

## MULTI-STATE MARKOV MODEL: AN APPLICATION TO LIVER CIRRHOSIS

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### ABSTRACT

The control and treatment of chronic diseases is a major public health challenge, particularly for patients suffering from liver disease. In this paper, we propose a frame to estimate survival and death probabilities of the patients suffering from liver cirrhosis and HCC in the presence of competing risks. Database of the admitted patients in a hospital in Delhi has been used for the study. A stochastic illness-death model has been developed describing two liver illness states (Cirrhosis and HCC) and two death states (death due to liver disease and death due to competing risk). Individuals in the study were observed for one year of life at any age  $x_i$ . The survival and death probabilities of the individuals suffering from liver cirrhosis and HCC have been estimated using the method of maximum likelihood. The probability of staying in the cirrhotic state is estimated to be threefold higher than that of developing HCC (0.64/0.21) in one year of life. The probability of cirrhotic patient moving to HCC state is twice (0.21/0.11) the probability of dying due to liver disease. HCC being the severe stage, the probability of patient dying due to HCC is three times that of cirrhosis. Markov model proves to be a useful tool for analysis of chronic degenerative disease like liver cirrhosis. It can provide in-depth insight for both the researchers and policy makers to resolve complex problems related to liver cirrhosis with irreversible transitions.

**Key words:** illness-death model, maximum likelihood, Cirrhosis, Hepatocellular Carcinoma (HCC).

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## 1. Introduction

Chronic disease is a long-lasting condition that can be controlled but not cured. Although chronic diseases are among the most common and costly health problems, they are also among the most preventable diseases and can be effectively controlled. Our health care system is heavily weighted in dealing with the problems that are best managed with the patient in a passive role. Chronic conditions and diseases such as heart disease, stroke, cancer, diabetes, etc. are leading causes of mortality and morbidity, accounting for 60% of total premature deaths all over the world out of which 53% is in India [WHO]. Research suggests that complex conditions such as diabetes & depression will impose an even greater health burden in the near future. Study after study, regardless of the underlying disease, has shown generally poor performance in caring for patients with chronic disease.

In studies of chronic disease progression, interest focuses on the rate at which individual progress through a defined set of disease states. The evolution of chronic degenerative disease is characterized by progression of the disease through intermediate states to advanced disease and death. Analysis of such studies can be successfully performed by multi-state models [4]. In the multi-state framework, issues of interest include the study of the relationship between covariates and disease evolution, estimation of transition probabilities and survival rates. A multi state Markov model is developed for survival data analysis for patients suffering from chronic liver disease. Stochastic multistate or competing models, like Markov chains are those best suited to the analysis of such phenomena [10-13]. In this research paper two illness states, viz. cirrhosis and HCC, and two death states, viz. death due to liver disease and death due to competing risk respectively are considered. Accordingly, transition probabilities from one state to another are estimated in the absence of covariates.

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 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.

In human population, all individuals are not equally healthy and their chance of dying varies from individual to individual. It is known that illness and death are two different types of events. Illness may be transient, repetitive and reversible, whereas death is an irreversible or absorbing state [11]. Further complexity is introduced when the probability of an individual dying from one cause is influenced by the presence of competition of other causes. Death is usually attributed to a single cause, however various risks compete for the life of an

individual. Competing risks can be defined as an event whose occurrence precludes the occurrence of another event under examination [8]. The expressions for survival and death probabilities of liver patients have been obtained by using the concept of crude probability of death under competing risks. The likelihood estimates of the survival and death probabilities have also been obtained. Several stochastic illness-death models have been proposed for studying progression of human diseases. Fix and Neyman proposed a model with two illness and two death states to study human cancer [7]. Grover et al. proposed an illness-death model for estimating survival and death probabilities under cardio vascular shocks in the presence of competing risks [9]. Various shock models categorizing shocks as major and minor have been developed for predicting the survival time function of CHD patients [2].

