed computer program.[8] The full model with five regression coefficients, model (4), the progression and regression model with two regression coefficients, model (5), and the progression minus regression model with only one regression coefficient, model (6), were fitted to each factor considered in this study (Table I). For each

Table I. Likelihood ratio test of single-covariable Markov models for various factors associated with diabetic retinopathy using the full model, the PR model, and the PMR model. All tests are compared to a basic model without covariates

Factors	Full model χ^2 (5)†	PR model χ^2 (2)	PMR model χ^2 (1)
Duration of diabetes	58·2	54·7*	47·5
Age	33·5*	26·3	20·2
Mean HbA_{1c}	27·2	22·2	22·2*
Diastolic blood pressure	12·0	10·9	10·5*
HbA_{1c} at the visit	10·7	9·0	8·9*
Gender	9·8*	3·6	1·6
Smoking	9·4	4·1	3·6*
Systolic blood pressure	6·7	6·4	6·1*
Cholesterol	5·0	4·5	4·4*
Family Hx hypertension	4·5	4·3*	0·9

* Best model based on likelihood ratio test

† The likelihood ratio statistic for testing no effect in the covariate with the associated degree of freedom in parenthesis

covariate, the most parsimonious model among these three was found using the likelihood ratio test. If a factor based on the best model was found to be significantly associated with the disease process, the parsimonious representation of this factor was later used for multiple regression analysis.

The duration of diabetes, the age of the subject, and the mean HbA_{1c} levels (mean of all assessments at or before visit time) were the factors most associated with transitions of diabetic retinopathy. Diastolic and systolic blood pressure and values of HbA_{1c} at visit times were also associated with the disease process. All other factors, including gender, mean cholesterol level levels (mean of all assessments at or before visit time), family history of hypertension, systolic blood pressure, and a history of smoking, were not significantly associated with changes in diabetic retinopathy. The significance of the association between these factors and transition times was tested using the likelihood ratio test (Table I). The only three factors in this study that are time-independent covariates are gender, family history of hypertension, and a history of smoking.

Duration of diabetes shows similar effects in all progressive transitions and similar effects in all regressive transitions. Model (5) is chosen as the best representation for the association of this factor and diabetic retinopathy. The regression coefficient estimates for this model were $\hat{\beta} = (0{\cdot}0528, -0{\cdot}2223)$, showing a significant departure from the assumption of model (6). Based on the standard errors of the estimates, (0·02774, 0·0456), and their correlation coefficient, $r = 0{\cdot}5295$, we can construct a Wald test for the hypothesis $H_0'': \beta_p = -\beta_r$, associated with model (6). By using $\mathbf{L} = (1, 1)'$, the Wald statistic is

$$W = (\mathbf{L}'\hat{\beta})'(\mathbf{L}'\hat{\mathbf{V}}_{\hat{\beta}}\mathbf{L})^{-1}(\mathbf{L}'\hat{\beta}) = \frac{0{\cdot}0288}{0{\cdot}0042} = 6{\cdot}80.$$

This value has an associated p-value lower than 0·01 based on the chi-square distribution with one degree of freedom. The equivalent likelihood ratio test for this hypothesis is $-2\log\{L_6/L_5\} = 54{\cdot}7 - 47{\cdot}5 = 7{\cdot}2$ (Table I). These two results confirm that the PMR model

Table II. Parameter estimates and standard errors for the final multiple regression model

Factor	Parameter	Estimate	Standard error
Baseline	λ_1	0·0566	0·0075
Baseline	λ_{21}	0·0121	0·0024
Baseline	λ_{23}	0·0163	0·0035
Baseline	λ_{32}	0·0746	0·0243
Baseline	λ_3	0·0024	0·0011
Duration of diabetes	β_{p1}	0·0729	0·0283
Duration of diabetes	β_{r1}	− 0·2084	0·0461
HbA_{1c}	$\beta_{p2} = -\beta_{r2}$	0·2128	0·0386
Diastolic blood pressure	$\beta_{p3} = -\beta_{r3}$	0·0178	0·0056

does not hold for duration of diabetes. Confidence intervals for the parameters in the model can be obtained by using a Wald-type test based on normal approximation.

Table II gives the estimates and the standard errors of the estimates for the parameters of the final multiple regression model. Duration of diabetes remained the most important factor for explaining changes in diabetic retinopathy. As expected, cumulative $HBA_{1c}$was the second most important clinical variable associated with transitions in retinopathy. The additional contribution of this factor in terms of the likelihood ratio chi-square test is slightly superior to the chi-square obtained without controlling for duration of diabetes. Diastolic blood pressure also remained in the model showing that it is an independent factor associated with diabetic retinopathy.

