STOCHASTIC MODEL ON EARLY-STAGE BREAST CANCER WITH TWO TYPES OF TREATMENTS

SUMAN [1], RAJEEV KUMAR [2]

•

[1, 2] Department of Mathematics, Maharshi Dayanand University, Rohtak
[1] suman.uiet@mdurohtak.ac.in, [2] profrajeevmdu@gmail.com

Abstract

The aim of the paper is to study effectiveness of the different treatments of early-stage breast cancer through analysis of a stochastic model. The early-stage breast cancer is a term used to describe breast cancer that is detected at an early stage of development, typically before it has spread to other parts of the body. Early detection of breast cancer is critical as it greatly increases the chances of successful treatment and saves lives. At early-stage breast cancer of the patient, two types of treatment namely, tamoxifen and tamoxifen combined with radiation therapy are commonly used. As it is essential to consider innovative and cost-effective strategies for early detection and treatment. Investigations through analysis of the stochastic model on early-stage breast cancer with these two types of treatments may help the stakeholders. Keeping this in view, in the present paper, a stochastic model is developed for the early-stage breast cancer considering two treatment types, namely tamoxifen and tamoxifen combined with radiation therapy. The model is analyzed by Markov process and regenerative point technique. Mean sojourn time refers to the average amount of time spent by a patient in a particular state before transitioning to another state and mean survival time refers to the average time a patient survives after diagnosis of breast cancer. Mean sojourn time and mean survival time have been calculated. Sensitivity analysis is a technique to understand how changes in input variables or parameters affect the output or outcome of a model and it helps assess the robustness, reliability, and stability of a model by quantifying the impact of variations in input factors. The paper also includes sensitivity and relative sensitivity analyses of the model which explore the impact of different parameters on the survivability of the patient. The MATLAB software has been used for numerical computing and plotting various graphs. The investigation through our analysis of the stochastic model shows that the mean survival time lessens with the rise in the rates of transition and mean survival time from the treatment, tamoxifen plus radiation is higher than the treatment, tamoxifen only. It is concluded that tamoxifen plus radiation is more effective and useful than only tamoxifen for treatment of early-stage breast cancer.

Keywords: Breast cancer, stochastic model, Markov process, regenerative point technique, mean sojourn time, mean survival time and sensitivity analysis

1. Introduction

Cancer is a leading global cause of adult deaths. According to IARC (International Agency for Research on Cancer), India reported approximately 635,000 cancer-related deaths in 2008. Breast cancer ranks as the most frequently diagnosed malignancy among women globally, with 2.3 million cases and 685,000 deaths in 2020. As of the end of 2020, 7.8 million women who had battled were still alive, making it the most common cancer globally.

A lot of work has been done on Markov modelling on breast cancer. Duffy et al. [6] proposed a Markov model indicating that progression to an advanced state is notably faster among individuals aged 40-49. Johnstone et al. [9] analyzed the historical data of untreated breast cancer patients Subsequently, Anthony et al. [1] and Cong et al. [4] found that the combined treatment of tamoxifen and radiation proves more effective in preventing breast cancer recurrence compared to tamoxifen alone. According to Schairer et al. [13], the probability of death, whether from breast cancer or other causes, was frequently higher in black patients compared to white patients. Understanding the parameters of cancer progression is crucial for evaluating screening policies' effectiveness, as highlighted by Harvey et al. [14]. These parameters include transition rates, preclinical sojourn time, sensitivity and the influence of various risk factors on the progression of cancer. Several studies have previously examined breast cancer and its facets. In 2014, Ventura et al. [15] demonstrated the use of a multi-state Markov model to analyze the progression of breast cancer, employing various methods for parametric estimation. Anthony et al. [3] evaluated that radiotherapy reduces the risk of breast and axillary recurrence in early-stage breast cancer when combined with breast-conserving surgery (BCS) and Tamoxifen, but it does not appear to significantly impact distant recurrence or overall survival. Dey et al. [5] provided insights into breast cancer history, risk factors, symptoms, and global and Indian mortality rates, along with available treatments. Grover et al. [7] developed a three-state Markov model based on CA15-3 marker ranges to track disease progression in breast cancer patients. Furthermore, Huang et al. [8] established a breast cancer transition model based on the Chinese population's natural history validating its applicability. Ruiz-Castro et al. [13] developed a discrete-time piecewise Markov model to study the behavior of a multi-state illness. Bayer et al. [2] developed and conducted an analysis of a Markov model designed to simulate and evaluate the treatment strategies for cancer. In 2022, Mubarik et al. [10] made estimations regarding the future trends of breast cancer-related mortality in East and South Asian countries. Moreover Newman et al. [11] discussed the breast cancer burden in low and middle-income countries.

The aim of the paper is to study effectiveness of the different treatments of early-stage breast cancer through analysis of a stochastic model. The early-stage breast cancer is a term used to describe breast cancer that is detected at an early stage of development, typically before it has spread to other parts of the body. Early detection of breast cancer is critical as it greatly increases the chances of successful treatment and saves lives. At early-stage breast cancer of the patient, two types of treatment namely, tamoxifen and tamoxifen combined with radiation therapy are commonly used. As it is essential to consider innovative and cost-effective strategies for early detection and treatment. Investigations through analysis of the stochastic model on early-stage breast cancer with these two types of treatments may help the stakeholders.

In the present paper, we develop a stochastic model for the early-stage breast cancer considering two treatment types, namely tamoxifen and tamoxifen combined with radiation therapy. Mean sojourn time and mean survival time have been calculated. In section 2, we described the stochastic model and its assumptions. In section 3, we define the states of the model and various notations used in the model. In section 4 and section 5, we find the steady-state probabilities and mean sojourn times. Section 6 and section 7 deal with computation of unconditional mean time and mean survival time (MST). A particular case has been considered in section 8. Numerical calculation and graphical analysis are done in section 9. Section 10 includes sensitivity analysis and relative sensitivity analysis. Finally, conclusion is presented in section 11.

2. Model Description and Assumptions

The present paper introduces a comprehensive six-state markov model for breast cancer. Any normal person may be infected with breast cancer symptoms. Whenever an early-stage breast cancer is diagnosed in a person then without taking the possibility of breast surgery, two types of treatments, namely tamoxifen (say, treatment-1) and tamoxifen plus radiation (say, treatment-2) have been considered. Here only these two treatments are assumed to be available to the patient that may perfectly cure the cancer. When the patient recovers using any of the treatments, then he/she will go to normal state, otherwise he/she will be in death state as the facility to carry out breast surgery of the patient is not available. Various assumptions for the model are as under:

- Initially the person is normal.
- Transition rates follow exponential distribution and other rates follow general distribution.
- All random variables are independent.

3. Model Development

Various states of the model and notations of different parameters are described in table 1 and table 2 respectively.

Table 1: *States specification*

States	Description
S_0	Normal State
S_1	The state when breast cancer is diagnosed.
S_2	The state in which treatment-1 is given to breast cancer patient.
S_3	The state in which treatment-2 is given to the breast cancer patient
S_4	The state in which no treatment is given to the breast cancer patient
S_5	Death state

Table 2: *Notations*

Notations	Description
λ_1	Transition rate from normal to diagnosed state
λ_2	Transition rate from normal to death state
λ_3	Transition rate from treatment-1 to death state
λ_4	Transition rate from treatment-2 to death state
λ_5	Transition rate from no treatment to death state
$h_1(t) / H_1(t)$	p.d.f. /c.d.f. of time of recovery from treatment-1.
$h_2(t) / H_2(t)$	p.d.f. /c.d.f. of time of recovery from treatment-2.
p / q	Probability that treatment is given/not given to the patient.
p_1 / q_1	Probability that treatment-1/treatment-2 is given to the patient.