Chronic infection with hepatitis C virus (HCV) has been estimated to affect 3.2 million persons in the United States and 130 million worldwide and is a leading cause of liver failure and the need for liver transplant [1,14]. Of patients exposed to the hepatitis C virus (HCV), approximately 80% develop chronic hepatitis C and of those, about 20–30% will develop cirrhosis over 20–30 years. Many of these patients have had concomitant alcohol use, and the true incidence of cirrhosis due to hepatitis C alone is unknown. HCV is a noncytopathic virus, and liver damage is probably immune-mediated. Progression of liver disease due to chronic hepatitis C is characterized by portal-based fibrosis with bridging fibrosis and nodularity developing, ultimately culminating in the development of cirrhosis. In cirrhosis due to chronic hepatitis C, the liver is small and shrunken with characteristic features of a mixed micro and macronodular cirrhosis seen on liver biopsy. In addition to the increased fibrosis that is seen in cirrhosis due to hepatitis C, an inflammatory infiltrate is found in portal areas with interface hepatitis and occasionally some lobular hepatocellular injury and inflammation.

Similar findings are seen in patients with cirrhosis due to chronic hepatitis B. Of patients exposed to hepatitis B, about 5% develop chronic hepatitis B, and about 20% of those patients will go on to develop cirrhosis. Special stains for HBc (hepatitis B core) and HBs (hepatitis B surface) antigen will be positive and ground glass hepatocytes signifying HBsAg (hepatitis B surface antigen) may be present. The worldwide incidence of HCC has increased, mostly due to persistent HBV or HCV infection; presently it constitutes the fifth most common cancer, representing around 5% of all cancers. Approximately 25% of these individuals may ultimately develop cirrhosis. Hepatocellular Carcinoma occurs at a rate of 1% to 4% per year after cirrhosis is established [5] and cirrhosis underlies HCC in approximately 80% to 90% of cases worldwide [3].

The purpose of this paper is to develop a stochastic illness-death model using the concept of competing risks theory. The survival and death probabilities of the individuals in different states of chronic liver disease have been estimated using the method of maximum likelihood.

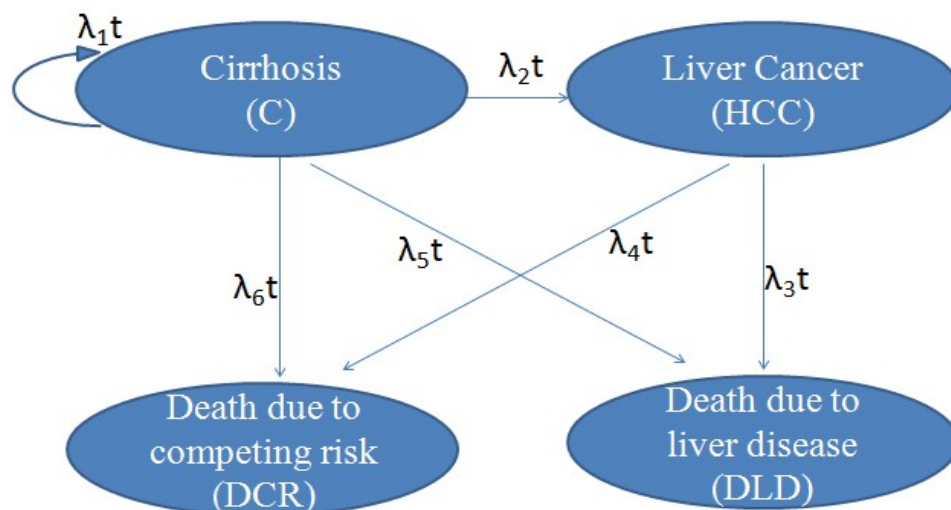
## 2. Materials and methods

In our model, we have considered two illness states viz. cirrhosis (C) and liver cancer (HCC) and two death states viz. death due to liver disease (DLD) and death due to competing risks (DCR).

A schematic representation of the illness-death model is provided in Fig.1. It is assumed that initially the patient is in cirrhosis stage from which he can transfer to liver cancer state, i.e. HCC, and then to DLD state, representing death due to liver disease or DCR state, representing death due to competing risks. Patient in HCC state can either die due to liver disease so he can transfer to DLD or he can die of competing risks so can move to DCR. It is assumed that liver cancer or hepatocellular carcinoma (HCC) is an irreversible disease therefore model does not allow a transfer from HCC back to cirrhosis.

