Optimal Control Applied to the Treatment Strategy for Chronic Liver Disease

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Abstract

Advanced liver cirrhosis has become life-threatening among the non-communicable diseases nowadays. Cirrhosis, the terminal stage of liver diseases in which the liver develops scarring as a result of various long-term continuous damages. In this paper, we develop a mathematical model to study the dynamics of chronic liver cirrhosis which can be controlled by vaccination as well as treatment. We formulate a five compartmental mathematical model of liver cirrhosis in terms of a set of nonlinear ordinary differential equations (ODEs) based on the characteristics of disease transmission by introducing two control measures. We formulate this model based on the optimal control theory using Pontryagin's Maximum Principle. For this, two types of controls such as vaccination and treatment according to underlying causes are employed to control the disease or to prevent people from being infected by liver cirrhosis. Finally, Numerical simulations are performed to illustrate the results. We observe that the optimal combination of two controls must be taken into consideration in order to reduce the liver cirrhosis transmission among the population.

Keywords
Liver cirrhosis, vaccination and treatment, optimal control, numerical analysis.

1. Introduction

Liver cirrhosis has become a major health problem worldwide as it leads to 1.34 million deaths every year (WHO, 2017). There is a large body of work to develop mathematical models and optimal control policies of infectious diseases. Biswas, 2014 (see also Biswas *et al*. 2014) investigated and analyzed the treatment of most devastating infectious diseases independently in which mathematical modeling and optimal control strategy was the key tool. Vaccination and treatment can control hepatitis B (HBV) virus infection which is also presented by formulating a mathematical model and applying optimal control strategy (Kamyad *et al*., 2014). Kumar *et al*. (2017) also presented a mathematical model showing that in a liver cirrhosis patient when hematocrit increases then blood pressure drops. In short, hematocrit is inversely proportional to blood pressure drop. Wang *et al*. (2017) formulated a computational model on the basis of hepatic circulation with the help of mathematical modeling to analyze the sensitivity of hepatic venous pressure gradient (HVPG) in liver cirrhosis. We refer readers the references within for more details on liver cirrhosis and some recent developments on mathematical modeling and control strategy.

In this paper, we develop a mathematical model to study the dynamics of chronic liver cirrhosis which can be controlled by vaccination as well as treatment. We consider two controls for the prevention and minimization of the disease. We determine the basic reproduction number and study the existence and stability of the disease free and endemic equilibrium points of the model. Finally numerical simulations are performed to show the effectiveness of vaccinations and proper treatment to control the chronic liver cirrhosis. The main aim of this work is to minimize the infection of liver cirrhosis and also the cost of vaccinations and treatment.

2. Mathematical Model of Liver Cirrhosis

In the basic model, we assume that the population size is fixed $N(t)$ and the incubation period of the infectious agent is slowest. There are five compartments in the fundamental assumption of the compartmental model. The individuals who are not affected by infections like hepatitis B virus (HBV), hepatitis C virus (HCV) or by any kind of liver diseases. But they are prone to become affected by these infections or diseases. These populations are denoted by $S(t)$ in the model. The disease transmission progress plays an important role in the dynamics of the diseases. For most of the non-communicable diseases, there are always different ranges of the incubation period. The non-communicable disease liver cirrhosis is developed from long term progression of viral diseases, alcoholic disease, fatty liver disease or other liver diseases which were not diagnosed before in the body. These diseases have a development period within the liver of the body. This incubation period of the diseases usually ranges from approximately 10 to 15 years. So considering this we create another compartment called exposed population denoted by $E(t)$. Here $E(t)$ is the number of infected individuals that are not infectious at time t. There are also some individuals $I(t)$ who are affected by infections (hepatitis B or hepatitis C), having fatty liver/ alcoholic liver or affected by any kind of liver diseases and can transmit any time. When these infections and diseases remain undiagnosed for a long time, they become horrible. Long-time progression of these infections and diseases leads to cause liver cirrhosis. Now we consider the population $L_C(t)$ who are affected by liver cirrhosis. The populations who are recovered and immunized from liver cirrhosis is denoted by $R(t)$. Then taking all the situation into consideration, the liver cirrhosis model can be formulated by the following system of nonlinear ordinary differential equations:

