## 1. Transition Probability Matrix:

For the multistate Markov model demonstrating the NAFLD disease process; the forward Kolomogrov differential equations are the following:

*The Kolmogrov differential equations are:*

*The set of equations of the first row:*

*The set of equations of the second row:*

*The set of equations of the third row:*

*The set of equations of the fourth row:*

Last 13 equations :

**The Kolmogrov Differential Equations For The First 4 Probabilities In The First 4 Rows Are:**

***The set of equations of the first row: ( first 4 probabilities )***

The differential equations for the first 4 PDFs’ as stated previously solved using Laplace method :

Putting these equations (1,2,3,4) in matrix notation :

.

***The determinant in the denominator :***

Determinant in the denominator is a polynomial of the 4 th degree with the following roots: r1, r2, r3, r4

, Then

Using the above technique for the set of equations of the second row ( first 4 probabilities) gives the following matrix:

Using the above technique for the set of equations of the third row ( first 4 probabilities) gives the following matrix:

Using the above technique for the set of equations of the third row ( first 4 probabilities) gives the following matrix:

***Then Using partial fraction to get inverse laplace:***

***Eguating R.H.S.with L.H.S.:***

This set of the four equations will be used repeatedly to calculate the inverse Laplace transform for the first four probabilities in the first four rows, the difference will be in the resultant vector for each : in matrix notation

The same procedure is used to solve the following PDFs’ ; what differs is the numerator of both sides, but the denominators on both sides are the same for all upcoming equations. In matrix notation :

**Solving the Last 5 Probabilities in the First Row by Using the Method of Integrating Factor**

Substitute for each then integrate both sides:

**Solving The Last 5 Probabilities In The second Row By Using The Method Of Integrating Factor**

Using the same procedure as in the last 5 probabilities in the first row, but what differ are the coefficients for each PDFs’:

**Solving The Last 5 Probabilities In The third Row By Using The Method Of Integrating Factor**

Using the same procedure as in the last 5 probabilities in the first row, but what differ are the coefficients for each PDFs’:

**Solving The Last 5 Probabilities In The fourth Row By Using The Method Of Integrating Factor**

Using the same procedure as in the last 5 probabilities in the first row, but what differ are the coefficients for each PDFs’:

Solving the last 12 equations in the system by integrating factor:

## 2. Estimation Of The Q Rate transiiton Matrix:

The Q matrix

The eigen-values of this matrix are obtained by finding the zeros of the characteristic polynomial (polynomial of the 9 th degree) ,this is achieved by solving the following equation ,

As obviously seen this 9th degree polynomial has 9 eigen-values and the full model has 22 transition rates.

The other roots:

The zeros for quadratic

The zeros for quadratic

Now differentiating each eigenvalue with respect to the rates forming this eigenvalue:

Starting with the last 4 roots or eigenvalues because they are simpler than the first 4 eigenvalues:

The first 4 roots or eigenvalues will be discussed as follows :

and , to construct the score vector

Hint: if the cell does not have counts, so the scalar corresponding to this cell is dropped.

The scaled score function is cross product with itself i.e

According to Kalbfliesch and Lawless (1985) the second derivative is assumed to be zero , the score function is crossed product and scaled for each pdf with the scalars (hint if the cell does not have counts, so the scalar of this cell is dropped ) :

The scaled matrices are summed up to get the scaled hessian matrix

with initial theta according to Klotz and Sharples (1994); the initial is

Substituting in Quasi-Newton method by the initial values, then the score and inverse of the hessian matrix are calculated to give the estimated rates.

## 3. Mean Sojourn Time

These times are independent so covariance between them is zero

.

## 4. State Probability Distribution:

To get the probability distribution of the states after a certain period of time the following equation should be solved:

### 4.1. Asymptotic Covariance of the Stationary Distribution

To obtain stationary probability distribution when t goes to infinity or in other words when the process does not depend on time the following equation is solved for

That is to mean solve the following system of equations:

In matrix notation:

To get the asymptotic covariance matrix of the state probability distribution, the derivative of the state probability distribution with respect to each parameter rate should be calculated as following:

Using multivariate delta method

## 5. Life Expectancy of a Patient Suffering from NAFLD in Various Stages:

Partitioning the differential equation into the following:

B is the transition rate matrix among the transient states and the column vector A is the transition rate from each transient state to the absorbing (death) state .

Steps:

1. First: specify the Q matrix
2. Second: remove the last column and the last row from Q matrix to obtain B matrix
3. Third: get the inverse of the B matrix
4. Forth: multiply the inverse by -1
5. Lastly and fifth: Apply the following formula of mean time to absorption

## 6. Expected Number of Patients in Each State:

## 7. Hypothetical Model:

To illustrate the above concepts and discussion, a hypothetical numerical example is introduced. It does not represent real data but it is for demonstrative purposes.

A study was conducted over 15 years on 1050 patients with risk factors for developing NAFLD such as type 2 diabetes mellitus, obesity, and hypertension acting alone or together as a metabolic syndrome. The patients were decided to be followed up every year by a liver biopsy to identify the NAFLD cases, but the actual observations were recorded with different intervals. The following is the final estimated rate matrix and its variance , this is followed by elaborate discussion of the steps; the estimated final transition rate matrix “Q” is :

where

are all zero matrices of size ( 8 by 14 ) , ( 14 by 8 ) and ( 14 by 14 ) respectively.

The estimated transition rate matrix Q is calculated utilizing procedure that is similar to the one used in the small model, as shown below in the following steps:

For each Δt , the observed transition counts in this interval are obtained, then applying the successive steps to get the estimated rate matrix:

**Step 1**: calculate the eigenvalues for the initial Q matrix obtained from the observed transition counts in this interval.

**Step 2**: calculate = t \* e^(eigenvalue \*t)\* partial derivative of each eigenvalues with each rate or theta to get score function.

**Step 3:** rearrange the score function, then scale it .

**Step 4**: multiply the rearranged scaled scored function with the transposed rearranged scaled score function to get the hessian matrix (22 by 22 matrix).