Patients enrolled in the study have been categorized into two groups namely, cirrhosis and HCC respectively depending upon their initial condition. Suppose that there are  $n_1$  patients in cirrhosis and  $n_2$  patients in HCC state, with the total sample size  $n = n_1 + n_2$ . Individuals in the study are observed for one year of life i.e. (0,1) at any age  $x_i$  so that one year of life means age interval  $(x_i, x_{i+1})$  which corresponds to (0,1).

Let  $\lambda_1t$  and  $\lambda_2t$  be the unknown morbidity intensity functions and  $\lambda_3t, \lambda_4t, \lambda_5t$  and  $\lambda_6t$  be the unknown mortality intensity functions. Each intensity function represents instantaneous transition between respective states at time  $t$  ( $x_i < t \leq x_{i+1}$ ).



**Figure 1.** Illustration of illness and death states along with possible transitions

### 2.1. Calculation of transition probabilities

Let

$$\lambda_1 t = - (\lambda_2 t + \lambda_5 t + \lambda_6 t)$$

and

$$\lambda_2 t = - (\lambda_3 t + \lambda_4 t)$$

The relationships between the intensity functions and transition probabilities for the general illness-death process are given by Chiang (1968). In the present case, the survival and death probabilities of an individual in different states of the model may be defined as follows:

$P_{11}(0,1) = P$  (of surviving one year of life while being in the cirrhotic state with hazard rate  $\lambda_1 t$ )

$$\Rightarrow P_{11}(0,1) = \exp \left\{ \int_0^1 \lambda_1 t dt \right\} \tag{1}$$

$P_{12}(0,1) = P$  (of surviving one year of life while being in HCC state with hazard rate  $\lambda_2 t$ )

$$\Rightarrow P_{12}(0,1) = \int_0^t \exp\left(\int_0^u \lambda_1 \tau d\tau\right) \lambda_2 u \exp\left(\int_u^t \lambda_2 \tau d\tau\right) dt \tag{2}$$

$Q_{13}(0,1) = P$  (of dying due to liver disease after experiencing HCC with hazard rate  $\lambda_3 t$  during period (0,1))

$$\Rightarrow Q_{13}(0,1) = \int_0^t \int_0^u \exp\left(\int_0^u \lambda_1 \tau d\tau\right) \lambda_2 u du \exp\left(\int_u^t \lambda_2 \tau d\tau\right) \lambda_3 t dt \tag{3}$$

$Q_{14}(0,1) = P$  (of dying from competing risks after experiencing HCC with hazard rate  $\lambda_4 t$  during period (0,1))

$$\Rightarrow Q_{14}(0,1) = \int_0^t \int_0^u \exp\left(\int_0^u \lambda_1 \tau d\tau\right) \lambda_2 u du \exp\left(\int_u^t \lambda_2 \tau d\tau\right) \lambda_4 t dt \tag{4}$$

$Q_{15}(0,1) = P$  (of dying due to liver disease without experiencing HCC with hazard rate  $\lambda_5 t$  during the period (0,1))

$$\Rightarrow Q_{15}(0,1) = \int_0^t \exp\left(\int_0^t \lambda_1 \tau d\tau\right) \lambda_5 t dt \tag{5}$$

$Q_{16}(0,1) = P$  (of dying from competing risks without experiencing HCC with hazard rate  $\lambda_6 t$  during the period (0,1))

$$\Rightarrow Q_{16}(0,1) = \int_0^t \exp\left(\int_0^t \lambda_1 \tau d\tau\right) \lambda_6 t dt \tag{6}$$

Using equations (1) to (6), it can be easily verified that

$$P_{11}(0,1) + P_{12}(0,1) + Q_{13}(0,1) + Q_{14}(0,1) + Q_{15}(0,1) + Q_{16}(0,1) = 1$$

Now, the survival and death probabilities of an individual in different states of the model, while being initially in HCC state, may be defined as follows:

$P_{22}(0,1) = P$  (of surviving the period  $(0,1)$  while being in HCC state with hazard rate  $\lambda_2t$  given that the individual was in HCC state at the time of the start of the study)

$$\Rightarrow P_{22}(0,1) = \exp\left(\int_0^t \lambda_2 t dt\right) \tag{7}$$

$Q_{23}(0,1) = P$  (of dying in the period  $(0,1)$  from liver disease with hazard rate  $\lambda_4t$  given that the individual was suffering from HCC at the time of the start of the study with hazard rate  $\lambda_2t$ )

$$\Rightarrow Q_{23}(0,1) = \int_0^t \exp\left(\int_0^\tau \lambda_2 \tau d\tau\right) \lambda_3 t dt \tag{8}$$