$$\frac{dS}{dt} = r - \alpha(I + \sigma L_c)S - \mu_0 S \qquad (1a)$$

$$\frac{dE}{dt} = \alpha(I + \sigma L_c)S - \mu_0 E - \beta E \qquad (1b)$$

$$\frac{dI}{dt} = \beta E - \mu_0 I - (\mu + \gamma)I \qquad (1c)$$

$$\frac{dL_c}{dt} = \mu I + p\gamma I - (\mu_0 + \delta + \varepsilon)L_c \qquad (1d)$$

$$\frac{dR}{dt} = \delta L_c + \gamma I - \mu_0 R - p\gamma I \qquad (1e)$$

with the boundary conditions

$S(0) = S_0 \geq 0,\ E(0) = I_0 \geq 0, I(0) = I_0 \geq 0, L_c(0) = L_{c0} \geq 0, R(0) = R_0 \geq 0$.

3. Analysis of the Model

The nonlinear system of equations (1) has qualitatively analyzed in this section so as to find the stability of a disease free equilibrium point and endemic equilibrium point. At first we find the positivity of the solutions then stability of the equilibrium points and basic reproduction number R_0. The basic reproduction ratio is important because it tells us if a disease will persist or extinct.

3.1. Positivity of the Solutions

We will show that the entire variables in the model (1) are positive.

Lemma 1: If $S(t) > 0,\ E(t) \geq 0,\ I(t) \geq 0,\ L_C(t) \geq 0,$ and $R(t) \geq 0$, then the solutions $S(t),\ E(t), I(t), L_C(t), R(t)$ of the model (1) are all positive.

Proof: To prove the Lemma 1, we have used the model (1).
From equation (1a), we get

$$\frac{dS}{dt} = r - \alpha(I + \sigma L_c)S - \mu_0 S \tag{2}$$

To find the positivity of equation (2), we have

$$\Rightarrow \frac{dS}{dt} + \mu_0 S \geq r \tag{3}$$

The integrating factor of (3)

$$I.F = e^{\int \mu_0 dt} = e^{\mu_0 t}$$

Multiplying $e^{\mu_0 t}$ on both sides of (3), we get

$$\Rightarrow \frac{d}{dt}(Se^{\mu_0 t}) \geq re^{\mu_0 t} \tag{4}$$

Integrating (4), we get

$$Se^{\mu_0 t} \geq \frac{re^{\mu_0 t}}{\mu_0} + c$$

$$\therefore S \geq \frac{r}{\mu_0} + ce^{-\mu_0 t} \tag{5}$$

where c is an integrating constant. Then putting the value of c into (5), we get

$$S \geq \frac{r}{\mu_0} + \left(S(0) - \frac{r}{\mu_0} \right) e^{-\mu_0 t}$$

Hence $S > 0$ at $t = 0$ and $t \to \infty$. Therefore $S > 0$ for all $t \geq 0$

Similarly we can find the positivity of E, I, L_C and R under the initial conditions.

Therefore, it is proved that $\left(S(t) > 0,\ E(t) \geq 0,\ I(t) \geq 0,\ L_C(t) \geq 0,\ R(t) \geq 0 \,\forall\, t \geq 0 \right)$

3.2. Equilibria (Disease Free and Endemic Equilibrium Point) Analysis

An equilibrium point of a system with no infections or diseases is called disease free equilibrium point. For the disease free equilibrium point of the model (1), we have to solve $\frac{dS^*}{dt} = \frac{dE^*}{dt} = \frac{dI^*}{dt} = \frac{dL_c^*}{dt} = \frac{dR^*}{dt} = 0$. Now the model (1) takes the following form

$$r - \alpha(I^* + \sigma L_c^*)S^* - \mu_0 S^* = 0 \tag{6}$$

$$\alpha(I^* + \sigma L_c^*)S^* - \mu_0 E^* - \beta E^* = 0 \tag{7}$$

$$\beta E^* - \mu_0 I^* - (\mu + \gamma)I^* = 0 \tag{8}$$

$$\mu I^* + p\gamma I^* - \left(\mu_0 + \delta + \varepsilon\right) L_c^* = 0 \tag{9}$$

$$\delta L_c^* + \gamma I^* - \mu_0 R^* - p\gamma I^* = 0 \tag{10}$$

For disease free equilibrium, we obtain

$E = 0,\ I = 0,\ L_c = 0,\ R = 0$ because there is no infections. Now putting the values in equation (6), we get

$$S^* = \frac{r}{\mu_0}$$

The disease free equilibrium point of the model (1) is $E(S^*, E^*, I^*, L_c^*, R^*) = E\left(\frac{r}{\mu_0}, 0, 0, 0, 0 \right)$

and the endemic equilibrium point is $(S^*, E^*, I^*, L_c^*, R^*)$.