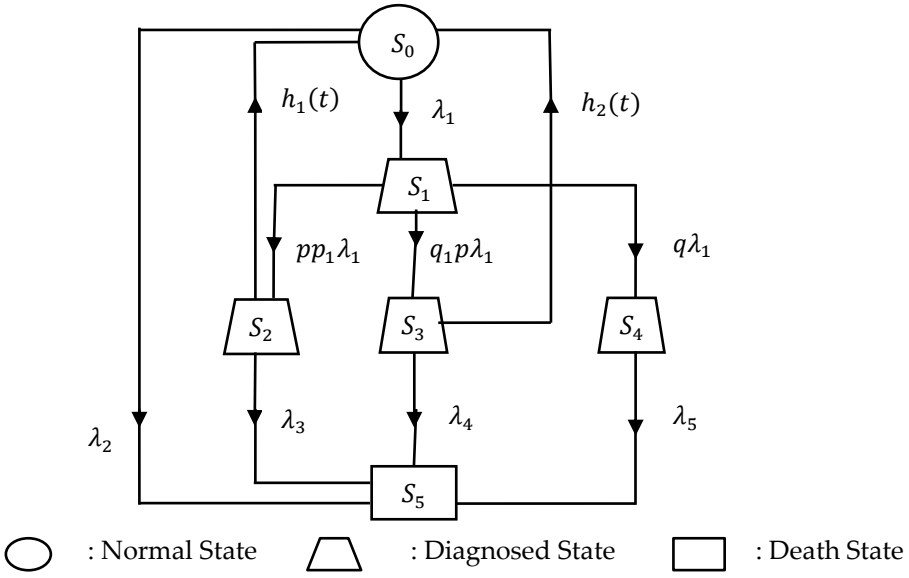

Figure 1. *State -Transition Diagram*

4. Transition Probabilities

The transition probabilities are

$q_{01}(t) = \lambda_1 e^{-(\lambda_1+\lambda_2)t}$; $q_{05}(t) = \lambda_2 e^{-(\lambda_1+\lambda_2)t}$; $q_{12}(t) = p_1 p\lambda_1 e^{-\lambda_1 t}$

$q_{13}(t) = q_1 p\lambda_1 e^{-\lambda_1 t}$; $q_{14}(t) = q\lambda_1 e^{-\lambda_1 t}$; $q_{20}(t) = h_1(t)\, e^{-\lambda_3 t}$

$q_{25}(t) = \lambda_3 e^{-\lambda_3 t}\overline{H_1(t)}$; $q_{30}(t) = h_2(t) e^{-\lambda_4 t}$; $q_{35}(t) = \lambda_4 e^{-\lambda_4 t}\overline{H_2(t)}$

$q_{45}(t) = \lambda_5 e^{-\lambda_5 t}$.

The steady-state probabilities $p_{ij} = \lim_{s\to 0} L\{q_{ij}(t)\}$ are obtained as

$p_{01} = \frac{\lambda_1}{\lambda_1+\lambda_2}$; $p_{05} = \frac{\lambda_2}{\lambda_1+\lambda_2}$; $p_{12} = pp_1$; $p_{13} = pq_1$

$p_{14} = q$; $p_{20} = h_1^*(\lambda_3)$; $p_{30} = h_2^*(\lambda_4)$; $p_{25} = 1 - h_1^*(\lambda_3)$

$p_{35} = 1 - h_2^*(\lambda_4)$; $p_{45} = 1$.

Clearly,

$p_{01} + p_{05} = 1$; $p_{12} + p_{13} + p_{14} = 1$; $p_{20} + p_{25} = 1$

$p_{30} + p_{35} = 1$; $p_{45} = 1$

5. Mean Sojourn Time

Expected time taken by the patient in state i before transiting to any other state is called mean sojourn time in that state.

It is denoted by μ_i and is given by

$$\mu_i = \int_0^\infty P(T_i > t)\,dt = \int_0^\infty R(t)\,dt$$

Then, we have

$$\mu_0 = \frac{1}{\lambda_1 + \lambda_2} \quad ; \quad \mu_1 = \frac{1}{\lambda_1} \quad ; \quad \mu_2 = \frac{1 - h_1^*(\lambda_3)}{\lambda_3}$$

$$\mu_3 = \frac{1 - h_2^*(\lambda_4)}{\lambda_4} \quad ; \quad \mu_4 = \frac{1}{\lambda_5}$$

6. Unconditional Mean Time

Unconditional mean time m_{ij} is mathematically stated as $m_{ij} = \int_0^\infty t\, q_{ij}(t)\,dt = -q_{ij}^{*'}(0)$.

Then, we have

$$m_{01} = \frac{\lambda_1}{(\lambda_1 + \lambda_2)^2} \quad ; \quad m_{05} = \frac{\lambda_2}{(\lambda_1 + \lambda_2)^2} \quad ; \quad m_{12} = \frac{p p_1}{\lambda_1}$$

$$m_{13} = \frac{p q_1}{\lambda_1} \quad ; \quad m_{14} = \frac{q}{\lambda_1} \quad ; \quad m_{20} = -h_1^{*'}(\lambda_3)$$

$$m_{25} = h_1^{*'}(\lambda_3) + \frac{1}{\lambda_3} - \frac{h_1^*(\lambda_3)}{\lambda_3}; \quad m_{30} = -h_2^{*'}(\lambda_4) \quad ; \quad m_{35} = h_2^{*'}(\lambda_4) + \frac{1}{\lambda_4} - \frac{h_2^*(\lambda_4)}{\lambda_4}$$

$$m_{45} = \frac{1}{\lambda_5}$$

Thus,

$$m_{01} + m_{05} = \mu_0 \quad ; \quad m_{12} + m_{13} + m_{14} = \mu_1 \quad ; \quad m_{20} + m_{25} = \mu_2$$

$$m_{30} + m_{35} = \mu_3 \quad ; \quad m_{45} = \mu_4$$

7. Mean Survival Time

Let $\phi_i(t)$ denotes the cumulative distribution function of first passage time from S_i to death state.

The following recursive relations are obtained for $\phi_i(t)$:

$$\phi_0(t) = Q_{01}(t) \textcircled{S} \phi_1(t) + Q_{05}(t)$$
$$\phi_1(t) = Q_{12}(t) \textcircled{S} \phi_2(t) + Q_{13}(t) \textcircled{S} \phi_3(t) + Q_{14}(t) \textcircled{S} \phi_4(t)$$
$$\phi_2(t) = Q_{20}(t) \textcircled{S} \phi_0(t) + Q_{25}(t)$$
$$\phi_3(t) = Q_{30}(t) \textcircled{S} \phi_0(t) + Q_{35}(t)$$
$$\phi_4(t) = Q_{45}(t)$$

Taking Laplace Stielje's Transform (L.S.T.) on both sides of above equations and solve for $\phi_0^{**}(s)$, we have

$$\phi_0^{**}(s) = \frac{N(s)}{D(s)} \qquad (1)$$

where $\phi_0^{**}(s)$ *is* Laplace Stielje's Transform of $\phi_0(t)$,

$$N(s) = Q_{05}^{**}(s) + Q_{01}^{**}(s)\left(Q_{12}^{**}(s)Q_{25}^{**}(s) + Q_{13}^{**}(s)Q_{35}^{**}(s) + Q_{14}^{**}(s)Q_{45}^{**}(s)\right)$$

and $D(s) = 1 - Q_{01}^{**}(s)Q_{20}^{**}(s)Q_{12}^{**}(s) - Q_{01}^{**}(s)Q_{30}^{**}(s)Q_{13}^{**}(s).$

Now, the mean survival time is given by

$$T_0 = \lim_{s \to 0} \frac{1 - \phi_0^{**}(s)}{s}$$

Using L'Hospital's rule and putting the value of $\phi_0^{**}(s)$ from equation (1), we get

$$T_0 = \frac{N}{D},$$

where

$$N = \mu_0 + \mu_1 p_{01} + \mu_2 p_{01} p_{12} + \mu_3 p_{01} p_{13} + \mu_4 p_{01} p_{14}$$

and $D = 1 - p_{01} p_{12} p_{20} - p_{01} p_{13} p_{30}$.