**Step 5**: scale the above hessian matrix, then resultant matrix can be partitioned into 4 matrices.

**Step 6**: invert the scaled hessian matrix (only the upper left is invertible).

**Step 7**: multiply the inverted scaled hessian matrix by the scaled score function.

**Step 8**: apply quasi-newton formula.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Observed counts of transitions during time interval Δt=1** | | | | | | | | | | |
|  | **State 1** | **State 2** | **State3** | **State 4** | **State 5** | **State 6** | **State 7** | **State 8** | **State 9** | **total** |
| **State 1** | 784 | 573 | 74 | 21 | 20 | 0 | 0 | 0 | 10 | 1482 |
| **State 2** | 9 | 333 | 130 | 21 | 19 | 0 | 0 | 0 | 6 | 518 |
| **State 3** | 4 | 11 | 103 | 44 | 19 | 0 | 0 | 10 | 9 | 200 |
| **State 4** | 0 | 0 | 4 | 33 | 21 | 0 | 0 | 8 | 7 | 73 |
| **State 5** | 0 | 0 | 0 | 0 | 35 | 12 | 10 | 4 | 6 | 67 |
| **State 6** | 0 | 0 | 0 | 0 | 0 | 1 | 8 | 0 | 1 | 10 |
| **State 7** | 0 | 0 | 0 | 0 | 0 | 0 | 10 | 0 | 7 | 17 |
| **State 8** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 5 | 15 | 20 |
| **State 9** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|  |  |  |  |  |  |  |  |  |  | 2387 |

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Initial Q matrix :** | | | | | | | | | **Step 1 : calculate eigenvalues for this Q matrix :** | |
| -.397 | .39 | 0 | 0 | 0 | 0 | 0 | 0 | .007 | **Eigenvalue 1** | -.45792 |
| .02 | -.28 | .25 | 0 | 0 | 0 | 0 | 0 | .01 | **Eigenvalue 2** | -.58993 |
| 0 | .05 | -.38 | .22 | 0 | 0 | 0 | .05 | .04 | **Eigenvalue 3** | -.16836 |
| 0 | 0 | .03 | -.53 | .28 | 0 | 0 | .11 | .09 | **Eigenvalue 4** | -.35079 |
| 0 | 0 | 0 | 0 | -.33 | .18 | 0 | .06 | .09 | **Eigenvalue 5** | -.33 |
| 0 | 0 | 0 | 0 | 0 | -.9 | .8 | 0 | .1 | **Eigenvalue 6** | -.9 |
| 0 | 0 | 0 | 0 | 0 | 0 | -.41 | 0 | .41 | **Eigenvalue 7** | -.41 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | -.75 | .75 | **Eigenvalue 8** | -.75 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | **Eigenvalue 9** | 0 |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Step 2 : calculate** | | **Step 3 : rearrange the score function then scale it by a factor =14204** | | |
| **Lambda 12** | -.6608 | **Lambda 12** | -.6608 | -9385 |
| **Lambda 18** | -.6751 | **Mu 21** | -.4841 | -6876 |
| **Lambda 19** | -.6751 | **Lambda 23** | -.7267 | -10323 |
| **Lambda 23** | -.7267 | **Mu 32** | -.5233 | -7433 |
| **Lambda 28** | -.7632 | **Lambda 34** | -.6736 | -9568 |
| **Lambda 29** | -.7632 | **Mu 43** | -.4503 | -6396 |
| **Mu 21** | -.4841 | **Lambda 79** | -.6637 | -9426 |
| **Lambda 34** | -.6736 | **Lambda 89** | -.4724 | -6709 |
| **Lambda 38** | -.7058 | **Lambda 18** | -.6751 | -9589 |
| **Lambda 39** | -.7058 | **Lambda 19** | -.6751 | -9589 |
| **Mu 32** | -.5233 | **Lambda 28** | -.7632 | -10841 |
| **Lambda 45** | -.592 | **Lambda 29** | -.7632 | -10841 |
| **Lambda 48** | -.592 | **Lambda 38** | -.7058 | -10025 |
| **Lambda 49** | -.592 | **Lambda 39** | -.7058 | -10025 |
| **Mu 43** | -.4503 | **Lambda 45** | -.5920 | -8409 |
| **Lambda 56** | -.7189 | **Lambda 48** | -.5920 | -8409 |
| **Lambda 58** | -.7189 | **Lambda 49** | -.5920 | -8409 |
| **Lambda 59** | -.7189 | **Lambda 56** | -.7189 | -10212 |
| **Lambda 67** | -.4066 | **Lambda 58** | -.7189 | -10212 |
| **Lambda 69** | -.4066 | **Lambda 59** | -.7189 | -10212 |
| **Lambda 79** | -.6637 | **Lambda 67** | -.4066 | -5775 |
| **Lambda 89** | -.4724 | **Lambda 69** | -.4066 | -5775 |

**Step 4**: multiply the rearranged scaled scored function with the transposed rearranged scaled score function to get the hessian matrix (22 by 22 matrix)

