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Research Paper

A multistate Markov model for the progression of liver cirrhosis in the presence of various prognostic factors

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Abstract

In recent years, multistate models have been studied widely in survival analysis. This article illustrates the use of multistate Markov model to estimate the incubation period of cirrhosis and HCC from prevalent cohorts and to evaluate the effect of various prognostic factors on the disease progression. This kind of study is being done for the first time on Indian population wherein a retrospective data of 824 admitted patients suffering from liver cirrhosis and HCC has been obtained and analyzed to evaluate the effect of covariates on the transition/survival of these patients. It is observed that presence of encephalopathy, LGI bleed, altered sensorium, older age and raised level of serum creatinine are the significant contributors for the death of patients due to liver disease who were initially diagnosed with liver cirrhosis. Also, presence of black stools and high creatinine levels plays an important role in transition from cirrhosis to HCC. Patients initially in HCC state with the presenting symptoms of ascites, LGI bleed and altered sensorium faces higher probability of death due to liver disease. Hence, it can be conclusively established that presence of ascites, encephalopathy and LGI bleed play a major role for liver disease patient in bridging a path to mortality.

Keywords: Multistate Markov model · Cirrhosis · HCC · Disease progression.

Mathematics Subject Classification: Primary 62N01 · Secondary 62N86.

1. Introduction

A multistate model for time to event data often referred to as Illness-death model in which all individuals start in one or possibly more initial states and eventually end up in one or more absorbing or final states. In between these transitions, there may be several intermediate states that may or may not be visited. Real life data presents a situation where all the individuals who were seen in the initial state may not last till the final or absorbing state due to a variety of reasons. Those individuals who manage to reach the final state while being alive are called censored observations. The main objective in such models is to identify all the possible movements among stages and to calculate the various probabilities and intensities of transition. These quantities give us a fair idea about the most probable

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states that a person is likely to be in a specific duration of time. In Illness-death process, the transition intensity functions may assumed to be time dependent/independent and the model is used to calculate the probability of death and probability of transitions between various illness and death states. The identification of covariates that affect the transition intensities provides an opportunity to study the factors that influence the various movements among these states.

In studies of chronic disease progression, data on the states are usually obtained at infrequent time points during follow-up and the interest focuses on the rate at which patient progress through a defined set of disease states. The exact transition time between disease states are generally not observed. Multistate model aims to obtain more biological insight into progression of disease and also to evaluate the effect of prognostic factors on different phases of the disease. When the present state of the disease summarizes all the previous information, the Markov model is appropriate.

In chronic liver disease, the deterioration of the liver functions occurs slowly, over a period of time. Patients who suffer from chronic liver disease may develop cirrhosis after years of disease. Cirrhosis is manifested as a silent disease. It is a form of chronic liver injury that represents an end stage of virtually any progressive liver disease. In 1977, the World Health Organization defined cirrhosis as a diffuse liver process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules. Liver failure/cancer occurs when the liver loses its ability to function properly. It is a progressive condition that causes severe damage to the liver. It may take months or even years for liver cancer to develop.

Markov models in continuous time have been used by various authors to analyze different diseases. Perez-Ocon et al. (2001), has applied this technique to examine the influence of three post surgical treatments (chemotherapy, radiotherapy, hormonal therapy) to 300 breast cancer patients on the life times and relapse times. The survival of the patients in the group where all three (CH-RT-HT) treatment combinations are given is more as compared to radiotherapy and chemotherapy group and radiotherapy group alone.

Bacchetti et al. (2011) applied non Markov multistate model to analyze the progression of liver fibrosis using biopsy measurement in untreated patients suffering with hepatitis C virus. Saint-Pierre et al. (2003) used a continuous-time Markov model with use of time dependant covariates and a Markov model with piecewise constant intensities to model asthma control evolution. In this study, the notion of asthma control grade for each visit was used to define subject's state at the time of visit as optimal control, sub-optimal control and unacceptable control. The author's confirmed that BMI and the number of exacerbations are important factors associated with asthma control. Bartolomeo et al. (2011) has employed a hidden Markov model to determine the transition probabilities incorporating various covariates for progression of liver cirrhosis to develop HCC and to death. Two illness states and one death state was considered and found that male patients have twice the probability of developing HCC as compared to female patients. Also, ample presence of concomitant diseases increases the risk of death in patients with HCC.