8. Particular Case

The following particular case is considered for analysis purpose:

$h_1(t) = \beta_1 e^{-\beta_1 (t)}$ and $h_2(t) = \beta_2 e^{-\beta_2 (t)}$, where β_1 and β_2 are recovery rate from treatment-1 and treatment-2, respectively. The transition probabilities are given by

$$p_{01} = \frac{\lambda_1}{\lambda_1 + \lambda_2} \quad ; \quad p_{05} = \frac{\lambda_2}{\lambda_1 + \lambda_2} \quad ; \quad p_{12} = pp_1 \quad ; \quad p_{13} = pq_1$$

$$p_{14} = q \quad ; \quad p_{20} = h_1^*(\lambda_3) \quad ; \quad p_{30} = h_2^*(\lambda_4) .$$

Mean sojourn time is given by

$$\mu_0 = \frac{1}{\lambda_1 + \lambda_2} \quad ; \quad \mu_1 = \frac{1}{\lambda_1} \quad ; \quad \mu_2 = \frac{1 - h_1^*(\lambda_3)}{\lambda_3} = \frac{1 - p_{20}}{\lambda_3}$$

$$\mu_3 = \frac{1 - h_2^*(\lambda_4)}{\lambda_4} = \frac{1 - p_{30}}{\lambda_4} \quad ; \quad \mu_4 = \frac{1}{\lambda_5},$$

where $h_1^*(\lambda_3) = p_{20} = \frac{\beta_1}{\lambda_3 + \beta_1}$ and $h_2^*(\lambda_4) = p_{30} = \frac{\beta_2}{\lambda_4 + \beta_2}$.

9. Numerical Computation and Graphical Analysis

For the numerical computation and graphical analysis, the above particular case is considered. The transition rates (λ_1, λ_2) are taken as given in Harvey et al. (2013) whereas other parameters $(\lambda_3, \lambda_4, \lambda_5, p_1, q_1, p, q)$ are assumed here. Various graphs have been plotted for mean survival time taking varying values to the parameters involved in its expression.

In the figures 2, 4, 6, 8 and 10, graphs exhibit the nature of mean survival time (T_0) versus transition rates $\lambda_1, \lambda_2, \lambda_3, \lambda_4$ and λ_5 for varying recovery rate β_1 *whereas* in the figures 3, 5, 7, 9 and 11, graphs exhibit the nature of mean survival time (T_0) versus transition rates $\lambda_1, \lambda_2, \lambda_3, \lambda_4$ and λ_5 for varying recovery rate β_2. In figure 12, graph presents the nature of mean survival time versus transition rate λ_1 for varying values of β_1 and β_2 .

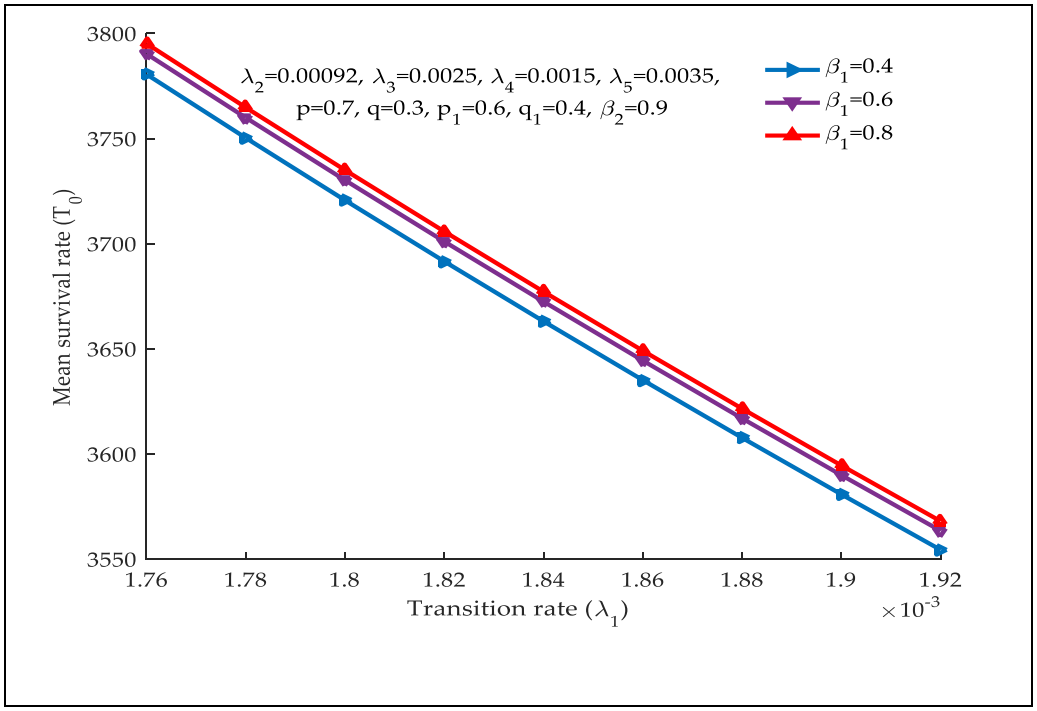

Figure 2. *Mean Survival Time* (T_0) *versus transition rate* (λ_1) *for varying recovery rate* (β_1)

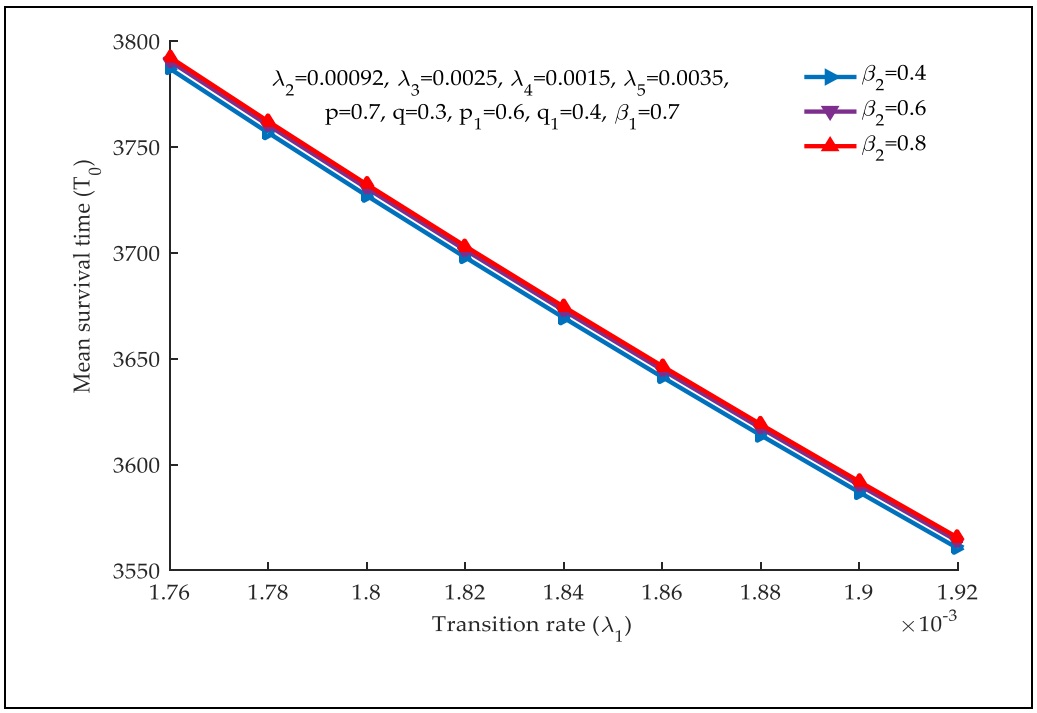

Figure 3. *Mean Survival Time* (T_0) *versus transition rate* (λ_1) *for varying recovery rate* (β_2)