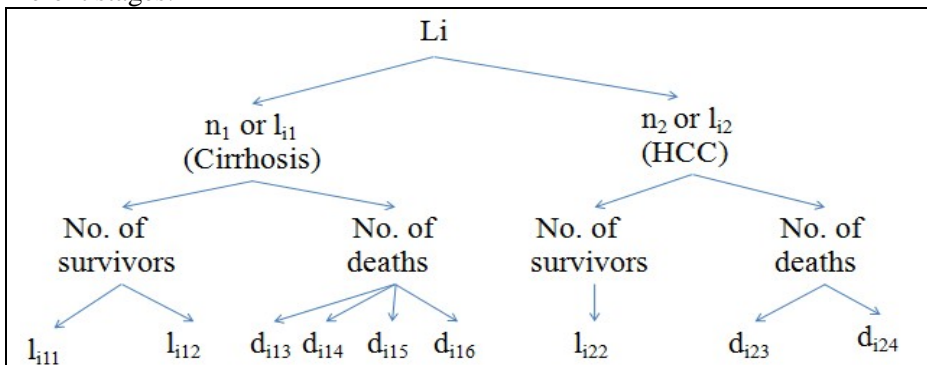
$Q_{24}(0,1) = P$  (of dying in the period  $(0,1)$  from a competing risk with hazard rate  $\lambda_4t$  given that the individual was suffering from HCC at the time of the start of the study with hazard rate  $\lambda_2t$ )

$$\Rightarrow Q_{24}(0,1) = \int_0^t \exp\left(\int_0^\tau \lambda_2 \tau d\tau\right) \lambda_4 t dt \tag{9}$$

It can be easily verified from the above mentioned (7) to (9) equations that  $P_{22}(0,1) + Q_{23}(0,1) + Q_{24}(0,1) = 1$

**2.2. Estimation of survival and death probabilities**

Maximum likelihood estimation is the recommended procedure for estimating the parameters of the foregoing model. As the data has been collected at specific time points so information on an individual’s passage through the states will not usually be complete, i.e. we will only know an individual’s status at several, possibly pre-chosen, points in time. Thus, if  $L_i$  patients are initially enrolled in the study, then after observing them for one year of their life, we found them in different stages.



**Figure2.** Graphical representation of the used notations

For  $n_i$  group of individuals:

$l_{i11}$ , number of survived persons in cirrhotic state during the age interval  $(x_i, x_{i+1})$ ;

$l_{i12}$ , number of survived persons who transfer from cirrhotic state to HCC state during the age interval  $(x_i, x_{i+1})$ ;

$d_{i13}$ , number of persons died due to liver disease after suffering from HCC during age interval  $(x_i, x_{i+1})$ ;

$d_{i14}$  = number of persons died due to competing risks after suffering from HCC during age interval  $(x_i, x_{i+1})$ ;

$d_{i15}$  = number of persons died due to liver disease after suffering from cirrhosis during age interval  $(x_i, x_{i+1})$ ;

$d_{i16}$  = number of persons died due to competing risks after suffering from cirrhosis during age interval  $(x_i, x_{i+1})$ ;

$d_{i1}$ , total number of dead persons who were in cirrhotic state at the beginning of the age interval  $(x_i, x_{i+1})$ ;

$d_{i1} = d_{i13} + d_{i14} + d_{i15} + d_{i16}$ ;

$P_{i1} = P$  (of surviving the age interval  $(x_i, x_{i+1})$  initially in cirrhotic state);

$Q_{i1} = P$  (of dying in the age interval  $(x_i, x_{i+1})$  initially in cirrhotic state).