In this study, we aim to develop a time dependent multistate Markov model for survival data analysis of patients suffering from chronic liver disease. Stochastic multistate or competing models, like Markov chains are those best suited for the analysis of such phenomena (Serio and Morabito (1986; 1988), Sacks and Chiang (1997), Putter et al. (2007)). For this study, two illness states viz. cirrhosis and hepatocellular carcinoma (HCC) and two death states viz. death due to liver disease and death due to any cause other than liver disease are considered. Accordingly, transition probabilities from one state to another are estimated in the presence of covariates. The refinement of this model over other existing models lies in the fact that it encompasses prognostic factors while also dealing with censored observations. Even though, many authors have attempted to use Markov models for studying

chronic liver disease, our work highlights a different and more relevant set of prognostic factors to model the transition intensities. Also, to the best of our knowledge, this is the first such study to have incorporated the effect of other death causes in the model.

2. Data

Retrospective data on a cohort of subjects admitted for the treatment of liver cirrhosis and hepatocellular carcinoma (HCC) was obtained from the Department of Gastroentrology, Pushpawati Singhania Research Institute, New Delhi, India. The institute is known for its expertise in liver disease ailments and thus caters to a large segment of population from Northern region of India. A total of 824 patients were admitted for the treatment of liver cirrhosis and HCC from January 2007 to December 2010 and monitored through subsequent follow-ups. Four states were considered for the progression of liver disease: State 1 (Cirrhosis), State 2 (HCC), State 3 (Death due to liver disease: DLD), State 4 (Death due to any cause other than liver disease: DOC), where state 3 and state 4 are absorbing states.

3. Methods

A schematic representation of the Illness-death model is provided in Figure 1. The model consists of two transient states i.e., Cirrhosis and HCC and two absorbing states i.e., death due to Liver disease and death due to any cause other than liver disease. It is assumed that initially the patient is in cirrhosis stage from which he can transfer to liver cancer state i.e. HCC or to DLD state, representing death due to liver disease or DOC state, representing death due to any cause other than liver disease. Patient in HCC state can either die due to liver disease so he can transfer to DLD or he can die of any cause other than liver disease so can move to DOC. A few cases of patients who underwent liver transplant were excluded. It is assumed that liver cancer or hepatocellular carcinoma (HCC) is an irreversible disease therefore model doesn't allow a transfer from HCC back to cirrhosis.

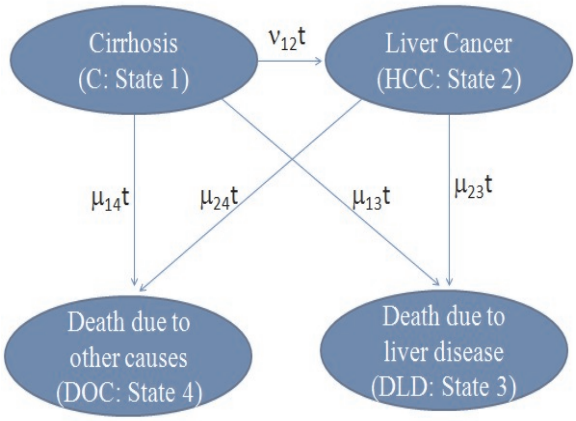

Figure 1. Four state Markov model with two transient and two absorbing states.

Let ν_{12} be the unknown morbidity intensity function and μ_{11}, μ_{12}, μ_{23} and μ_{24} be the mortality intensity functions. Each intensity function represents instantaneous transition between respective states at time t ($x_i \leq t \leq x_{i+1}$). These intensity functions are assumed to be dependent on time dependent covariates throughout the follow-up period. The intensity function for this model is given by the equations given below (Chiang, 1968):

The intensity of transition from,

- Cirrhosis state to HCC state:

$$\nu_{12}t = \nu_{12}\exp(\beta_1 Z_j)$$

- Cirrhosis state to death due to liver disease state:

$$\mu_{13}t = \mu_{13}\exp(\beta_2 Z_j)$$

- Cirrhosis state to death due to any cause other than liver disease:

$$\mu_{14}t = \mu_{14}\exp(\beta_3 Z_j)$$

- HCC state to death due to liver disease state:

$$\mu_{23}t = \mu_{23}\exp(\beta_4 Z_j)$$

- HCC state to death due to any cause other than liver disease:

$$\mu_{24}t = \mu_{24}\exp(\beta_5 Z_j)$$

where $Z_j = (z_{j1}, z_{j2}, z_{j3}, \ldots, z_{jp})$, is the initial set of time dependent covariates for the j^{th} individual, $\beta'_k = (\beta_{k1}, \beta_{k2}, \beta_{k3}, \ldots, \beta_{kp})$, are the coefficients associated with z_j for k^{th} intensity function, and $k = 1, 2, 3, 4, 5, \ldots, n$.