The baseline parameters represent the transition rates from one stage to another for a subject with average risk factors (in our study these numbers are 10·7 years of duration of diabetes a HbA_{1c} value of 11·8 per cent, and a value of diastolic blood pressure of 70) for a given period of time, in this study one month. By multiplying the baseline transition estimate from stage 3 to stage 4 for 12 month and 100 subjects, we conclude that an average of 2·88 (= 0·0024 × 12 × 100) transitions will occur from stage 3 to stage 4 in a period of one year in a group of subjects with average risk factors. Similar conclusions can be made from the remaining baseline transition estimates. The parameters associated with the covariates can be interpreted similarly to the regression coefficients in the Cox regression model. The increment of one year of duration of diabetes will increase the risk of progression on the disease process 7·5 per cent ($e^{0·0729} = 1·075$) and reduces the chances of regression in the disease process 19 per cent ($e^{-0·2084} = 0·81$).

Figure 2 shows estimated survival curves of the probability of remaining free of state 4 (grade VI) retinopathy for a subject with eight years since the onset of diabetes, 12 per cent of HbA_{1c}, and a diastolic blood pressure of 70. The three curves represent the survival curves for starting in one of the three transient stages. Figure 2 shows that the probabilities of remaining free of state 4 (grade VI) retinopathy during a period of five years are 96 per cent, 94 per cent, and 86 per cent starting from stage 1, 2 and 3 at time zero, respectively. These probabilities dramatically decrease during a period of 10 years to 77 per cent, 75 per cent, and 65 per cent, respectively.

These probabilities and Figure 2 also show that staying in stage 2 does not significantly increase the risk of progressing to diabetic retinopathy. However, stage 3 shows a significant reduction during the first five years of the probability of staying free of retinopathy and has similar reduction in the second five-year period when compared to the probabilities of stages 1 and 2.

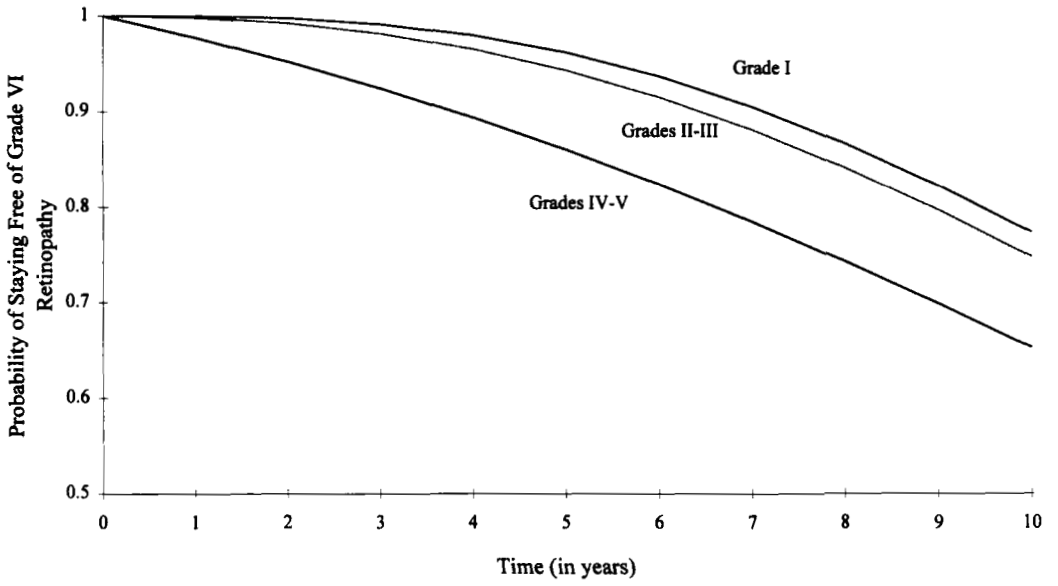

Figure 2. Survival-type curves for the probability of staying free of grade VI retinopathy by eye grades

DISCUSSION

This paper has demonstrated that a multi-state Markov model is not only an innovative statistical tool for the analysis of longitudinal and event history data, but with the introduction of the PR and PMR models it is also a feasible regression technique.

The results of the multi-state model have confirmed much of what is known about the natural course and the factors affecting diabetic retinopathy. However, using the Markov model we have learned more about how the different factors affect the disease process over time.

As many cross-sectional studies have shown, duration of diabetes is the single most important factor associated with the rate of progression among the different stages of diabetic retinopathy. Some of the factors found to be significantly associated with eye complications were not longer significant when duration of diabetes was included in the model. In a multivariate model we found that cumulative mean HbA_{1c} and diastolic blood pressure remained significant even after adjusting for the duration of the disease.

The regression analyses in the context of multi-state Markov models becomes a feasible statistical technique when the number of parameters associated with the different covariates are significantly reduced by introducing the PR and PMR models. This not only prevents overfitting the data with redundant parameters, but also provides meaningful clinical information about the effects of different risk factors in the disease process. Almost all factors found to be significantly associated with diabetic retinopathy had their best representation in the PMR model. Duration of diabetes was not only the most important factor associated with changes in eye complications, but was the only variable for which the PR model was the best representation. Although age in years had its best representation in the full model, the likelihood ratio between the full model and the PR model was not significant at the 5 per cent level ($p = 0{\cdot}066$).

Multi-state regression modelling should become an increasingly important and attractive statistical technique for the analysis of longitudinal data dealing with stages of chronic disease.

However, this will only be possible when more computer programs for the models reviewed in this paper become more accessible and easy to use.

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