**Step 5**: scale the above hessian matrix by a factor of 606523.3, the resultant matrix can be partitioned into 4 matrices, the upper left matrix of size (8 by 8) is the matrix needs to be inverted but it may be singular or close to be singular so the pseudo-inverse using singular value decomposition is applied. The lower right matrix is (14 by 14) has repeated rows. The matrices on the secondary diagonal, the upper right (8 by 14) and the lower left (14 by 8) have repeated rows so the only invertible matrix is the upper left.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Step 6: invert the scaled hessian matrix ( only the upper left is invertible)** | | | | | | | |
|  | | | | | | | |
| .4574 | .3351 | .503 | .3622 | .4663 | .3117 | .4594 | .327 |
| .3351 | .2455 | .3686 | .2654 | .3416 | .2284 | .3366 | .2396 |
| .503 | .3686 | .5533 | .3984 | .5128 | .3428 | .5052 | .3596 |
| .3622 | .2654 | .3984 | .2869 | .3693 | .2469 | .3638 | .2589 |
| .4663 | .3416 | .5128 | .3693 | .4753 | .3178 | .4683 | .3333 |
| .3117 | .2284 | .3428 | .2469 | .3178 | .2124 | .3131 | .2228 |
| .4594 | .3366 | .5052 | .3638 | .4683 | .3131 | .4614 | .3284 |
| .327 | .2396 | .3596 | .2589 | .3333 | .2228 | .3284 | .2337 |

|  |  |  |
| --- | --- | --- |
| **Step 7 : multiply inverted hessian matrix by scaled score function** | **Step 8: apply quasi-Newton formula to get the estimated rates in Δt=1** | |
| -.2746 \* | **Lambda 12** | .39 |
| -.2012 \* | **Mu 21** | .02 |
| -.3020 \* | **Lambda 23** | .25 |
| -.2175 \* | **Mu 32** | .05 |
| -.2799 \* | **Lambda 34** | .22 |
| -.1871 \* | **Mu 43** | .05 |
| -.2758 \* | **Lambda 79** | .41 |
| -.1963 \* | **Lambda 89** | .75 |
| 0 | **Lambda 18** | 0 |
| 0 | **Lambda 19** | .007 |
| 0 | **Lambda 28** | 0 |
| 0 | **Lambda 29** | .01 |
| 0 | **Lambda 38** | .05 |
| 0 | **Lambda 39** | .04 |
| 0 | **Lambda 45** | .28 |
| 0 | **Lambda 48** | .11 |
| 0 | **Lambda 49** | .09 |
| 0 | **Lambda 56** | .18 |
| 0 | **Lambda 58** | .06 |
| 0 | **Lambda 59** | .09 |
| 0 | **Lambda 67** | .8 |
| 0 | **Lambda 69** | .1 |

The same steps are performed for the transitions occurred in time interval =2 :

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Observed counts of transitions during time interval Δt=2** | | | | | | | | | | |
|  | **State 1** | **State 2** | **State3** | **State 4** | **State 5** | **State 6** | **State 7** | **State 8** | **State 9** | **total** |
| **State 1** | 313 | 229 | 30 | 9 | 8 | 0 | 0 | 0 | 4 | 593 |
| **State 2** | 4 | 133 | 52 | 8 | 7 | 0 | 0 | 0 | 3 | 207 |
| **State 3** | 2 | 4 | 40 | 19 | 8 | 0 | 0 | 3 | 4 | 80 |
| **State 4** | 0 | 0 | 1 | 13 | 8 | 0 | 0 | 3 | 4 | 29 |
| **State 5** | 0 | 0 | 0 | 0 | 13 | 5 | 4 | 2 | 3 | 27 |
| **State 6** | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 1 | 4 |
| **State 7** | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | 3 | 7 |
| **State 8** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 6 | 8 |
| **State 9** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|  |  |  |  |  |  |  |  |  |  | 955 |

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Initial Q matrix :** | | | | | | | | | **Step 1 : calculate eigenvalues for this Q matrix :** | |
| -.397 | .39 | 0 | 0 | 0 | 0 | 0 | 0 | .007 | **Eigenvalue 1** | -.46595 |
| .02 | -.28 | .25 | 0 | 0 | 0 | 0 | 0 | .01 | **Eigenvalue 2** | -.59304 |
| 0 | .05 | -.38 | .24 | 0 | 0 | 0 | .04 | .05 | **Eigenvalue 3** | -.17668 |
| 0 | 0 | .03 | -.55 | .28 | 0 | 0 | .1 | .14 | **Eigenvalue 4** | -.37133 |
| 0 | 0 | 0 | 0 | -.37 | .19 | 0 | .07 | .11 | **Eigenvalue 5** | -.37 |
| 0 | 0 | 0 | 0 | 0 | -1 | .75 | 0 | .25 | **Eigenvalue 6** | -1 |
| 0 | 0 | 0 | 0 | 0 | 0 | -.43 | 0 | .43 | **Eigenvalue 7** | -.43 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | -.75 | .75 | **Eigenvalue 8** | -.75 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | **Eigenvalue 9** | 0 |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Step 2 : calculate** | | **Step 3 : rearrange the score function then scale it by a factor =5678** | | |
| **Lambda 12** | -.8781 | **Lambda 12** | -.8781 | -4986.1 |
| **Lambda 18** | -.9194 | **Mu 21** | -.3807 | -2161.4 |
| **Lambda 19** | -.9194 | **Lambda 23** | -1.0806 | -6135.9 |
| **Lambda 23** | -1.0806 | **Mu 32** | -.4458 | -2531.3 |
| **Lambda 28** | -1.186 | **Lambda 34** | -.9245 | -5249.1 |
| **Lambda 29** | -1.186 | **Mu 43** | -.2905 | -1649.6 |
| **Mu 21** | -.3807 | **Lambda 79** | -.8463 | -4805.4 |
| **Lambda 34** | -.9245 | **Lambda 89** | -.4463 | -2533.9 |
| **Lambda 38** | -.9727 | **Lambda 18** | -.9194 | -5220.6 |
| **Lambda 39** | -.9727 | **Lambda 19** | -.9194 | -5220.6 |
| **Mu 32** | -.4458 | **Lambda 28** | -1.186 | -6734.2 |
| **Lambda 45** | -.6766 | **Lambda 29** | -1.186 | -6734.2 |
| **Lambda 48** | -.6766 | **Lambda 38** | -.9727 | -5523.2 |
| **Lambda 49** | -.6766 | **Lambda 39** | -.9727 | -5523.2 |
| **Mu 43** | -.2905 | **Lambda 45** | -.6766 | -3841.7 |
| **Lambda 56** | -.9542 | **Lambda 48** | -.6766 | -3841.7 |
| **Lambda 58** | -.9542 | **Lambda 49** | -.6766 | -3841.7 |
| **Lambda 59** | -.9542 | **Lambda 56** | -.9542 | -5418.1 |
| **Lambda 67** | -.2707 | **Lambda 58** | -.9542 | -5418.1 |
| **Lambda 69** | -.2707 | **Lambda 59** | -.9542 | -5418.1 |
| **Lambda 79** | -.8463 | **Lambda 67** | -.2707 | -1536.9 |
| **Lambda 89** | -.4463 | **Lambda 69** | -.2707 | -1536.9 |