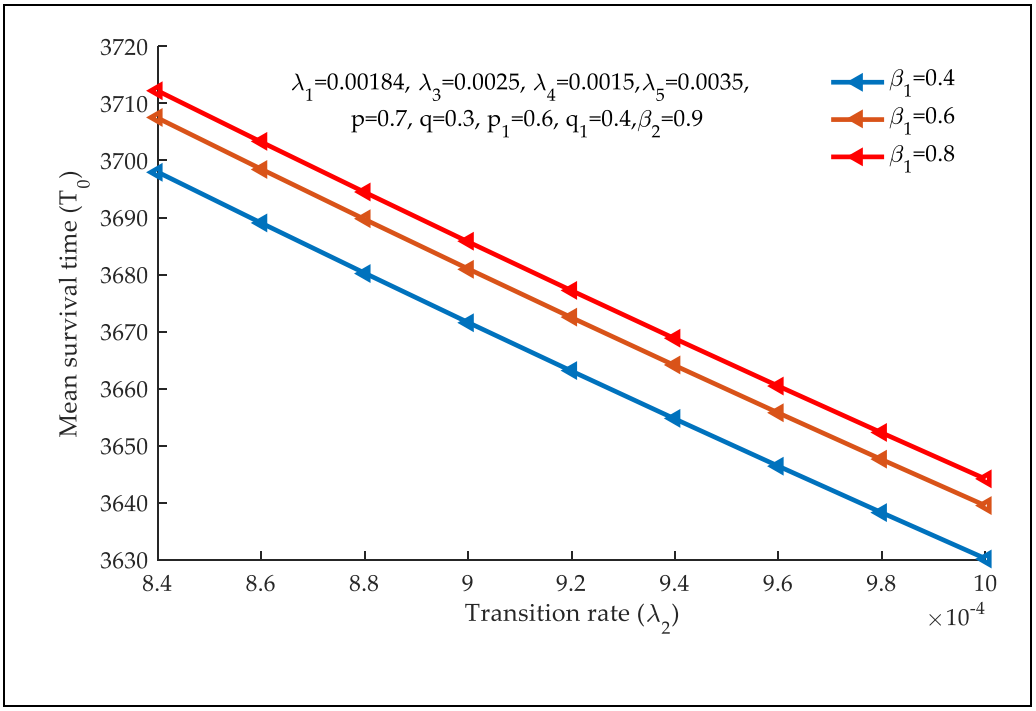

Figure 4. *Mean Survival Time* (T_0) *versus transition rate* (λ_2) *for varying recovery rate* (β_1)

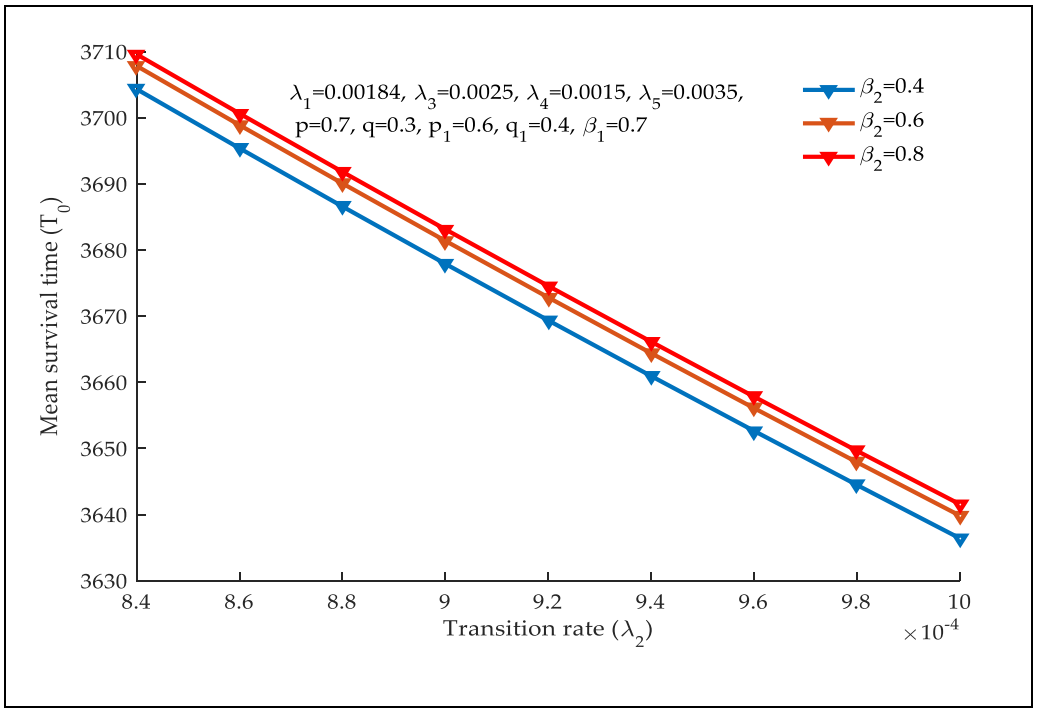

Figure 5. *Mean Survival Time* (T_0) *versus transition rate* (λ_2) *for varying recovery rate* (β_2)