For the time interval $x_i \leq t \leq x_{i+1}$, the corresponding illness - death transition probabilities of the individuals in the specific interval are given by P_{11}, P_{12}, Q_{13}, Q_{14}, Q_{23}, Q_{24}, where

$$\begin{aligned} P_{11}(x_i, x_{i+1}) &= P(\text{of an individual remaining in cirrhosis during } (x_i, x_{i+1})) \\ &= \exp\left(-\int_{x_i}^{x_{i+1}} -(\nu_{12}t + \mu_{13}t + \mu_{14}t)udu\right) \qquad (1) \\ P_{12}(x_i, x_{i+1}) &= P(\text{of an individual moving from cirrhosis to HCC state during } (x_i, x_{i+1})) \\ &= \int_{x_i}^{x_{i+1}} \exp\left(-\int_{x_i}^{t} -(\nu_{12}t + \mu_{13}t + \mu_{14}t)udu\right)\nu_{12}tdt \qquad (2) \\ Q_{13}(x_i, x_{i+1}) &= P(\text{of an individual moving from illness state cirrhosis to death state DLD} \\ &\quad \text{during the period } (x_i, x_{i+1}) \text{ without experiencing HCC}) \\ &= \int_{x_i}^{x_{i+1}} \exp\left(-\int_{x_i}^{t} -(\nu_{12}t + \mu_{13}t + \mu_{14}t)udu\right)\mu_{13}tdt \qquad (3) \\ Q_{14}(x_i, x_{i+1}) &= P(\text{of an individual moving from illness state cirrhosis to death state DOC} \\ &\quad \text{during the period } (x_i, x_{i+1}) \text{ without experiencing HCC}) \\ &= \int_{x_i}^{x_{i+1}} \exp\left(-\int_{x_i}^{t} -(\nu_{12}t + \mu_{13}t + \mu_{14}t)udu\right)\mu_{14}tdt \qquad (4) \end{aligned}$$

$$
\begin{aligned}
Q_{123}(x_i, x_{i+1}) &= P(\text{of an individual moving from illness state cirrhosis to death state DLD} \\
&\qquad \text{during the period } (x_i, x_{i+1}) \text{ after experiencing HCC}) \\
&= \int_{xi}^{xi+1} \left(\int_{xi}^{t} \exp\left[- \int_{xi}^{u} -(\nu_{12}t + \mu_{13}t + \mu_{14}t)\tau d\tau \right] \nu_{12} u du \right) \\
&\qquad \cdot \exp\left[- \int_{u}^{t} -(\mu_{23}t + \mu_{24}t)\tau d\tau \right] \mu_{23} t dt \\
Q_{124}(x_i, x_{i+1}) &= P(\text{of an individual moving from illness state cirrhosis to death state DOC} \\
&\qquad \text{during the period } (x_i, x_{i+1}) \text{ after experiencing HCC}) \\
&= \int_{xi}^{xi+1} \left(\int_{xi}^{t} \exp\left[- \int_{xi}^{u} -(\nu_{12}t + \mu_{13}t + \mu_{14}t)\tau d\tau \right] \nu_{12} u du \right) \\
&\qquad \cdot \exp\left[- \int_{u}^{t} -(\mu_{23}t + \mu_{24}t)\tau d\tau \right] \mu_{24} t dt
\end{aligned}
$$

For the individuals initially in HCC state,

$$
\begin{aligned}
P_{22}(x_i, x_{i+1}) &= P(\text{of an individual remaining state HCC state during the period } (x_i, x_{i+1})) \\
&= \exp\left(- \int_{xi}^{t} (\mu_{23}t + \mu_{24}t) u \right) du \\
Q_{23}(x_i, x_{i+1}) &= P(\text{of an individual dying in DLD state} \mid \text{he was alive in HCC state at } x_i) \\
&= \int_{xi}^{xi+1} \exp\left[- \int_{xi}^{t} (\mu_{23}t + \mu_{24}t) u du \right] \mu_{24} t dt \\
Q_{24}(x_i, x_{i+1}) &= P(\text{of an individual dying in DOC state} \mid \text{he was alive in HCC state at } x_i) \\
&= \int_{xi}^{xi+1} \exp\left[- \int_{xi}^{t} (\mu_{23}t + \mu_{24}t) u du \right] \mu_{23} t dt
\end{aligned}
$$

The new matrix $P(t)$ formed of the transition probabilities which takes into account the covariates is calculated by taking the matrix exponential of the scaled transition intensity matrix, Cox and Miller (1965), i.e.