**Table 1.** The number of survivors and the number of deaths due to various risks in the  $i$ th age interval with corresponding probabilities

		Frequency	Probability
No. of deaths	Due to liver disease after suffering from HCC	$d_{i13}$	$Q_{i3}$
	Due to CR after suffering from HCC	$d_{i14}$	$Q_{i4}$
	Due to liver disease after suffering from Cirrhosis	$d_{i15}$	$Q_{i5}$
	Due to CR after suffering from cirrhosis	$d_{i16}$	$Q_{i6}$
No. of survivors	Individuals in cirrhotic state	$l_{i11}$	$P_{i1}$
	Individuals in HCC state	$l_{i12}$	$P_{i2}$
Total		$l_{i1+1} + d_{i1}$	1

Given  $l_{i1}$  individuals alive at the beginning of the age interval  $(x_i, x_{i+1})$ , the joint distribution of  $l_{i11}, l_{i12}, d_{i13}, d_{i14}, d_{i15}$  and  $d_{i16}$  is multinomial with probability function

$$f_{i1} = \frac{l_{i1}!}{\prod_{j=1}^2 l_{i1j}! \prod_{k=3}^6 d_{i1k}!} \frac{1}{\prod_{j=1}^2 P_{ij} \prod_{k=3}^6 Q_{ik}}$$

For a sample of  $u$  age intervals, the likelihood function is given by

$$L_1 = \prod_{i=0}^u \frac{l_{i1}!}{\prod_{j=1}^2 l_{ij}! \prod_{k=3}^6 d_{ik}!} \frac{1}{\prod_{j=1}^2 P_{ij} \prod_{k=3}^6 Q_{ik}} \text{-----(a)}$$

although it is both biologically and mathematically pleasing that the proposed model has arisen from consideration of a progression of events in a stochastic process. It is more expedient for parameter estimation and subsequent interpretation to deal in terms of probability distributions of the random variables arising from the process. Using the equation (a), maximum likelihood estimates of  $P_{ij}$  and  $Q_{ik}$  can be computed.

For a group of individuals initially in HCC state,

$l_{i2}$ , number of survived individuals in HCC state at the beginning of the age interval  $(x_i, x_{i+1})$ ,

$l_{i22}$ , number of survived individuals in HCC state surviving the age interval  $(x_i, x_{i+1})$ ,

$d_{i23}$ , number of died individuals due to liver disease in the age interval  $(x_i, x_{i+1})$ ,

$d_{i24}$ , number of died individuals due to competing risks in the age interval  $(x_i, x_{i+1})$ ,

$d_{i2}$ , total number of individuals dying in the age interval  $(x_i, x_{i+1})$  and were in HCC state in the beginning of the interval,

$\Rightarrow d_{i2} = d_{i23} + d_{i24}$ ,

$l_{i2+1} = l_{i22}$ ,

$P_{i2} = P$  (of surviving the age interval  $(x_i, x_{i+1})$  when an individual is in HCC state at time  $x_i$ ),

$Q_{i2} = P$  (of dying in the age interval  $(x_i, x_{i+1})$  when an individual is in HCC state at time  $x_i$ ).

**Table 2.** The number of deaths due to various risks and the number of survivors in the  $i^{th}$  age interval with corresponding probabilities

		Frequency	Probability
No. of deaths	Due to HCC	$d_{i23}$	$Q_{i3}$
	Due to competing risk	$d_{i24}$	$Q_{i4}$
No. of survivors	In HCC state	$l_{i22}$	$P_{i2}$
		$d_{i2} + l_{i2+1}$	1

Given  $l_{i2}$  individuals in HCC state alive at the beginning of the age interval  $(x_i, x_{i+1})$ , the joint distribution of  $l_{i22}$ ,  $l_{i27}$  and  $l_{i28}$  is multinomial with probability function



$$f_{i2} = \frac{l_{i2}!}{l_{i22}!d_{i27}!d_{i28}!} P_{i3}^{l_{i22}} Q_{i7}^{d_{i27}} Q_{i8}^{d_{i28}}$$

For a sample of u age intervals, the likelihood function is given by

$$L_2 = \prod_{i=0}^u f_{i2}$$

$$\Rightarrow L_2 = \prod_{i=0}^u \frac{l_{i2}!}{l_{i22}!d_{i27}!d_{i28}!} P_{i3}^{l_{i22}} Q_{i7}^{d_{i27}} Q_{i8}^{d_{i28}}$$

Similar method can be applied as mentioned above to obtain estimates of  $P_{ij}$  and  $Q_{ik}$  for the patients initially in HCC state.