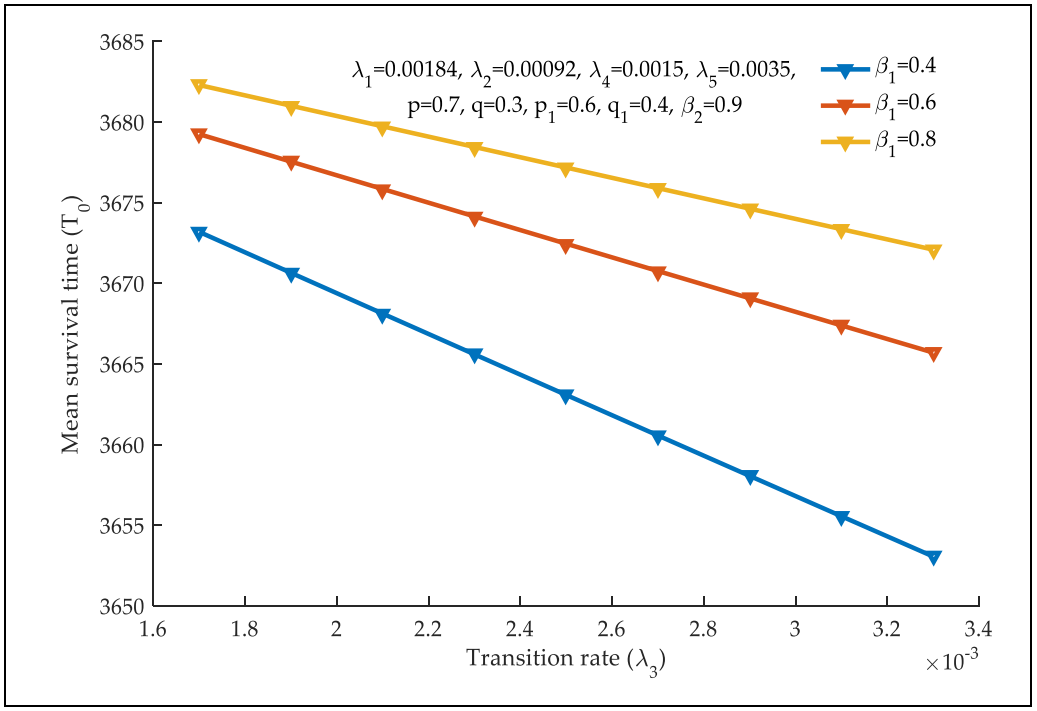

Figure 6. *Mean Survival Time* (T_0) *versus transition rate* (λ_3) *for varying recovery rate* (β_1)

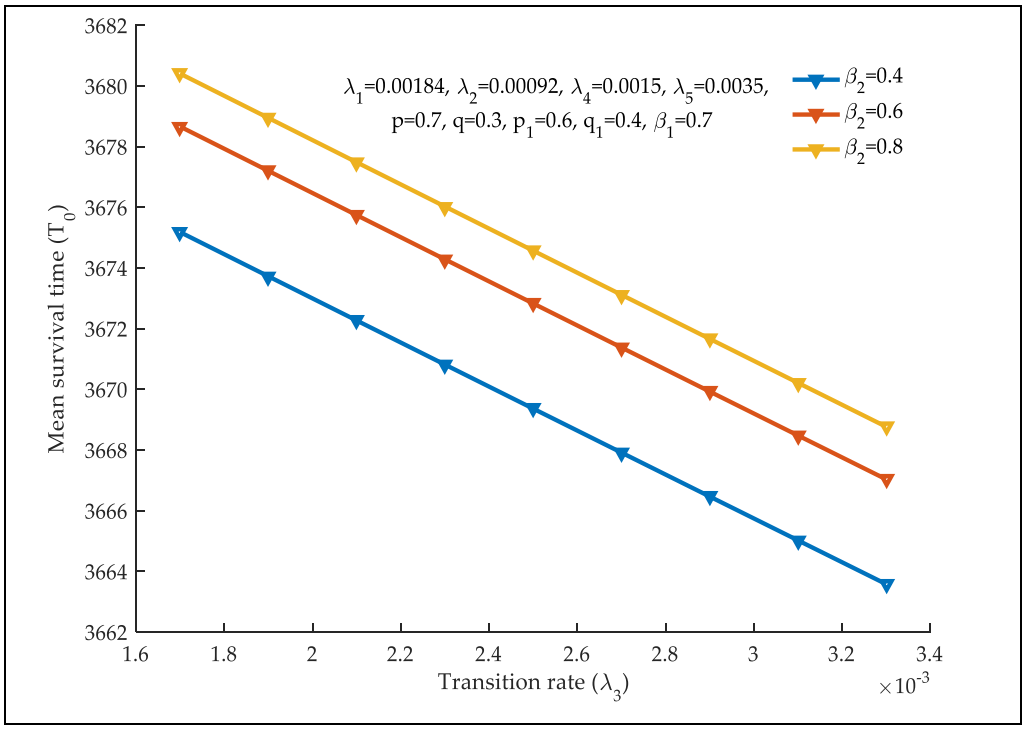

Figure 7. *Mean Survival Time* (T_0) *versus transition rate* (λ_3) *for varying recovery rate* (β_2)

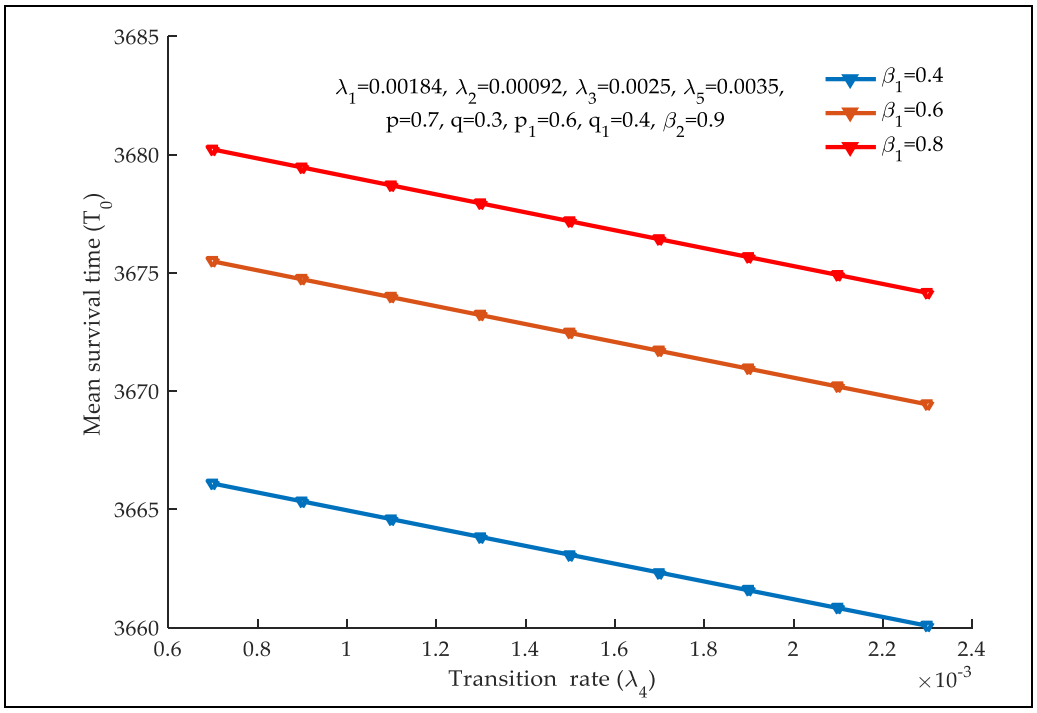

Figure 8. *Mean Survival Time* (T_0) *versus transition rate* (λ_4) *for varying recovery rate* (β_1)