$$P(t) = \exp(Qt)$$

where

$$
Q = \begin{pmatrix}
-(\nu_{12}t + \mu_{13}t + \mu_{14}t) & \nu_{12}t & \mu_{13}t & \mu_{14}t \\
0 & -(\mu_{23}t + \mu_{24}t) & \mu_{23}t & \mu_{24}t \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0
\end{pmatrix}
$$

The estimates of transition intensities of matrix Q have been obtained as described by Kalbfleich and Lawless (1985) and Kay (1986). In addition, it is possible to use Cox proportional hazards model to relate probabilities $q_{ij}(t)$ to time t with covariates vectors z, by

$$q_{ij}[t|z] = q_{ij,0}(t) \exp\{\beta_{ij}^T z\}$$

where $q_{ij,0}(t)$ is the baseline hazard of transition $i \to j$, and β_{ij} is the vector of regression coefficients that describe the effect of z on transition $i \to j$.

An alternative way of writing this model (Andersen et al. 1991) is as

$$q_{ij}(t|z) = q_{ij,0}(t) \exp(\beta_{ij}^T z_{ij})$$

where z_{ij} is a vector of covariates specific to transition $i \to j$, defined for the patients based on his/her covariates z.

The estimates $\hat{\beta}$ can be obtained by maximizing the partial likelihood function is given by

$$L(\beta) = \prod_{k=1}^{n} \frac{\exp(\beta_{ij}^T z_{ij,k})}{\sum_{l \in R(t_{ij},k)} \exp(\beta_{ij}^T z_{ij,l})}$$

where $z_{ij,k}$ is the covariate vector for patient k, and $R(t_{ij,k})$ is the risk set at time t for making transition from $i \to j$. The detailed estimation procedure is stated in Kay (1982), Kalfleisch and Lawless (1985).

The statistical analysis is performed using R 2.14.1. Methods for multistate modeling such as hidden Markov model (Jackson et al., 2002) and multistate Markov model with classification error (Jackson et al., 2003) as implemented in the "msm" package for R (available at http://cran.r-project.org/web/packages/msm/index.html), deal with many of these difficulties and have been used to analyze various diseases, but they make strong simplifying assumption that previous history of progression does not impact current risk of progression - the so called memory less or Markov assumption. However, due to irregular nature of follow up, observations of the actual time of entry into a disease state are frequently interval censored. The proposed Markov model has been applied in context for the progression of liver cirrhosis to HCC in the presence of various prognostic factors which include both clinical and laboratory parameters.

The prognostic factors inserted in the model were Age, Gender, HB, TLC, Platelet, Serum Creatinine, Serum Bilirubin, PT, Sodium, Potassium, SGOT, SGPT, Total Protein and Albumin, Ascites, Encephalopathy, Fever, Weakness, Edema, Anorexia, Black Stool, Jaundice, Altered Sensorium and Abdominal Distention assessing the patient's clinical severity.

4. Results

A total number of 824 admitted patients suffering from Cirrhosis and HCC were studied retrospectively. Out of which, 666 (81%) and 158 (19%) were identified as patients suffering from cirrhosis and HCC respectively shown in Table 1.

Table 1. Summary of number of transitions between various states

To →			Death due to			
From↓	Cirrhosis	HCC	Liver disease	Other causes	Lost to follow-up	Total
Cirrhosis	320	68	102	9	167	666
HCC	0	44	89	4	21	158

The baseline characteristics of patients suffering from liver cirrhosis and HCC are reported in Table 2. Comparison of baseline characteristics in the two groups of cirrhosis and HCC showed significant difference in total leukocyte count with mean difference of

(8904.3 vs. 7713.6) in both the groups. Patients with liver cirrhosis were observed to have significantly higher level of serum bilirubin and serum albumin as compared to HCC group with a mean difference of (1.3 vs. 1.1) and (6.8 vs. 5.0) respectively. However, SGPT in HCC group is reported to be significantly higher than that in cirrhosis group. All other characteristics like age, haemoglobin, sodium, potassium, SGOT, total protein and serum albumin were statistically similar in the two groups. For example the average age was 50.7 in cirrhotics vs. 52.0 in HCC patients. Majority of patients were male as compared to female in both the groups (86% vs. 14%). Clinical symptoms also play a major role in the progression of the disease. The presenting symptoms such as ascites (31% vs. 22%), encephalopathy (81% vs. 19%), Abdominal distention, weakness, altered sensorium (12.1% vs. 8.3) and black stools were noted to be significantly different in the two groups. Also, these symptoms contribute significantly in disease progression.

Table 2. Baseline laboratory and clinical characteristics of Cirrhotic and HCC patients.