**Step 4**: multiply the rearranged scaled scored function with the transposed rearranged scaled score function to get the hessian matrix (22 by 22 matrix)

**Step 5**: scale the above hessian matrix by a factor of 235355.8, the resultant matrix can be partitioned into 4 matrices, the upper left matrix of size (8 by 8) is the matrix needs to be inverted but it may be singular or close to be singular so the pseudo-inverse using singular value decomposition is applied. The lower right matrix is (14 by 14) has repeated rows. The matrices on the secondary diagonal, the upper right (8 by 14) and the lower left (14 by 8) have repeated rows so the only invertible matrix is the upper left.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Step 6: invert the scaled hessian matrix ( only the upper left is invertible)** | | | | | | | |
|  | | | | | | | |
| .5938 | .2574 | .7307 | .3015 | .6251 | .1964 | .5723 | .3018 |
| .2574 | .1116 | .3168 | .1307 | .271 | .0852 | .2481 | .1308 |
| .7307 | .3168 | .8992 | .371 | .7693 | .2417 | .7042 | .3713 |
| .3015 | .1307 | .371 | .153 | .3174 | .0997 | .2905 | .1532 |
| .6251 | .271 | .7693 | .3174 | .6581 | .2068 | .6025 | .3177 |
| .1964 | .0852 | .2417 | .0997 | .2068 | .065 | .1893 | .0998 |
| .5723 | .2481 | .7042 | .2905 | .6025 | .1893 | .5515 | .2908 |
| .3018 | .1308 | .3713 | .1532 | .3177 | .0998 | .2908 | .1533 |

|  |  |  |
| --- | --- | --- |
| **Step 7 : multiply inverted hessian matrix by scaled score function** | **Step 8: apply quasi-Newton formula to get the estimated rates in Δt=2** | |
| -.1588 \* | **Lambda 12** | .39 |
| -.0689 \* | **Mu 21** | .02 |
| -.1955 \* | **Lambda 23** | .25 |
| -.0806 \* | **Mu 32** | .05 |
| -.1672 \* | **Lambda 34** | .24 |
| -.0525 \* | **Mu 43** | .03 |
| -.1531 \* | **Lambda 79** | .43 |
| -.0807\* | **Lambda 89** | .75 |
| 0 | **Lambda 18** | 0 |
| 0 | **Lambda 19** | .007 |
| 0 | **Lambda 28** | 0 |
| 0 | **Lambda 29** | .01 |
| 0 | **Lambda 38** | .04 |
| 0 | **Lambda 39** | .05 |
| 0 | **Lambda 45** | .28 |
| 0 | **Lambda 48** | .1 |
| 0 | **Lambda 49** | .14 |
| 0 | **Lambda 56** | .19 |
| 0 | **Lambda 58** | .07 |
| 0 | **Lambda 59** | .11 |
| 0 | **Lambda 67** | .75 |
| 0 | **Lambda 69** | .25 |

The same steps are performed for transitions occurred in time interval =3

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Observed counts of transitions during time interval Δ t=3** | | | | | | | | | | |
|  | **State 1** | **State 2** | **State3** | **State 4** | **State 5** | **State 6** | **State 7** | **State 8** | **State 9** | **total** |
| **State 1** | 78 | 57 | 8 | 2 | 2 | 0 | 0 | 0 | 1 | 148 |
| **State 2** | 1 | 32 | 13 | 2 | 2 | 0 | 0 | 0 | 1 | 51 |
| **State 3** | 0 | 0 | 9 | 4 | 2 | 0 | 0 | 2 | 1 | 18 |
| **State 4** | 0 | 0 | 0 | 3 | 2 | 0 | 0 | 1 | 1 | 7 |
| **State 5** | 0 | 0 | 0 | 0 | 3 | 2 | 1 | 0 | 1 | 7 |
| **State 6** | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 2 |
| **State 7** | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 2 |
| **State 8** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 2 | 3 |
| **State 9** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|  |  |  |  |  |  |  |  |  |  | 238 |