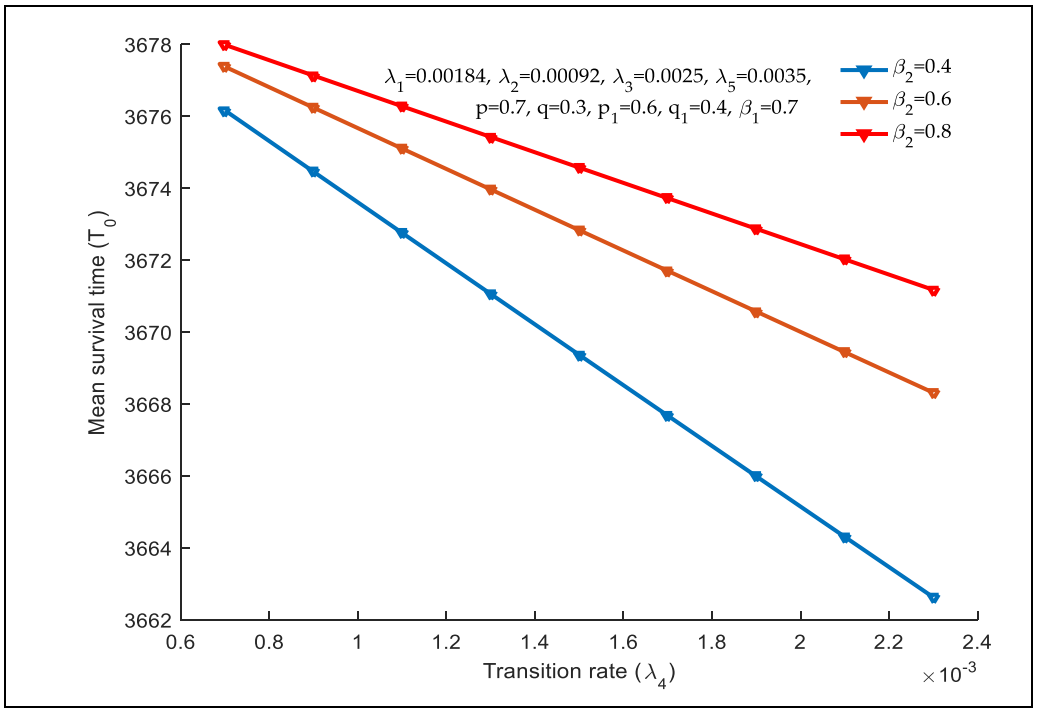

Figure 9. *Mean Survival Time* (T_0) *versus transition rate* (λ_4) *for varying recovery rate* (β_2)

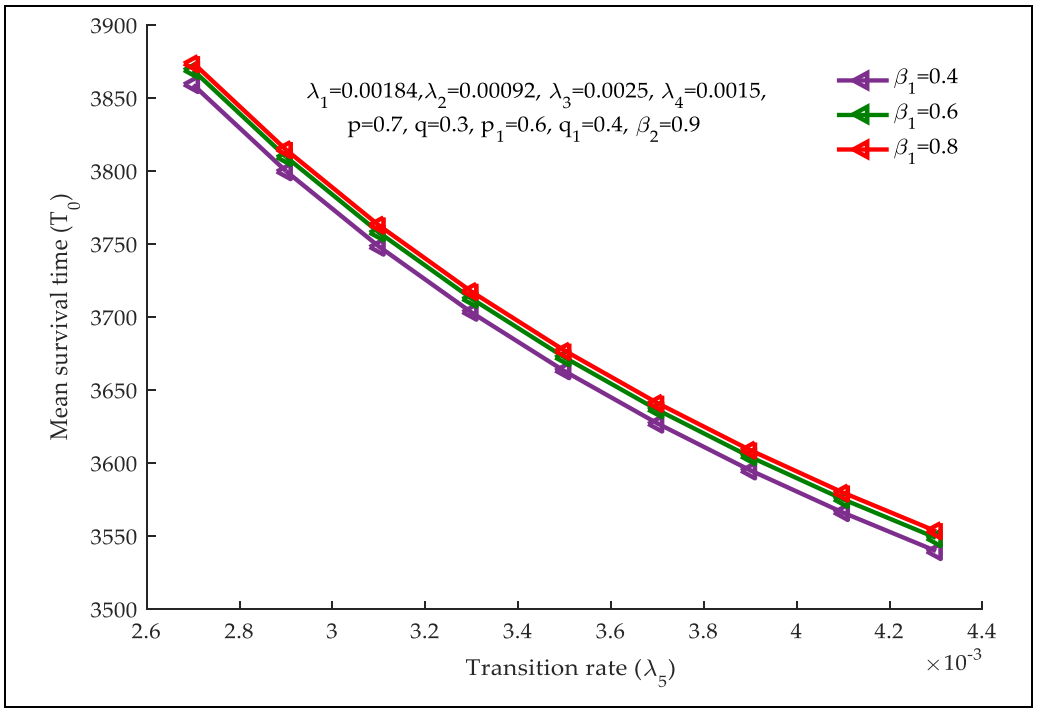

Figure 10. *Mean Survival Time* (T_0) *versus transition rate* (λ_5) *for varying recovery rate* (β_1)

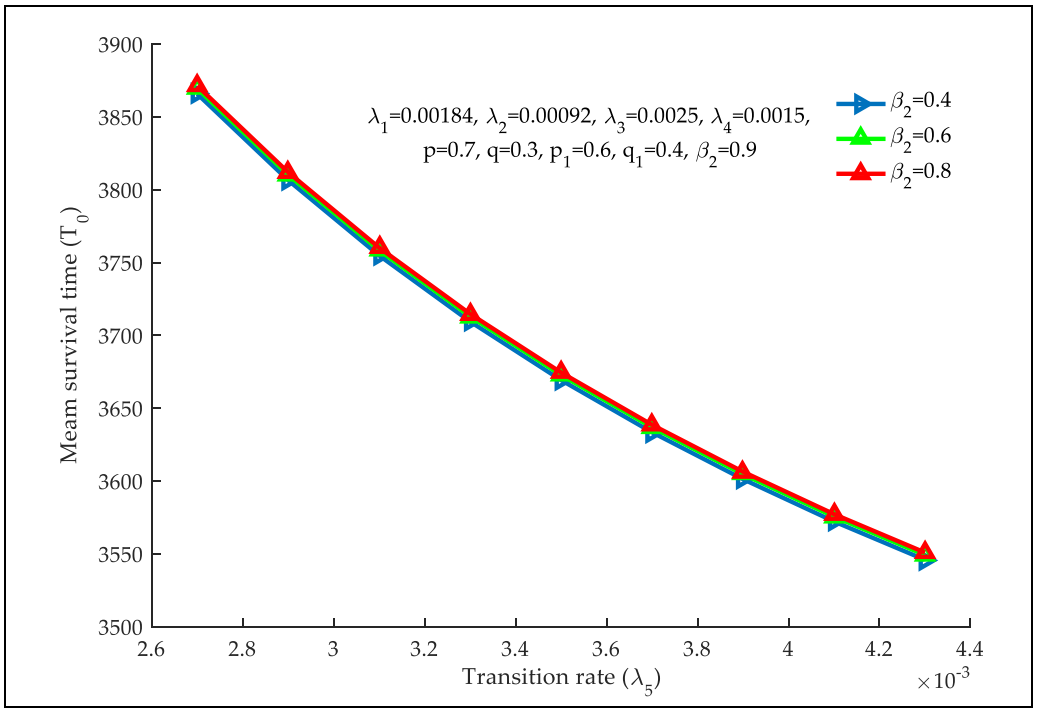

Figure 11. *Mean Survival Time* (T_0) *versus transition rate* (λ_5) *for varying recovery rate* (β_2)