Covariates	Mean ± Std Dev (Range)		Covariates	Number (%)	
	Cirrhosis	HCC		Cirrhosis	HCC
Age (years)	50.7 ± 12.38 (19-85)	52.0 ± 14.56 (22-89)	Gender Male Female	 567 (85.1) 99 (14.9)	 137 (86.7) 21 (13.3)
Total Leucocyte Count ($/\mu$l)*	8904.35 ± 6218.84 (1000-75000)	7713.6 ± 4250.59 (1060 - 28100)	Ascites* Mild	 270 (31.1)	 13 (22.0)
Platelet ($10^3/mm^3$)	123.9 ± 87.73 (4.5-697)	134.1 ± 96.31 (26 - 540)	Encephalopathy* Grade 1 Grade 2 Grade 3	 64 (9.6) 62 (9.3) 22 (3.3)	 7 (4.4) 6 (3.8) 3 (1.9)
Haemoglobin (g/dl)	10.1 ± 2.36 (3 - 18)	10.2 ± 2.08 (3.3 - 15.7)	Fever	192 (28.8)	15 (25)
Prothrombin Time*	23.2 ± 7.75 (11.3-64.3)	21.3 ± 5.78 (11.6 - 45)	Abdominal* Distention	338 (51.0)	35 (58.3)
Serum Creatinine* (mg/dl)	1.3 ± 1.15 (0.2-10)	1.1 ± 0.86 (0.5 - 9.8)	Weakness*	131 (20.0)	12 (20)
Sodium (mEq/L)	132.8 ± 7.37 (103-150)	133.3 ± 7.87 (106-150)	Anorexia	146 (22.0)	20 (33.3)
Potassium (mEq/l)	4.1 ± 0.82 (2-8.6)	4.1 ± 0.76 (2.3 - 7.7)	Edema	160 (24.0)	10 (16.6)
Serum Bilirubin* (mg/dl)	6.8 ± 9.07 (0.08-71.9)	5.0 ± 6.58 (0.4 - 31.7)	LGI Bleed	46 (7.0)	2 (3.3)
SGOT (U/L)	94.5 ± 91.49 (4-809)	105.4 ± 102.03 (17-685)	UGI Bleed	87 (10.4)	3 (5)
SGPT (U/L)*	48.8 ± 59.28 (10-903)	63.7 ± 67.02 (10 - 513)	Altered Sensorium*	101 (12.1)	5 (8.3)
Total Protein (g/dl)	7.0 ± 1.08 (0.4-10.4)	6.8 ± 1.16 (1 - 9.2)	Jaundice	224 (26.8)	13 (21.7)
Albumin (g/dl)	2.9 ± 0.67 (0.7-6.4)	2.8 ± 0.61 (0.3 - 4.5)	Black Stools*	56 (6.7)	2 (3.3)

* Significant at 5% level

The transition intensities estimated for the Markov model with covariates set at their mean values are illustrated in Table 3. The estimates report that the probability of a cirrhotic patient moving to HCC state is twice the probability of dying due to cirrhosis i.e. patients are twice likely to move to HCC state than remaining in same cirrhotic state. The probability of death is nine fold higher in the patients suffering with liver cancer as compared to the patients with liver cirrhosis. Patients with liver cancer have very high probability of dying during the span of 60 months. Patients initially in HCC state has thrice the probability of dying due to causes other than liver disease as compared to the

patients who are initially in cirrhosis state.

Table 3. Estimated Transition intensities (covariates set at their mean values)

	Intensities	95% CI	
q_{11}	−0.01093	−0.01289	−0.009258
q_{12}	0.00601	0.00443	0.00815
q_{13}	0.0039	0.00278	0.00560
q_{14}	0.0009	0.00055	0.00170
q_{22}	−0.0406	−0.0518	−0.0319
q_{23}	0.03764	0.02908	0.04870
q_{24}	0.00301	0.00146	0.00622