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Initial Q matrix :** | | | | | | | | | **Step 1 : calculate eigenvalues for this Q matrix :** | |
| -.397 | .39 | 0 | 0 | 0 | 0 | 0 | 0 | .007 | **Eigenvalue 1** | -.48277 |
| .02 | -.29 | .25 | 0 | 0 | 0 | 0 | 0 | .02 | **Eigenvalue 2** | -.57 |
| 0 | .05 | -.36 | .21 | 0 | 0 | 0 | .05 | .05 | **Eigenvalue 3** | -.18296 |
| 0 | 0 | 0 | -.57 | .29 | 0 | 0 | .14 | .14 | **Eigenvalue 4** | -.38128 |
| 0 | 0 | 0 | 0 | -.43 | .29 | 0 | 0 | .14 | **Eigenvalue 5** | -.43 |
| 0 | 0 | 0 | 0 | 0 | -1 | .5 | 0 | .5 | **Eigenvalue 6** | -1 |
| 0 | 0 | 0 | 0 | 0 | 0 | -.5 | 0 | .5 | **Eigenvalue 7** | -.5 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | -.67 | .67 | **Eigenvalue 8** | -.67 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | **Eigenvalue 9** | 0 |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Step 2 : calculate** | | **Step 3 : rearrange the score function then scale it by a factor =1354** | | |
| **Lambda 12** | -.8815 | **Lambda 12** | -.8815 | -1193.6 |
| **Lambda 18** | -.9480 | **Mu 21** | -.0671 | -90.9 |
| **Lambda 19** | -.9480 | **Lambda 23** | -1.189 | -1609.9 |
| **Lambda 23** | -1.189 | **Mu 32** | -.2052 | -277.8 |
| **Lambda 28** | -1.3642 | **Lambda 34** | -1.0813 | -1464 |
| **Lambda 29** | -1.3642 | **Mu 43** | -.0554 | -75 |
| **Mu 21** | -.0671 | **Lambda 79** | -.6694 | -906.4 |
| **Lambda 34** | -1.0813 | **Lambda 89** | -.4020 | -544.3 |
| **Lambda 38** | -1.0813 | **Lambda 18** | -.9480 | -1283.6 |
| **Lambda 39** | -1.0813 | **Lambda 19** | -.9480 | -1283.6 |
| **Mu 32** | -.2052 | **Lambda 28** | -1.3642 | -1847.1 |
| **Lambda 45** | -.5426 | **Lambda 29** | -1.3642 | -1847.1 |
| **Lambda 48** | -.5426 | **Lambda 38** | -1.0813 | -1464 |
| **Lambda 49** | -.5426 | **Lambda 39** | -1.0813 | -1464 |
| **Mu 43** | -.0554 | **Lambda 45** | -.5426 | -734.7 |
| **Lambda 56** | -.8258 | **Lambda 48** | -.5426 | -734.7 |
| **Lambda 58** | -.8258 | **Lambda 49** | -.5426 | -734.7 |
| **Lambda 59** | -.8258 | **Lambda 56** | -.8258 | -1118.1 |
| **Lambda 67** | -.1494 | **Lambda 58** | -.8258 | -1118.1 |
| **Lambda 69** | -.1494 | **Lambda 59** | -.8258 | -1118.1 |
| **Lambda 79** | -.6694 | **Lambda 67** | -.1494 | -202.2 |
| **Lambda 89** | -.4020 | **Lambda 69** | -.1494 | -202.2 |

**Step 4**: multiply the rearranged scaled scored function with the transposed rearranged scaled score function to get the hessian matrix (22 by 22 matrix)

**Step 5**: scale the above hessian matrix by a factor of 56367.63, the resultant matrix can be partitioned into 4 matrices, the upper left matrix of size (8 by 8) is the matrix needs to be inverted but it may be singular or close to be singular so the pseudo-inverse using singular value decomposition is applied. The lower right matrix is (14 by 14) has repeated rows. The matrices on the secondary diagonal, the upper right (8 by 14) and the lower left (14 by 8) have repeated rows so the only invertible matrix is the upper left.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Step 6: invert the scaled hessian matrix ( only the upper left is invertible)** | | | | | | | |
|  | | | | | | | |
| .4655 | .0354 | .6278 | .1084 | .571 | .0292 | .3535 | .2123 |
| .0354 | .0027 | .0478 | .0082 | .0435 | .0022 | .0269 | .0162 |
| .6278 | .0478 | .8468 | .1461 | .7701 | .0394 | .4768 | .2863 |
| .1084 | .0082 | .1461 | .0252 | .1329 | .0068 | .0823 | .0494 |
| .571 | .0435 | .7701 | .1329 | .7004 | .0359 | .4336 | .2604 |
| .0292 | .0022 | .0394 | .0068 | .0359 | .0018 | .0222 | .0133 |
| .3535 | .0269 | .4768 | .0823 | .4336 | .0222 | .2684 | .1612 |
| .2123 | .0162 | .2863 | .0494 | .2604 | .0133 | .1612 | .0968 |

|  |  |  |
| --- | --- | --- |
| **Step 7 : multiply inverted hessian matrix by scaled score function** | **Step 8: apply quasi-Newton formula to get the estimated rates in Δt=3** | |
| -.2874 \* | **Lambda 12** | .39 |
| -.0219 \* | **Mu 21** | .02 |
| -.3876 \* | **Lambda 23** | .25 |
| -.0669 \* | **Mu 32** | .05 |
| -.3525 \* | **Lambda 34** | .21 |
| -.0180 \* | **Mu 43** | 0 |
| -.2182 \* | **Lambda 79** | .5 |
| -.1310\* | **Lambda 89** | .67 |
| 0 | **Lambda 18** | 0 |
| 0 | **Lambda 19** | .007 |
| 0 | **Lambda 28** | 0 |
| 0 | **Lambda 29** | .02 |
| 0 | **Lambda 38** | .05 |
| 0 | **Lambda 39** | .05 |
| 0 | **Lambda 45** | .29 |
| 0 | **Lambda 48** | .14 |
| 0 | **Lambda 49** | .14 |
| 0 | **Lambda 56** | .29 |
| 0 | **Lambda 58** | 0 |
| 0 | **Lambda 59** | .14 |
| 0 | **Lambda 67** | .5 |
| 0 | **Lambda 69** | .5 |

Number of transitions observed in first interval corresponds to (2/3) of the total 3580 transitions while the number of transitions observed in the second interval corresponds to (4/15) of the total 3580 transitions and the number of transitions observed in the third interval corresponds to (1/15) of the total 3580 transitions.