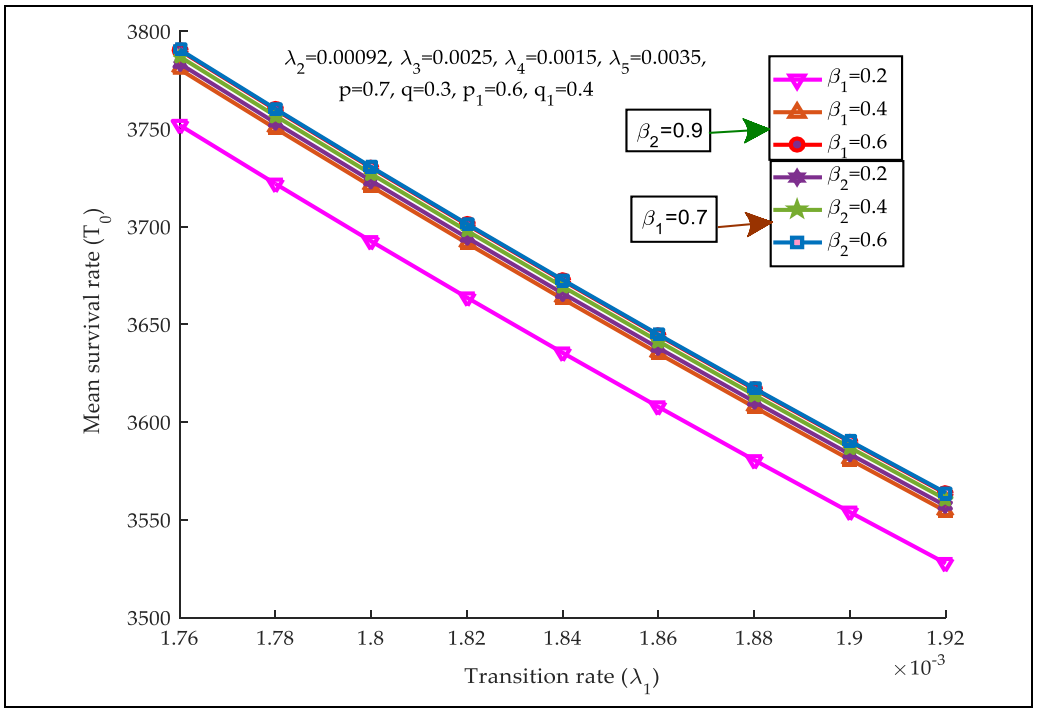

Figure 12. *Mean Survival Time* (T_0) *versus transition rate* (λ_1) *for varying recovery rates* β_1 *and* β_2

The following interpretations have been drawn from the plotted graphs from the figure 2 to figure12. It can be observed that mean survival time decreases as transition rates $\lambda_1, \lambda_2, \lambda_3, \lambda_4$ and λ_5 increases and gives higher values with higher value of recovery rates β_1 and β_2. Further, the mean survival time (T_0) in case of the treatment-2 is higher than that in case of treatment-1.

10. Sensitivity and Relative Sensitivity Analysis

Sensitivity analysis is performed to find out how the variation in involved parameters affect the specific mean survival time under certain specific conditions. Since, there is significance difference between the values of parameters, therefore to compare their effects on mean survival time (MST), relative sensitivity function is used. The sensitivity and relative sensitivity functions for mean survival time (MST) are formulated as under:

$$\pi_k = \frac{\partial(\text{MST})}{\partial k} \text{ and } \delta_k = \pi_k \left(\frac{k}{\text{MST}} \right),$$

where $k = \lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5, \beta_1, \beta_2$

Table1: *Sensitivity and relative sensitivity analysis of MST* (T_0) *with transition rate* (λ_1) *for* $\lambda_2 = 0.00092$, $\lambda_3 = 0.0025, \lambda_4 = 0.0015, \lambda_5 = 0.0035, \beta_1 = 0.7, \beta_2 = 0.9, p = 0.7, q = 0.3,\ p_1 = 0.6, q_1 = 0.4$

λ_1	$\pi_{\lambda_1} = \frac{\partial(\mathrm{MST})}{\partial\lambda_1}$	$\delta_{\lambda_1} = \pi_{\lambda_1}\left(\frac{\lambda_1}{\mathrm{MST}}\right)$
0.00176	- 2.4884	- 0.2953
0.00178	- 2.4678	- 0.2972
0.00180	- 2.4475	- 0.2991
0.00182	- 2.4274	- 0.3009
0.00184	- 2.4076	- 0.3027
0.00186	- 2.3880	- 0.3045
0.00188	- 2.3686	- 0.3063
0.00190	- 2.3495	- 0.3081
0.00192	- 2.3306	- 0.3098

Table 2: *Sensitivity and relative sensitivity analysis of MST* (T_0) *with transition rate* (λ_2) *for* $\lambda_1 = 0.00184$, $\lambda_3 = 0.0025, \lambda_4 = 0.0015, \lambda_5 = 0.0035, \beta_1 = 0.7, \beta_2 = 0.9, p = 0.7, q = 0.3,\ p_1 = 0.6, q_1 = 0.4$

λ_2	$\pi_{\lambda_2} = \frac{\partial(\mathrm{MST})}{\partial\lambda_2}$	$\delta_{\lambda_2} = \pi_{\lambda_2}\left(\frac{\lambda_2}{\mathrm{MST}}\right)$
0.00084	- 1.1087	- 0.6019
0.00086	- 1.0776	- 0.6075
0.00088	- 1.0478	- 0.6130
0.00090	- 1.0192	- 0.6183
0.00092	- 9.9172	- 0.6235
0.00094	- 9.6537	- 0.6285
0.00096	- 9.4006	- 0.6334
0.00098	- 9.1574	- 0.6382
0.00100	- 8.9234	- 0.6428

Table 3: *Sensitivity and relative sensitivity analysis of MST* (T_0) *with transition rate* (λ_3) *for* $\lambda_1 = 0.00184$, $\lambda_2 = 0.00092,\ \lambda_4 = 0.0015, \lambda_5 = 0.0035, \beta_1 = 0.7, \beta_2 = 0.9, p = 0.7, q = 0.3,\ p_1 = 0.6, q_1 = 0.4$

λ_3	$\pi_{\lambda_3} = \frac{\partial(\mathrm{MST})}{\partial\lambda_3}$	$\delta_{\lambda_3} = \pi_{\lambda_3}\left(\frac{\lambda_3}{\mathrm{MST}}\right)$
0.0017	- 1.0919	- 0.0013
0.0019	- 1.0910	- 0.0014
0.0021	- 1.090	- 0.0016
0.0023	- 1.0891	- 0.0017
0.0025	- 1.0881	- 0.0019
0.0027	- 1.0872	- 0.0020
0.0029	- 1.0863	- 0.0022
0.0031	- 1.0853	- 0.0023
0.0033	- 1.0844	- 0.0024

Table 4: *Sensitivity and relative sensitivity analysis* of $MST(T_0)$ *with transition rate* (λ_4) for $\lambda_1 = 0.00184$, $\lambda_2 = 0.00092,\ \lambda_3 = 0.0025, \lambda_5 = 0.0035, \beta_1 = 0.7, \beta_2 = 0.9, p = 0.7, q = 0.3,\ p_1 = 0.6, q_1 = 0.4$

λ_4	$\pi_{\lambda_4} = \frac{\partial(\mathrm{MST})}{\partial\lambda_4}$	$\delta_{\lambda_4} = \pi_{\lambda_4}\left(\frac{\lambda_4}{\mathrm{MST}}\right)$
0.0007	- 567.6037	- 2.7142
0.0009	- 567.2638	- 3.4879
0.0011	- 566.9242	- 4.2608
0.0013	- 566.5849	- 5.0329
0.0015	- 566.246	- 5.8041
0.0017	- 565.9073	- 6.5746
0.0019	- 565.5689	- 7.3442
0.0021	- 565.2309	- 8.1131
0.0023	- 564.8931	- 8.0011

Table 5: *Sensitivity and relative sensitivity analysis of* $MST(T_0)$ *with transition rate* (λ_5) *for* $\lambda_1 = 0.00184$, $\lambda_2 = 0.00092,\ \lambda_3 = 0.0025,\ \lambda_4 = 0.0015, \beta_1 = 0.7, \beta_2 = 0.9, p = 0.7, q = 0.3,\ p_1 = 0.6, q_1 = 0.4$