Table 4 presents the prognostic factors included in the study with the estimated hazard ratios and their corresponding 95% confidence limits of the multivariate model. These adjusting covariates were included in the model as time dependent covariates and their values have been obtained using maximum likelihood ratio test. It can be noted that after the onset of liver cirrhosis, the probability of death due to liver disease is 86% higher in males as compared to females. Also, male gender, encephalopathy, LGI bleed, altered sensorium, older age and raised level of serum creatinine are the significant contributors in the death of the patient initially diagnosed with liver cirrhosis. The risk of disease progression is 1.34 and 1.03 times greater, respectively, for the individuals with higher level of serum creatinine and serum Bilirubin. Patients with presenting symptoms of encephalopathy, LGI bleed and altered sensorium are likely to face the hazard 64%, 41% and 3.81 times more respectively than the patients without these symptoms. Moreover, patients with black stools and encephalopathy as symptoms and raised level of serum creatinine appeared to develop disease more rapidly i.e a quick transition from cirrhosis to HCC. However, while dealing with other causes we found ascites and altered sensorium to be significant factors while accounting for transitions from state 1 to state 4. Once the patient enters into HCC state then the model does not allow a transfer from HCC back to cirrhosis, HCC being an irreversible disease. It was observed that the risk of death due to liver disease while being in HCC state, patients with ascites and altered sensorium are respectively 1.98 and 2.63 times more likely to die due to liver disease as compared to patients without these ailments. Also, LGI and UGI bleed increase the chances of mortality due to liver disease by a significant 149% and 47% respectively. We took competing risk into account but found sample size to be very small in this group. However, in our data base there were only 13 deaths due to causes other than liver disease which includes 3 patients suffering from gastric cancer, 3 from chronic kidney disease, 2 from intracerebral haemorrhage, 3 from cardiac arrest and 2 from tuberculosis. Hence, analysis due to these individual death causes was not possible. Rather, a single group comprising of all these causes aptly named as “death due causes other than liver disease” is incorporated in the model to study their overall influence on the transition probabilities. Literature suggests that majority of liver cirrhosis patients are susceptible to intracerebral haemorrhage (Gronbaek et al., 2008), chronic kidney disease and gastric cancer (Wu et al., 2013) and our results corroborate the earlier findings.

Figure 2 depicts the clear picture of the movement of patients suffering from liver cirrhosis into various stages. Survival and death probabilities of the patients initially suffering from cirrhosis is illustrated in the graph at quarterly intervals. A sharp decline in the curve (P_{11}) can be noticed in the first quarter representing that out of the total patients initially in the cirrhosis stage, a few remains in the same stage by the end of follow up but with very less probability. The probability of moving to HCC (P_{12}) stage showed a steep increment from first quarter itself and can be observed till the 60th month. It shows that

Table 4. Estimated Multivariate Hazard Ratio with 95% confidence interval of progression from illness to absorbing states.

	State 1 - State 2			State 1 - State 3			State 1 - State 4			State 2 - State 3			State 2 - State 4		
Covariates	HR	LL	UL	HR	LL	UL	HR	LL	UL	HR	LL	UL	HR	LL	UL
Gender															
Male															
Female	0.49	0.24	1.04	1.86	1.26	2.95	2.97	0.36	24.19	0.85	0.47	1.53	0.75	0.08	6.59
Ascites	0.96	0.66	1.37	1.37	0.6	3.13	5.84	1.14	29.87	1.98	1.32	2.97	0.63	0.16	2.44
Encephalopathy	1.16	1.06	1.51	1.64	1.09	2.46	0.03	0.001	7.15	0.39	0.22	0.72	0.99	0.47	2.09
Fever	1.22	0.78	1.91	0.51	0.11	2.37	8.96	0.88	90.37	1.19	0.8	1.79	0.22	0.02	2.47
Abdominal Distension	0.84	0.53	1.32	1.44	0.53	3.86	3.69	0.33	41.21	0.99	0.65	1.51	0.79	0.23	2.78
LGI Bleed	0.93	0.42	2.02	1.41	1.36	5.53	3.69	0.33	41.21	2.49	1.24	4.99	1.44	0.11	19.02
UGI Bleed	0.67	0.31	1.49	1.8	1.37	8.7	6.15	0.58	65.15	1.47	1.16	1.87	0.06	0	18.87
Altered Sensorium	0.31	0.13	0.78	3.81	1.15	12.54	47.82	2.56	89.78	2.63	1.17	5.93	1.09	0.09	12.52
Jaundice	1.34	0.85	2.11	0.58	0.15	2.21	0.29	0.02	3.98	0.95	0.61	1.47	1.84	0.52	6.47
Black Stool	2.02	1.02	4.01	0.26	0.02	3.89	3.22	0.22	47.85	0.2	0.05	0.83	2	0.37	10.73
Age	0.98	0.96	1.01	1.04	1.01	1.07	0.96	0.91	1.02	0.99	0.98	1.01	0.94	0.9	0.99
Serum Creatinine	1.19	1.04	1.35	1.34	1.11	1.62	1.17	0.78	1.76	1.02	0.84	1.24	1.21	0.85	1.73
Serum Bilirubin	0.99	0.96	1.02	1.03	1.01	1.06	1.01	0.81	1.24	0.92	0.87	0.97	0.97	0.88	1.06
Sodium	1.01	0.97	1.03	0.94	0.91	0.98	1.19	0.79	1.78	1.03	0.77	1.06	0.98	0.9	1.07
Potassium	0.93	0.72	1.21	1.83	0.87	3.88	2.39	0.19	30.6	0.84	0.65	1.08	0.81	0.43	1.52
Total Protein	1.02	0.83	1.27	1.25	0.73	2.13	0.71	0.29	1.73	1.08	0.89	1.29	0.82	0.55	1.23
Serum Albumin	0.65	0.46	0.93	1.29	0.49	3.37	2.79	0.96	8.12	1.15	0.83	1.6	0.88	0.36	2.13