Scaling the vector of theta or rates estimated in each interval by these correspondent weights in each interval and then summing up the weighted vectors, the final vector of rates or thetas is obtained which is:

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |  |  |  |  |
| 0.39 | 0.02 | 0.25 | 0.05 | 0.225 | 0.041 | 0.421 | 0.745 | 0 | .007 | 0 |

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |  |  |  |  |
| 0.011 | 0.047 | 0.043 | 0.281 | 0.109 | 0.107 | 0.19 | 0.059 | 0.099 | 0.767 | 0.167 |

Doing the same procedure for the inverted scaled hessian matrix the final matrix which is the estimated variance of the rates:

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | | | | | | | |
| .3293 | .0327 | .4414 | .0827 | .4004 | .0268 | .2540 | .1517 |
| .0327 | .0064 | .0428 | .0108 | .0385 | .0053 | .0268 | .0159 |
| .4414 | .0428 | .5922 | .1100 | .5373 | .0350 | .3400 | .2032 |
| .0827 | .0108 | .1100 | .0228 | .0995 | .0088 | .0650 | .0387 |
| .4004 | .0385 | .5373 | .0995 | .4876 | .0315 | .3082 | .1843 |
| .0268 | .0053 | .0350 | .0088 | .0315 | .0044 | .0219 | .0130 |
| .254 | .0268 | .3400 | .0650 | .3082 | .0219 | .1967 | .1174 |
| .1517 | .0159 | .2032 | .0387 | .1843 | .0130 | .1174 | .0702 |

**Mean sojourn time for each state:**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **For state 1** | **For state 2** | **For state 3** | **For state 4** | **For state 5** | **For state 6** | **For state 7** | **For state 8** |
| 2.5189 years | 3.5587 years | 2.7397 years | 1.8587 years | 2.8736 years | 1.0707 years | 2.3753 years | 1.3423 years |

Mean time spent by the patient in state 1 is approximately 2 years and 6 months, in state 2 the mean sojourn time is approximately 3 years and 6 months , in state 3 it is approximately 2 years and 9 months , in state 4 it is approximately 1 years and 10 months , in state 5 it is approximately 2 years and 10 months, in state 6 it is approximately 1 years and 1 month , in state 7 it is approximately 2 years and 5 months and lastly in state 8 the mean sojourn time is approximately 1 years and 4 months.

**Variance of the sojourn time**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **For state 1** | **For state 2** | **For state 3** | **For state 4** | **For state 5** | **For state 6** | **For state 7** | **For state 8** |
|  |  |  |  |  |  |  |  |

**The life expectancy of NAFLD patient or the mean time to absorption:**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **From state 1** | **From state 2** | **From state 3** | **From state 4** | **From state 5** | **From state 6** | **From state 7** | **From state 8** |
| 13.6762 years | 11.3576 years | 7.6718 years | 5.1966 years | 4.7507 years | 3.0213 years | 2.3753 years | 1.3423 years |

Mean time for a patient in state 1 to absorption or death is approximately 13 years and 8 month, for a patient in state 2 it is approximately 11 years and 4 months, for a patient in state 3 it is approximately 7 years and 2 months, for a patient is state 4 it is approximately 5 years and 2 months ,for a patient is state 5 it is approximately 4 years and 9 months, for a patient is state 6 it is approximately 3 years, for a patient in state 7 it is approximately 2 years and 4 and a half months, for patient in state 8 it is approximately 1 year and 4 months.

Transition probability matrix at 1 year:

If a cohort of 5000 NAFLD patients have initial distribution of and initial counts of patients in each state arethen at 1 year the state probability distribution is and the expected counts of patients are .

Transition probability matrix at 50 year:

For the above same cohort of 5000 NAFLD patients, at 50 year the state probability distribution is , and the estimated variance-covariance matrix of this distribution is :

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | | | | | | | | |
| .01 | .0316 | .033 | .02 | .0257 | .0088 | .0239 | .0115 | 0 |
| .0316 | .0998 | .1043 | .0632 | .0813 | .0278 | .0757 | .0364 | 0 |
| .0330 | .1043 | .1090 | .0661 | .0850 | .0291 | .0791 | .0380 | 0 |
| .02 | .0632 | .0661 | .0400 | .0515 | .0176 | .0479 | .0230 | 0 |
| .0257 | .0813 | .0850 | .0515 | .0662 | .0226 | .0616 | .0296 | 0 |
| .0088 | .0278 | .0291 | .0176 | .0226 | .0077 | .0211 | .0101 | 0 |
| .0239 | .0757 | .0791 | .0479 | .0616 | .0211 | .0574 | .0276 | 0 |
| .0115 | .0364 | .0380 | .0230 | .0296 | .0101 | .0276 | .0133 | 0 |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

steps for evaluation of the transition probabilities are demonstrated and as explained in the text :

**Step 1**: Laplace transform method is applied to solve the 4 differential equations in the first four rows along with Cramer rule using initial value , the determinant is a 4th degree polynomial which has 4 roots equal to the first four eigenvalues of the Q transition rate matrix. So once the Q rate matrix is estimated, the 4th degree polynomial can be solved for its , **Step2**: the numerator for each probability is given by substitution for as illustrated in the discussion in text, this can be summarized in the following table:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Coefficient of s3 | Coefficient of s2 | Coefficient of s | Constant |
| DP\*(s)11 | 1 | 1.184 | .428388 | .045862745 |
| DP\*(s)12 | 0 | .39 | .35217 | .07298655 |
| DP\*(s)13 | 0 | 0 | .0975 | .052455 |
| DP\*(s)14 | 0 | 0 | 0 | .0219375 |
| DP\*(s)21 | 0 | .02 | .01806 | .0037429 |
| DP\*(s)22 | 1 | 1.3 | .545636 | .074296565 |
| DP\*(s)23 | 0 | .25 | .23375 | .0533965 |
| DP\*(s)24 | 0 | 0 | .05625 | .02233125 |
| DP\*(s)31 | 0 | 0 | .001 | .000538 |
| DP\*(s)32 | 0 | .05 | .04675 | .0106793 |
| DP\*(s)33 | 1 | 1.216 | .468521 | .055821266 |
| DP\*(s)34 | 0 | .225 | .15255 | .023345325 |
| DP\*(s)41 | 0 | 0 | 0 | .000041 |
| DP\*(s)42 | 0 | 0 | .00205 | .00081385 |
| DP\*(s)43 | 0 | .041 | .027798 | .004254037 |
| DP\*(s)44 | 1 | 1.043 | .338727 | .032908805 |