where $S^* = \frac{\varphi_1\varphi_3\varphi_4}{\alpha\beta\varphi_3 + \alpha\beta\varphi_1\varphi_2\sigma}$, $E^* = \frac{r}{\varphi_4} - \mu_0\left(\frac{\varphi_1\varphi_3}{\alpha\beta\varphi_3 + \alpha\beta\varphi_1\varphi_2\sigma}\right)$, $I^* = \frac{\beta}{\varphi_1}\left\{\frac{r}{\varphi_4} - \mu_0\left(\frac{\varphi_1\varphi_3}{\alpha\beta\varphi_3 + \alpha\beta\varphi_1\varphi_2\sigma}\right)\right\}$,

$L_c^* = \frac{\beta\varphi_2}{\varphi_1\varphi_3}\left\{\frac{r}{\varphi_4} - \mu_0\left(\frac{\varphi_1\varphi_3}{\alpha\beta\varphi_3 + \alpha\beta\varphi_1\varphi_2\sigma}\right)\right\}$ and $R^* = \frac{1}{\mu_0}\left(\frac{\beta\delta\varphi_2 + \mu\beta\varphi_3 - p\gamma\beta\varphi_3}{\varphi_1\varphi_3}\right)\left\{\frac{r}{\varphi_4} - \mu_0\left(\frac{\varphi_1\varphi_3}{\alpha\beta\varphi_3 + \alpha\beta\varphi_1\varphi_2\sigma}\right)\right\}$.

3.3. Basic Reproduction Ratio R_0

The basic reproduction number is defined as the secondary infections produced by one primary infection in a wholly susceptible population. It is a key epidemiological quantity, because it determines the size and duration of epidemics. Here the F_i is the gains to infectious compartments, V is the losses from infectious compartments.

The associated matrix is given by

$$F = \begin{pmatrix} 0 & \alpha S & \alpha\sigma S \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix} \text{ and } V = \begin{pmatrix} \varphi_4 & 0 & 0 \\ -\beta & \varphi_1 & 0 \\ 0 & -\varphi_2 & \varphi_3 \end{pmatrix}$$

At the disease free equilibrium point we have,

$$F = \begin{pmatrix} 0 & \frac{\alpha r}{\mu_0} & \frac{\alpha\sigma r}{\mu_0} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}$$

Therefore, $V^{-1} = \frac{1}{|V|} \times Adj(V)$

$$V^{-1} = \frac{1}{\varphi_1\varphi_3\varphi_4}\begin{bmatrix} \varphi_1\varphi_3 & 0 & 0 \\ \beta\varphi_3 & \varphi_4\varphi_3 & 0 \\ \beta\varphi_2 & \varphi_4\varphi_2 & \varphi_1\varphi_4 \end{bmatrix}$$

$$G = FV^{-1} = \begin{bmatrix} \frac{\alpha\beta r}{\varphi_4\varphi_1\mu_0} + \frac{\alpha\beta\sigma\varphi_2}{\varphi_1\varphi_3\varphi_4} & \frac{\alpha r}{\varphi_1\mu_0} + \frac{\alpha\sigma\beta r}{\varphi_1\varphi_3\mu_0} & \frac{\alpha\sigma r}{\varphi_3\mu_0} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \quad (11)$$

The characteristic equation is $|G - \lambda I| = 0$

$$\begin{bmatrix} \frac{\alpha\beta r}{\varphi_4\varphi_1\mu_0} + \frac{\alpha\beta\sigma\varphi_2}{\varphi_1\varphi_3\varphi_4} - \lambda & \frac{\alpha r}{\varphi_1\mu_0} + \frac{\alpha\sigma\beta r}{\varphi_1\varphi_3\mu_0} & \frac{\alpha\sigma r}{\varphi_3\mu_0} \\ 0 & -\lambda & 0 \\ 0 & 0 & -\lambda \end{bmatrix} = 0$$

$$\Rightarrow \left\{\frac{\alpha\beta r}{\varphi_4\varphi_1\mu_0} + \frac{\alpha\beta\sigma\varphi_2}{\varphi_1\varphi_3\varphi_4\mu_0} - \lambda\right\}\lambda^2 = 0$$

$$\therefore \lambda = \frac{\alpha\beta r}{\varphi_4\varphi_1\mu_0} + \frac{\alpha\beta\sigma\varphi_2}{\varphi_1\varphi_3\varphi_4}, 0, 0 \quad (12)$$