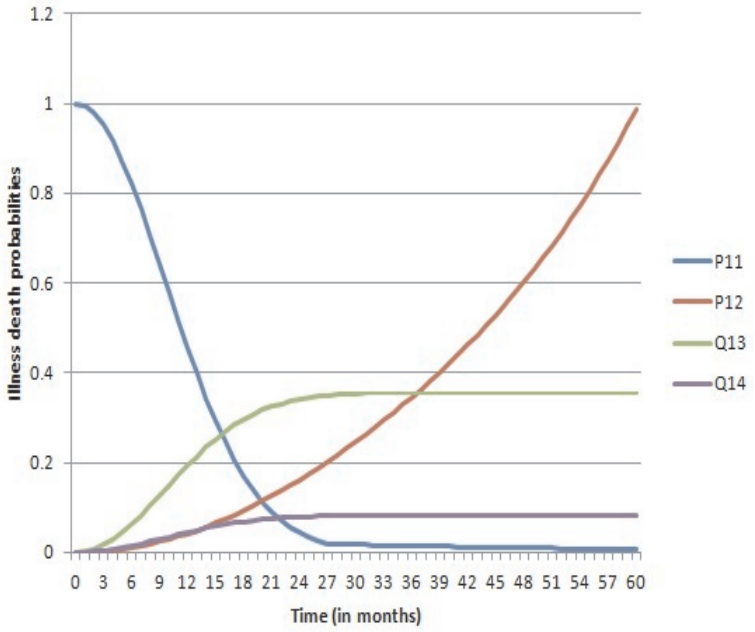

Figure 2. Illness and death transition probabilities for stages 1-4, over the period of 60 months for the patients initially in Cirrhosis stage.

people suffering from cirrhosis will move to HCC almost with probability 1 by the end of 5 years. The probability of moving from cirrhosis to death due to liver disease (Q_{13}) showed a sharp increase from 1st quarter to 8th quarter but remained almost constant till last quarter (60th month). The intensity of moving to death stage due causes other than liver disease (Q_{24}), remain parallel to x axis after 8th quarter acting like a tangent to x-axis.

Figure 3 gives a depiction of the movement of the patients initially suffering from HCC to two stages viz. death due to liver disease (Q_{23}) and death due to cause other than liver disease. (Q_{24}). The probability of patients remaining in HCC state shows a steep

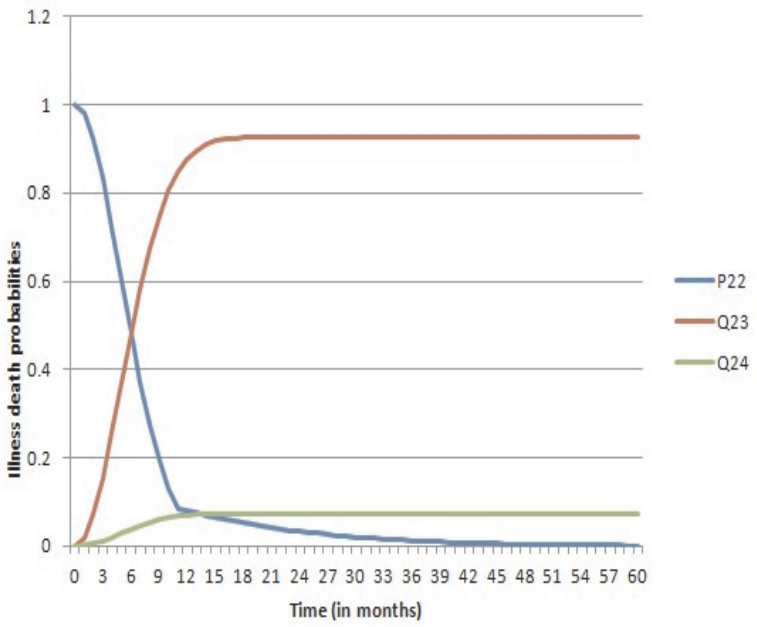

Figure 3. Illness and death transition probabilities for stages 1-4, over the period of 60 months for the patients initially in HCC stage.