To get the inverse Laplace, partial fraction method is used and this needs the following calculations :

|  |  |  |  |
| --- | --- | --- | --- |
| **Step 3** : construct (K) matrix | | | |
| 1 | 1 | 1 | 1 |
| 1.12005634 | .991227769 | 1.409099675 | 1.222616213 |
| .37435313 | .306037387 | .648411308 | .452470172 |
| .03633368 | .028397028 | .097427266 | .046731407 |

|  |  |  |  |
| --- | --- | --- | --- |
| **Step 4** : invert (K) matrix | | | |
| -25.644304 | 55.6343565 | -120.696652 | 261.84686 |
| 16.4685712 | -27.92361 | 47.346434 | -80.27918609 |
| -.2255193 | 1.311918 | -7.631857 | 44.39699213 |
| 10.4012519 | -29.02266 | 80.9820756 | -225.9646 |

**Step 5**: calculate the coefficient of the first four in the first four rows; let them be called , , , , it is calculated by multiplying the inverted K matrix by the

|  |  |  |  |
| --- | --- | --- | --- |
| **Coefficient of P11** | **Coefficient of P12** | **Coefficient of P13** | **Coefficient of P14** |
| **A11****=** .5307928 | **A12****=** -1.69704167 | **A13 =** 1.9672538 | **A14****=** 5.74426567 |
| **B11****=** .00784714 | **B12****=** -.07551577 | **B13****=** .40523268 | **B14****=** -1.7611246 |
| **C11****=** .094564365 | **C12****=** 1.06432039 | **C13****=** 1.58473813 | **C14****=** .97395901 |
| **D11****=** .366808118 | **D12****=** .70823704 | **D13** **=** -3.95722461 | **D14****=** -4.9571 |
| **Coefficient of P21** | **Coefficient of P22** | **Coefficient of P23** | **Coefficient of P24** |
| **A21 =** -.0870278 | **A22 =** .2782437 | **A23 =** -.322547186 | **A24 =** -.9418189 |
| **B21 =** -.0038726 | **B22 =** .0373265 | **B23 =** -.200301556 | **B24 =** .87050238 |
| **C21 =** .0545805 | **C22 =** .614303 | **C23 =** .914677019 | **C24 =** .56214835 |
| **D21 =** .0363198 | **D22 =** .0701267 | **D23 =** -.391828278 | **D24 =** -.4908319 |
| **Coefficient of P31** | **Coefficient of P32** | **Coefficient of P33** | **Coefficient of P34** |
| **A31 =** .020176962 | **A32 =** -.06450944 | **A33 =** .07478098 | **A34 =** .21835606 |
| **B31 =** .004156233 | **B32 =** -.04006031 | **B33 =** .21497162 | **B34 =** -.9342579 |
| **C31 =** .016253724 | **C32 =** .1829354 | **C33 =** .27238481 | **C34 =** .16740409 |
| **D31 =** -.04058692 | **D32 =** -.07836566 | **D33 =** .43786259 | **D34 =** .54849772 |
| **Coefficient of P41** | **Coefficient of P42** | **Coefficient of P43** | **Coefficient of P44** |
| **A41 =** .0107357 | **A42 =** -.0343241 | **A43 =** .0397889327 | **A44 =** .1161825 |
| **B41 =** -.0032914 | **B42 =** .031725 | **B43 =** -.17024246 | **B44 =** .73986714 |
| **C41 =** .0018203 | **C42 =** .02048718 | **C43 =** .030504745 | **C44 =** .01874781 |
| **D41 =** -.0092646 | **D42 =** -.0178881 | **D43 =** .099948473 | **D44 =** .12520254 |

**Step 6**: calculate the inverse Laplace for each PDF, which equals:

|  |  |  |  |
| --- | --- | --- | --- |
| **P11 =** .675065196 | **P12 =**.27897024 | **P13 =** .03452831 | **P14 =** .00246831 |
| **P21 =** .0143062 | **P22 =** .7624677 | **P23 =** .181919657 | **P24 =** .01902779 |
| **P31 =** .000354137 | **P32 =** .03638393 | **P33 =** .70170095 | **P34 =** .14396966 |
| **P41 =** 4.61E-06 | **P42 =** .0006935 | **P43 =** .026234471 | **P44 =** .58677589 |

**Step 7**: calculation of the last four probabilities in the first row:

|  |  |  |  |
| --- | --- | --- | --- |
| For P15: |  |  |  |
| G1=λ45\*A14 | 1.6141387 | G1/(w+r1)=F1 | -14.29154 |
| G2=λ45\*B14 | -.494876 | G2/(w+r2)=F2 | 2.04686 |
| G3=λ45\*C14 | .2736825 | G3/(w+r3)=F3 | 1.5541339 |
| G4=λ45\*D14 | -1.392945 | G4/(w+r4)=F4 | 134.14616 |
|  |  | F5=-(F1+F2+F3+F4) | -1234556 |

|  |  |  |  |
| --- | --- | --- | --- |
| For P16: |  |  |  |
| G5=λ56\*F1 | -2.715392 | G5/(u+r1)=F6 | -5.740103 |
| G6=λ56\*F2 | .3889051 | G6/(u+r2)=F7 | 1.1297899 |
| G7=λ56\*F3 | .2952855 | G7/(u+r3)=F8 | .387463 |
| G8=λ56\*F4 | 25.48777 | G8/(u+r4)=F9 | 44.279103 |
| G9=λ56\*F5 | -23.45657 | G9/(u-w)=F10 | -40.02827 |
|  |  | F11=-(F6+F7+F8+F9+F10) | -.02798 |

|  |  |  |  |
| --- | --- | --- | --- |
| For P17: |  |  |  |
| G10=λ67\*F6 | -4.402659 | G10/(λ79+r1)=F12 | 110.2217 |
| G11=λ67\*F7 | .86654887 | G11/(λ79+r2)=F13 | -5.134428 |
| G12=λ67\*F8 | .29718414 | G12/(λ79+r3)=F14 | 1.193033 |
| G13=λ67\*F9 | 33.9620721 | G13/(λ79+r4)=F15 | 542.38463 |
| G14=λ67\*F10 | -30.701685 | G14/(λ79-w)=F16 | -420.57103 |
| G15=λ67\*F11 | -.0214606 | G15/(λ79-u)=F17 | .04183347 |
|  |  | F18=-(F12+F13+F14+F15+F16+F17) | -228.13579 |