### 3. Application

A total of 366 patients suffering from liver cirrhosis and 30 suffering from HCC were admitted in the years 2007-2008 at Pushpawati Singhania Research Institute (PSRI). Data on these patients were collected retrospectively and in total 66 censored patients were excluded from the analysis. Patients were observed for one year of life, i.e. (0,1) at any age  $x_i$ . 310 cirrhotic and 20 HCC patients moved through various stages (Figure.1) and were observed for one year of their life as shown in the Table 3.

**Table 3.** Number of patients observed in various stages after 1 year

State at the beginning of the study	Transition in the interval (0,1)	State after one year	Number of individuals
Cirrhosis	Cirrhosis → Cirrhosis	Cirrhosis	204
	Cirrhosis → HCC Cirrhosis → HCC → DLD Cirrhosis → HCC → DCR	HCC	20
		Death due to liver disease	8
		Death due to competing risk	2
	Cirrhosis → DLD	Death due to liver disease	70
	Cirrhosis → DCR	Death due to competing risk	6
HCC	HCC → HCC	HCC	8
	HCC → DLD	Death due to liver disease	10
	HCC → DCR	Death due to competing risk	2

#### 4. Results

**Table 4.** The estimated intensities and the corresponding survival and death probabilities of patients initially in cirrhosis state

Parameters	Intensities	Probabilities
$\lambda_1$	-0.88961	$P_{11}(0,1) = 0.640149$
$\lambda_2$	0.60526	$P_{12}(0,1) = 0.208471$
$\lambda_3$	0.50000	$Q_{13}(0,1) = 0.036499$
$\lambda_4$	0.10526	$Q_{14}(0,1) = 0.007680$
$\lambda_5$	0.26415	$Q_{15}(0,1) = 0.106612$
$\lambda_6$	0.02020	$Q_{16}(0,1) = 0.008152$

**Table 5.** The estimated intensities and the corresponding survival and death probabilities of patients initially in HCC state

Parameters	Intensities	Probabilities
$\lambda_2$	-0.77196	$P_{22}(0,1) = 0.61402$
$\lambda_3$	0.66667	$Q_{23}(0,1) = 0.33334$
$\lambda_4$	0.10526	$Q_{24}(0,1) = 0.05263$

The estimated intensities and their corresponding survival and death probabilities for Markov model (as explained in Figure1) are presented in Table 4 and Table 5. It can be inferred from Table 4. that the probability of patients who are initially in cirrhosis stage has higher chances of staying in the same stage than that of moving to HCC stage, i.e. the probability of remaining in cirrhosis stage is threefold higher than that of moving in HCC stage (0.640/0.208) during 1 year of time span. It may also be noted that probability of a cirrhotic patient moving in HCC stage is almost twice the probability of the patient dying due to liver disease (0.208/0.107), i.e. patients are more likely to move to HCC stage than that of dying from cirrhosis. Also, the probability of patients dying due to competing risk is almost equal, irrespective of their disease severity.

On comparing both the above Tables (4 and 5), it can be inferred that the probability of patients dying due to HCC is three times the probability of patient

dying due to cirrhosis. Also, we have found that in one year of time span patients initially in cirrhosis stage are less likely to die from liver disease than the patients initially in HCC stage. The reason could be that one year of time span might be less to witness all the stages of chronic liver disease. The above discussed intensities and probabilities have been depicted by the graphs shown below.