downfall from 1st quarter itself. After 4th quarter, it decreases smoothly but after 19th quarter the patients remaining in HCC state survive with very less probability. Once patient reaches HCC state, the probability of death due to the disease rises. A sharp increase can be observed (Q_{23}) from 1st to 4th quarter and then the probability remains almost constant at 0.9. This implies that most of the deaths occur in the first year after HCC has been diagnosed. But after 1st year also the probability of death remains very high. The probability of patients moving from HCC to death stage due to cause other than liver disease (Q_{24}) increases slowly but after 4th quarter it becomes parallel to the x axis with probability 0.1

Also we have made an attempt to assess the goodness of fit of our multistate Markov model by comparing the observed prevalence of states with expected prevalence under the model at a series of times. The model was found to be fitting well (confirmed by prevalence.msm plot, not shown here) to this dataset.

5. Discussion

Multistate models are an approach to analyzing categorical longitudinal data. These types of model are used particularly in medical applications in which stages or levels of a disease are represented by the states in the model. Such models have been used in a wide range of medical applications, for instance HIV/AIDS (Aalen et al., 1997), breast cancer (Duffy et al., 1995), psoriatic arthritis (Cook et al., 2004), dementia (Joly et al., 2002), diabetic retinopathy (Kosorok et al., 1996), myocardial infarctions (Grover et al., 2010) and smoking prevention (Cook et al., 2002). The discrete states of the model may either represent clinically defined stages of a disease, e.g. number of damaged joints in patients with psoriatic arthritis, or alternatively be a discretisation of a continuous marker, e.g. CD4 count in patients infected with HIV.

By exploiting the properties of Markov models, we have illustrated the usefulness of multi stage illness death model in the analysis of follow-up study of chronic liver disease. We have calculated the temporal intensities of transition with covariates set at their mean

values and hazard ratio during the degenerative course of chronic liver cirrhosis. Many studies have evaluated the risk factors for the progression of liver cirrhosis to HCC by using parametric and semi parametric approach. Sarbah et al. (2004) have employed Cox model with the principal aim of determining the risk factors for the progression of cirrhosis to HCC. Degos et al. (2000) studied progression to HCC and death using Kaplan Meier method in a small cohort of subjects with diagnosis of HCV related cirrhosis. In particular, homogeneous Markov model with covariates has been used.

We explored the impact of sex, altered sensorium, LGI bleed, age, serum creatinine and serum Bilirubin on survival time of the patients initially suffering from liver cirrhosis. In various longitudinal studies it has been shown that advanced age and the male sex are associated with an increased risk of death in cirrhotic patients (Said et al., 2004) as was also shown in the present paper. In fact male, cirrhotic subjects are likely to face the hazard 86% more as compared to female subjects, while middle aged patients have a higher risk of degeneration of the liver disease and especially of dying while affected by liver cirrhosis. It may be due to the early exposure to alcohol and heavy drinking habit.

Serum creatinine is a strong and independent prognostic factor for liver cirrhosis and our findings in illness death model is in conformity with previous reports Attia et al. (2008) indicated poor survival of patients with high level of creatinine. Botta et al. (2003) compared the survival of cirrhotic patients at 6 months and 12 months and found creatinine as one of the factor for lower survival.

Altered Sensorium is another significant factor contributing to poor survival. Said et al. (2004) followed cirrhotic patients for one year and concluded that altered sensorium is an independent significant factor for lower survival of cirrhotic patients.

Said et al. (2004) also noted that in one year follow up of cirrhotic patients, male gender, MELD score, Child-Pugh score and encephalopathy, were associated with increased mortality. Independent predictors were the Child-Pugh and encephalopathy. Serum Bilirubin is a part of Child-Pugh score and MELD score but in our study it turned out to be an independent predictor.

Ascites, LGI bleed, UGI bleed, altered sensorium and serum sodium were found to be significant independent prognostic factors affecting the survival time of patients initially suffering from HCC. Aslawat et al. (2013) observed 363 patients for consecutive 5 years and reported portal hypertention, serum bilirubin and altered sensorium as significant factors.

The results of the multistate markov model have confirmed much of what is known about the natural course and the factors affecting the progression of liver cirrhosis. Using this type of multistate model helped us to learn more about the various factors affecting the disease process over time.

A further improvement of the model could be that of including interaction terms of various prognostic factors. Also, the model can be extended by taking three illness states (Chronic hepatitis, cirrhosis, HCC) instead of two. In our case, due to paucity of such observations, it was not possible to consider this type of model.

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