|  |  |  |  |
| --- | --- | --- | --- |
| For P18: |  |  |  |
| G16=λ18\*A11+ λ28\*A12+ λ38\*A13+ λ48\*A14+ λ58\*F1 | -.1246149 | G10/(λ89+r1)=F19 | -.438697828 |
| G17= λ18\*B11+ λ28\*B12+ λ38\*B13+ λ48\*B14+ λ58\*F2 | -.0521514 | G10/(λ89+r2)=F20 | -.335966911 |
| G18= λ18\*C11+ λ28\*C12+ λ38\*C13+ λ48\*C14+ λ58\*F3 | .2723381 | G10/(λ89+r3)=F21 | .475202028 |
| G19= λ18\*D11+ λ28\*D12+ λ38\*D13+ λ48\*D14+ λ58\*F4 | 7.1883097 | G10/(λ89+r4)=F22 | 18.5928823 |
| G20= λ58\*F5 | -7.2838816 | G10/(λ89-w)=F23 | -18.34730875 |
|  |  | F24=-(F19+F20+F21+F22+F23) | .0538892 |

|  |  |  |  |
| --- | --- | --- | --- |
| for P19: |  |  |  |
| G21=λ19\*A11+λ29\*A12+λ39\*A13+λ49\*A14+λ59\*F1+λ69\*F6+λ79\*F12+λ89\*F19 | 44.387339 | G21/r1=F25 | -96.296671 |
| G22=λ19\*B11+λ29\*B12+λ39\*B13+λ49\*B14+λ59\*F2+λ69\*F7+λ79\*F13+λ89\*F20 | -2.1923658 | G22/r2=F26 | 3.71730926 |
| G23=λ19\*C11+λ29\*C12+λ39\*C13+λ49\*C14+λ59\*F3+λ69\*F8+λ79\*F14+λ89\*F21 | 1.2595848 | G23/r3=F27 | -7.327414 |
| G24=λ19\*D11+λ29\*D12+λ39\*D13+λ49\*D14+λ59\*F4+λ69\*F9+λ79\*F15+λ89\*F22 | 262.1805 | G24/r4=F28 | -731.5635 |
| G25=λ59\*F5+λ69\*F10+λ79\*F16+λ89\*F23 | -209.63598 | F29=-G25/w | 602.402231 |
| G26=λ69\*F11+λ79\*F17 | 0.0129392 | F30=-G26/u | -0.0138536 |
| G27=λ79\*F18 | -96.045167 | F31=-G27/λ79 | 228.135788 |
| G28=λ89\*F24 | 0.0401474 | F32=-G28/λ89 | -0.0538892 |
|  |  | F33=-F25-F26-F27-F28+F29+  F30+F31+F32 | 1 |
|  |  |  |

The same substitution is used to calculate the last 5 probabilities in 2nd , 3rd , 4th rows as demonstrated in text .

The same is true for the last 12 PDFs’ in the subsequent 4 rows while P99=1

The transition probability matrix at 1 year is

Of those patients (patients with susceptible risk factors) starting at stage S1 (NAFLD with no fibrosis), that is to mean only steatosis, about 30 % of them will move to S2 (NASH with no fibrosis), 3.5% will move to S3 (NASH with fibrosis whether F1, F2 or F3). They are less likely to develop liver cirrhosis whether compensated or decompensated (S4 and S5 respectively), as only; 0.25% of them will get S4 and 0.02% will get S5. Less than 1% of them, about 0.06% will develop HCC (S8=hepatocellular carcinoma) and 0.82% will die (S9). While the majority, about 67.51 % will remain stable in S1. These patients are not candidate for liver transplantation.

Once the patient starts to develop S2 (NASH with no fibrosis), 18.2% of those patients will progress to develop S3 and about 2% will develop S4 (compensated liver cirrhosis), while; they are less likely to get S5 as only 0.18% will get S5 (decompensated liver cirrhosis).They are more likely to develop S8 (0.44% v.s. 0.06% for those starting at S1) and 1.6% will die, however; only 1.4% will regress to S1. And 76.25 % will remain stable in S2. These patients are also not candidate for liver transplantation.

Those patients at S3, about 14.4% of them will progress to S4 (compensated liver cirrhosis), while 2.1% will develop S5 (decompensated liver cirrhosis). Because they are not highly recommended for liver transplantation, only 0.12% of them will survive the first year after liver transplantation (S6) and 0.02% will survive longer than the first year after liver transplantation (S7), however about 3.5% of them will get HCC (S8) and 6.06% will die. Only 0.04 % of them will regress to S1, 3.64% will regress to S2, and 70.17 % will remain stable in S3.

Of the compensated liver cirrhosis patients (S4), about 18% will be decompensated (S5) and because they are putting on waiting list for liver transplantation, so; 1.5% of them will survive the first year after liver transplantation (S6) and 0.39% will survive longer than the first year after liver transplantation (S7), however about 6.3 % of them will get HCC (S8) and 12.37% will die, no one will regress to S1, 0.07% will regress to S2, 2.62% will regress to S3 and 58.68 % will remain stable in S4.

Once the patient develops decompensated liver cirrhosis (S5), they are highly candidate for liver transplantation, thus; 10.15% of them will survive the first year after liver transplantation (S6) and 4.16% will survive longer than the first year after liver transplantation (S7), however about 3.44% of them will get HCC (S8) and 11.63% will die, and 70.61 % will remain stable in S5, but no regression to previous stages (S1, S2, S3, S4).

Of the patients who had survived the first year, 39.38 % of them would be surviving after this year and 21.32% would die.

The patients who had survived for more than one year after liver transplantation, 34.36 % of them would die. And 52.53 % of patients with HCC (S8) would die.