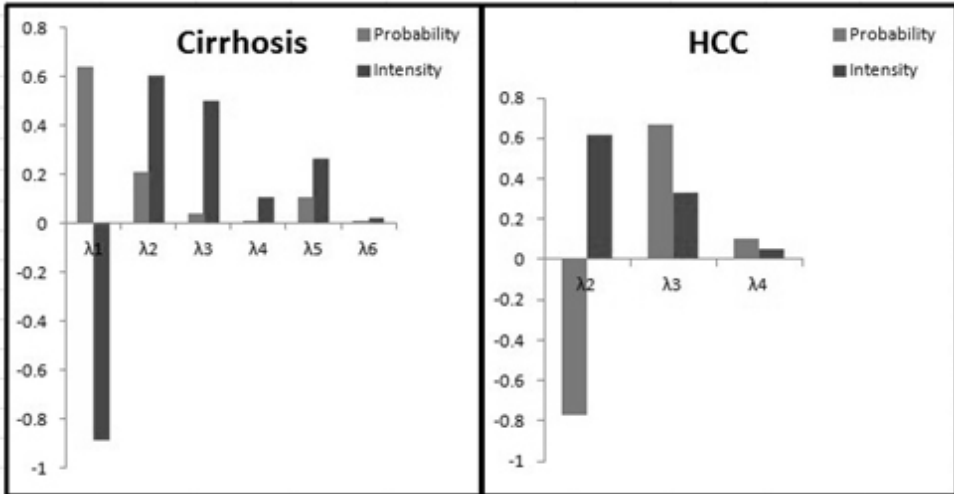


Figure 3. Survival and death probabilities and intensities

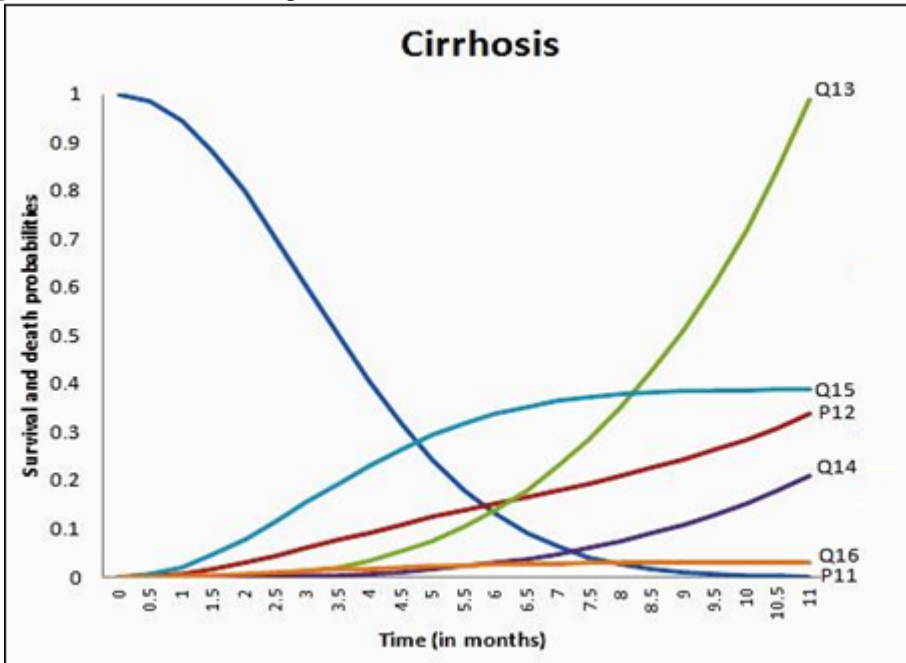
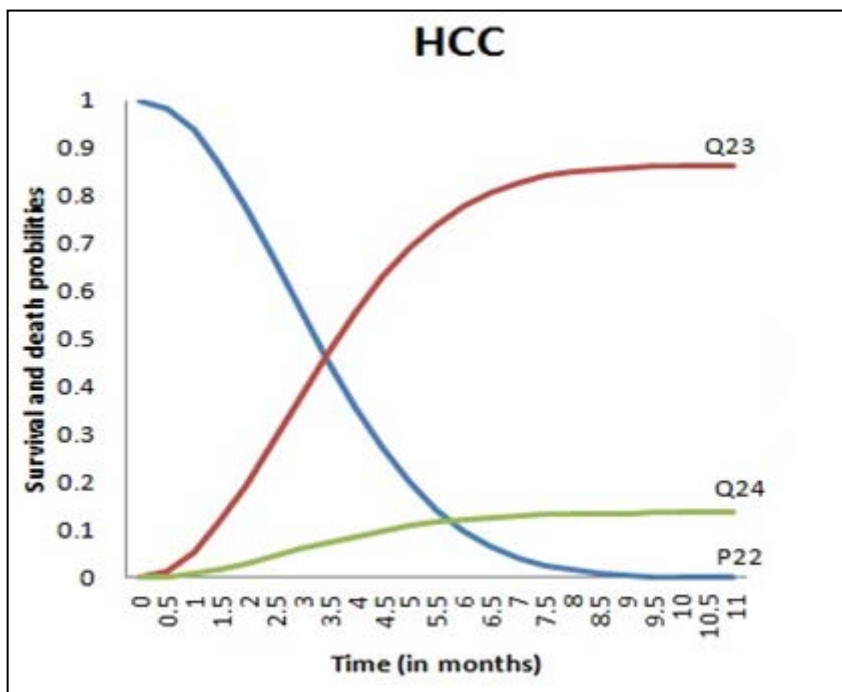