Equation (12) follows that the basic reproduction number which is given by the largest eigen value for the model system of equations (1) is $R_0 = \frac{\alpha\beta r}{\varphi_4\varphi_1\mu_0} + \frac{\alpha\beta\sigma\varphi_2}{\varphi_1\varphi_3\varphi_4}$

3.4. Stability Analysis at Disease Free and Endemic Equilibrium Point

We perform stability analysis at disease free and endemic equilibrium point by establishing Theorem 1 and Theorem 2.

Theorem 1: The disease free equilibrium point is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.

Proof: The Jacobian matrix of model (1) at the disease free equilibrium point $E\left(\frac{r}{\mu_0}, 0, 0, 0, 0\right)$ is given by

$$J = \begin{pmatrix} -\mu_0 & 0 & -\frac{\alpha r}{\mu_0} & -\frac{\alpha\sigma r}{\mu_0} & 0 \\ 0 & -\varphi_4 & \frac{\alpha r}{\mu_0} & \frac{\alpha\sigma r}{\mu_0} & 0 \\ 0 & \beta & -\varphi_1 & 0 & 0 \\ 0 & 0 & \varphi_2 & -\varphi_3 & 0 \\ 0 & 0 & (1-p)\gamma & 0 & -\mu_0 \end{pmatrix} \quad (13)$$

The matrix is 5×5 matrix and the characteristic equation for eigenvalue λ is given by $|J - \lambda I| = 0$

$$\begin{pmatrix} -\mu_0 - \lambda & 0 & -\frac{\alpha r}{\mu_0} & -\frac{\alpha\sigma r}{\mu_0} & 0 \\ 0 & -\varphi_4 - \lambda & \frac{\alpha r}{\mu_0} & \frac{\alpha\sigma r}{\mu_0} & 0 \\ 0 & \beta & -\varphi_1 - \lambda & 0 & 0 \\ 0 & 0 & \varphi_2 & -\varphi_3 - \lambda & 0 \\ 0 & 0 & (\mu - p\gamma) & 0 & -\mu_0 - \lambda \end{pmatrix} = 0 \quad (14)$$

$$\Rightarrow (\mu_0 + \lambda)(\varphi_4 + \lambda)(\varphi_1 + \lambda)\{b_0\lambda^2 + b_1\lambda + b_2\} = 0$$

where $b_0 = 1 > 0$

$$b_1 = \frac{\alpha r\beta}{\mu_0} > 0$$

$$b_2 = \varphi_3\beta(1 - R_0) + \mu_0\left(\frac{\alpha\beta r\varphi_3 + \alpha\beta\sigma\varphi_2}{\varphi_3}\right)$$

The three eigen values are $(\lambda_1, \lambda_2, \lambda_3) = (-\mu_0, -\varphi_1, -\varphi_4)$

Using Routh-Hurwitz criterion we see that the disease free equilibrium point is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.

Theorem 2: The endemic equilibrium point is locally asymptotically stable if $R_0 > 1$ and unstable if $R_0 < 1$.

Proof: In the similar way we prove that the endemic equilibrium point is locally asymptotically stable if $R_0 > 1$ and unstable if $R_0 < 1$.

4. Mathematical Model of Liver Cirrhosis with Optimal Control

We consider two controls in the previous model as vaccination (u_1) and antiviral treatment control (u_2). Then the optimal control becomes the following form

$$\text{Minimize } J(u_1,u_2) = \int_0^T \left(S(t) + L_c(t) + \frac{A}{2}u_1^2(t) + \frac{B}{2}u_2^2(t) \right) dt \tag{15}$$

where A and B are the weight parameters. These constants A and B respectively represent the costs associated with vaccination of susceptible and treatment of liver cirrhosis populations.