λ_5	$\pi_{\lambda_5} = \frac{\partial(MST)}{\partial\lambda_5}$	$\delta_{\lambda_5} = \pi_{\lambda_5}\left(\frac{\lambda_5}{MST}\right)$
0.0027	- 5.1318	- 0.0927
0.0029	- 4.4481	- 0.0868
0.0031	- 3.8926	- 0.0817
0.0033	- 3.4351	- 0.0771
0.0035	- 3.0537	- 0.0730
0.0037	- 2.7325	- 0.0694
0.0039	- 2.4595	- 0.0660
0.0041	- 2.2254	- 0.0630
0.0043	- 2.0232	- 0.0603

Table 6: *Sensitivity and relative sensitivity analysis of* $MST(T_0)$ *with recovery rate* (β_1) $\lambda_1 = 0.0018$, $\lambda_2 = 0.00092, \lambda_3 = 0.0025, \lambda_4 = 0.0015, \lambda_5 = 0.0035, \beta_2 = 0.9, p = 0.7, q = 0.3,\ p_1 = 0.6, q_1 = 0.4$

β_1	$\pi_{(\beta 1)} = \frac{\partial(MST)}{\partial\beta_1}$	$\delta_{\beta_1} = \pi_{\beta_1}\left(\frac{\beta_1}{MST}\right)$
0.4	8.5702	0.0023
0.6	3.8331	0.0016
0.8	2.1629	0.0012
1.0	1.3869	9.4735
1.2	0.9643	7.9033
1.4	0.7091	6.7796
1.6	0.5433	5.9357
1.8	0.4295	5.2786

Table 7: *Sensitivity and relative sensitivity analysis of MST* (T_0) *with recovery rate* (β_2) *for* $\lambda_1 = 0.0018$, $\lambda_2 = 0.00092, \lambda_3 = 0.0025, \lambda_4 = 0.0015, \lambda_5 = 0.0035, \beta_1 = 0.7, p = 0.7, q = 0.3, p_1 = 0.6, q_1 = 0.4$

β_2	$\pi_{\beta_2} = \frac{\partial(MST)}{\partial\beta_2}$	$\delta_{\beta_2} = \pi_{\beta_2}\left(\frac{\beta_2}{MST}\right)$
0.4	2.5847	7.0676
0.6	1.1526	4.7265
0.8	0.6494	3.5504
1.0	0.4161	2.8430
1.2	0.2891	2.3707
1.4	0.2125	2.0329
1.6	0.1628	1.7794
1.8	0.1286	1.5821

The sensitivity and relative sensitivity analyses of mean survival time are carried out with involved parameters $(\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5, \beta_1, \beta_2)$. The sensitivity and relative sensitivity analyses of mean survival time with these parameters are tabulated in table 1 to table 7. Tables 1-5 show that signs of the sensitivity of mean survival time with parameters $\lambda_1, \lambda_2, \lambda_3, \lambda_4$ and λ_5 are negative which implies that increase in these parameters decline the value of MST. Tables 6-7 show that signs of the sensitivity of mean survival time with parameters β_1 and β_2 are positive which lead to the conclusion that increase in these parameters improve the value of mean survival time. As transition rates $\lambda_1, \lambda_2, \lambda_3, \lambda_4$ and λ_5 increase, sensitivity function increases whereas relative sensitivity function decreases and whenever recovery rates β_1 and β_2 increase, sensitivity function decreases.

11. Conclusion

Breast cancer is indeed one of the most common cancers diagnosed in women globally. It is a major public health concern and significant impact on women's health. In the paper, the evaluated expressions for mean sojourn time in the different states of the model gives estimates of the times for patient remains in a particular stage. The investigation through the stochastic analysis of the model on breast cancer considering two types of treatments in various progression stages concludes that the mean survival time lessens with the rise in the rates of transition. It has been observed that mean survival time from tamoxifen plus radiation is higher than tamoxifen only. It is concluded that tamoxifen plus radiation is more effective and useful than only tamoxifen for treatment of early-stage breast cancer.

References

[1] Anthony, W.F., David, R.M., Lee, A.M., Maureen, E.T., Patricia, M., Melania, P., Lorna, M.W. and Ivo, A.O. (2004). Tamoxifen with or without Breast irradiation in Women 50 Years of Age or Older with Early Breast Cancer. *Journal of Medicine*, 351(10):963-970.

[2] Bayer, P., Brown, J.S., Dubbeldam, J. and Broom, M. (2021). A Markov chain model of cancer treatment. doi: https://doi.org/10.1101/2021.06.16.448669.

[3] Chesney, T.R., Jennifer, X. Y., Rajaee, N., Andrea, C. T. and Anthony, W. (2017). Tamoxifen with radiotherapy compared with Tamoxifen alone in elderly women with early-stage breast cancer treated with breast conserving surgery: A systematic review and meta-analysis.

Journal of radiotherapy and oncology,127:1-9.

[4] Cong, C. and Tsokos, C. P. (2009). Markov Modelling of Breast Cancer. *Journal of Modern Applied Statistical Methods*, 8(2):626-631.

[5] Dey, B. and Arun, K. (2018). A Review Article on Breast Cancer. *International Journal of Pharmacy and Pharmaceutical Research*, 11(2):284-298.

[6] Duffy, S.W., Day, N.E. Taba´r, L., Chen, H. and Smith, T. C. (1997). Markov Models of Breast Tumor Progression: Some Age-Specific Results. *Journal of the National Cancer Institute*, 22:93-97.

[7] Grover, G., Prafulla, K. S., Komal, G. and Vikas, S. (2018). Multistate Markov Modelling for Disease Progression of Breast Cancer Patients Based on CA 15-3 Marker. *Thailand Statistician*,16(2):129-139.

[8] Huang, Y., Li, Q., Torres-Rueda, S. and Li, J. (2020). The Structure and Parameterization of the Breast Cancer Transition Model Among Chinese Women. *Values in Health Regional Issues*, 21(C):29-38.

[9] Johnstone, P.A.S., Northon, M. S. and Riffenburgh, R. H. (2000). Survival of Patients with Untreated Breast Cancer. *Journal of Surgical Oncology*, 73:273-277.

[10] Mubarik, S., Sharma, R., Hussain, S.R., Iqbal, M., Nawsherwan, Liu, X. and Yu, C. (2022). Breast Cancer Mortality Trends and predictions to 2030 and its Attributable Risk Factors in East and South Asian Countries. *Original Research*, 9:1-15.

[11] Newman, L.A. (2022). Breast cancer screening in low and middle-income countries. *Best Practice & Research Clinical Obstetrics and Gynecology*, 83:15-23.

[12] Ruiz-Castro, J. E. and Zenda, M. (2020). A General Piecewise Multi-State Survival Model: Application to Breast Cancer. *Statistical Methods & Applications*, 29:813-843.

[13] Schairer, C., Mink, P. J., Carroll, L. and Devesa S.S (2004). Probabilities of Death from Breast Cancer and Other Causes among Female Breast Cancer Patients. *Journal of National Cancer Institute*, 96(17):1311-1321.

[14] Taghipour, S., Banjevic, D., Miller, A. B., Montgomery, N., Jardine, A.K.S., and Harvey, B. J. (2013). Parameter estimates for invasive breast cancer progression in the Canadian National Breast Screening Study. *British Journal of Cancer*, 108:542–548, doi: 10.1038/bjc.2012.596.

[15] Ventura, L., Carreras, G., Puliti, D., Paci, E., Zappa, M. and Miccinesi, G. (2014). Comparison of multistate markov models for cancer progression with different procedures for parameter estimation. An Application to Breast Cancer. *Journal of Epidemiology and public Health*, 11:1-10.