Figure 4. Illness and death transition probabilities for stages 1-4, over the period of 12 months for the patients initially in cirrhosis stage

The graph above depicts the clear picture of the movement of patients suffering from liver cirrhosis into various stages as defined in Fig1. Survival and death probabilities of the patients initially suffering from cirrhosis are illustrated in the graph at monthly intervals. A sharp decline in the curve ( $P_{11}$ ) can be noticed in the first month representing that out of the patients initially in the cirrhosis stage, a few remains in the same stage after one year of their life but with very less probability. The intensity of moving to HCC ( $P_{12}$ ) stage showed increment from the first month onwards, i.e. increasing with time at normal pace. The intensity of patients moving from cirrhosis to HCC and then to death is showing a parabolic trend, i.e.  $Q_{13}$  shows a steep curve depicting a sharp increase from the 6.5<sup>th</sup> month onwards. It simply shows that once the patient reaches HCC stage the probability of reaching death stage increases rapidly. The probability of patients dying due to various opportunistic causes/competing risks after suffering from HCC showed an increasing trend after the 6<sup>th</sup> month. The intensity of moving from cirrhosis to death showed a sharp increase in the 3<sup>rd</sup> month, until the 8<sup>th</sup> month it increases slowly but after that it almost remained constant. The intensity of moving to death stage due to various opportunistic causes/competing risks remains parallel to x axis after 2<sup>nd</sup> month acting like a tangent to x-axis.



**Figure 5.** Illness and death transition probabilities for stages 1-4, over the period of 12 months for the patients initially in HCC stage

Figure 5 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

competing risks ( $Q_{24}$ ). A steep downfall can be observed in the intensity of patients remaining in the HCC stage after one year of their life, i.e. the probability of patients remaining in HCC state after one year is very low. Patients quickly move to death stage once they reach the HCC stage. Vice versa, intensity of moving from HCC to death stage depicts a sharp increase from 1<sup>st</sup> month onward. It increased swiftly until the 7<sup>th</sup> month and then it became almost constant with probability of 0.9. As discussed above, there are higher chances of patients moving to death stage if they are in HCC stage. The intensity of moving to death stage due to competing risks increases after 2<sup>nd</sup> month and then became constant after 7<sup>th</sup> month.

## 5. Discussion

In studies of many chronic medical conditions, the health status of a patient may be characterized using a finite number of disease states. When patients are observed over time, the dynamic nature of the disease process may then be examined by modeling the rates at which patients make transitions among these states. Markov models provide a convenient framework for such analyses and have been very widely adopted in fields such as infectious disease [Bailey, 1982], neurology [Hassani and Ebbutt, 1996], and rheumatology [Gladman, Farewell, and Nadeau, 1995]. Frequently, only two states are of interest to represent, e.g., the presence or absence of symptoms [Frank et al., 1990] or the presence or absence of infection [de Vlas et al., 1993]. Such disease processes operate in continuous time, but for practical and economic reasons, subjects are often only observed at discrete time points. Indeed, under the most general scenario, the observation times may be irregularly spaced and may be unique to each subject. Data obtained from such an observation scheme are termed panel data. Kalbfleisch and Lawless (1985) developed an efficient algorithm for obtaining maximum likelihood estimates of the transition rates from panel data under a time-homogeneous Markov assumption and derived the form of an asymptotic covariance matrix for the corresponding estimators based on the expected information matrix. Grover et al. have also considered a similar problem taking cardiac arrest as disease with 4 states viz. normal state, illness state and two death states. In this research paper, we have illustrated the usefulness of Markov models in the analysis of chronic liver disease. We have implemented methods introduced by Chiang [4] that allow quite general models to be fitted. Various intensities and their corresponding transition probabilities have been computed for all four stages. These results have been obtained in the absence of covariates. We have reported the risk in terms of probability and also compared the probability of death from both (cirrhosis and HCC) the illness states. The concept of competing risk has been introduced for the first time in the study related to liver cirrhosis. A further improvement of the model could be that of considering covariates. Also, survival time and stay time in every state can be computed.

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