Subject to

$$\frac{dS}{dt} = r - \alpha(I + \sigma L_c)S - \mu_0 S - u_1 S \tag{16a}$$

$$\frac{dE}{dt} = \alpha(I + \sigma L_c)S - \mu_0 E - \beta E \tag{16b}$$

$$\frac{dI}{dt} = \beta E - \mu_0 I - (\mu + \gamma)I \tag{16c}$$

$$\frac{dL_c}{dt} = \mu I + p\gamma I - (\mu_0 + \delta + \varepsilon)L_c - u_2 S \tag{16d}$$

$$\frac{dR}{dt} = \delta L_c - \mu_0 R + \gamma I - p\gamma I + u_1 S + u_2 S \tag{16e}$$

with the conditions, $S(0) = S_0 \geq 0,\ E(0) = E_0,\ I(0) = I_0 \geq 0,\ L_c(t) = L_{c0} \geq 0,\ R(0) = R_0 \geq 0$

The Hamiltonian of the optimal control model is given by

$$H\left(t, S(t), E(t), I(t), L_c(t), R(t)\right) = S(t) + L_c(t) + \frac{1}{2}\left(Au_1^2 + Bu_2^2\right) + \sum_{i=1}^{5} \lambda_i g_i\left(t, x(t), u(t)\right) \tag{17}$$

The optimality conditions are $\frac{\partial H}{\partial u_1} = Au_1 - \lambda_1 S + \lambda_5 S = 0$ and $\frac{\partial H}{\partial u_2} = Bu_2 + \lambda_5 L_c - \lambda_4 L_c = 0$

Applying Pontryagin's Maximum Principle we have the following theorem and proving Theorem 3, we show the existence of controls.

Theorem 3: There exists optimal control $\left(u_1^*, u_2^*\right)$ that minimizes the objective function J over Ω given by

$$u_1^* = \max\left\{0, \min\left(1, \frac{(\lambda_1 - \lambda_5)S^*}{A}\right)\right\} \text{ and } u_2^* = \max\left\{0, \min\left(1, \frac{(\lambda_4 - \lambda_5)L_c^*}{B}\right)\right\}.$$

5. Numerical Analysis

In this section, we have performed numerical simulations of liver cirrhosis transmission model (1) which has discussed in the previous section. We use a set of logical parameter values presented in Table 1.

The model system has been simulated using ODE45 solvers written in MATLAB programming language. We have again performed numerical simulations of the optimal control model (16) to observe the optimal behaviours of the model. Graphical results are displayed using the following values: $S = 5.54,\ E = 0.835,\ I = 0.5,\ L_c = 0.65,\ R = 0.2$. In Table 1 we present a description of all the parameters with their estimated values used in all our simulations. The results obtained from the equations (1) using the values in Table 1 are presented in Figures 1, 2 and 3. We also perform numerical simulations of the optimal control model (16) and the simulations are presented in Figure 4.

Table 1. Parameter specifications of model (1) and (16)

Descriptions	Parameters	Values
Source term of susceptible population	r	0.0121
Natural death rate of population	μ_0	0.95
Transmission rate	α	0.16
Infectiousness of liver cirrhosis relative to acute infections	σ	0.00693
Rate of moving from exposed to acute	β	6 (per year)
Disease induced death rate	ε	0.3
Rate of moving from infections to recover	μ	0.25
Rate of moving from infection to liver cirrhosis	γ	4 (per year)
Recovered rate from liver cirrhosis	δ	0.03
Rate of moving from recover to liver cirrhosis carriers	p	0.25

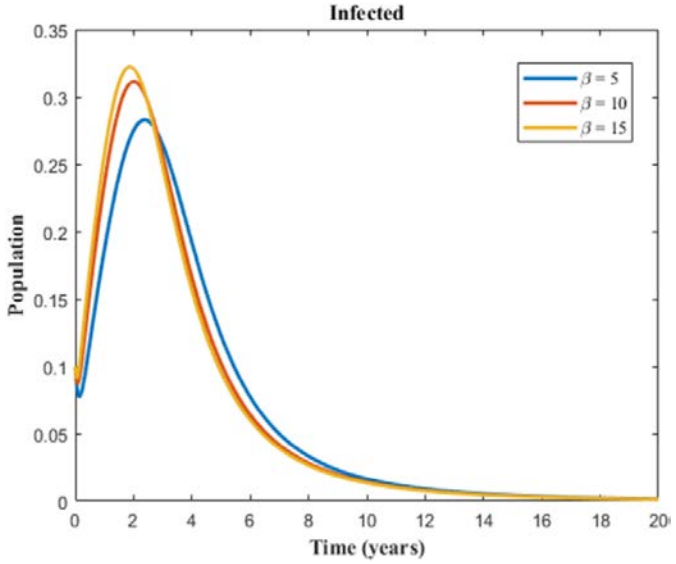

Figure 1. Variation of the infected population for different values of β.

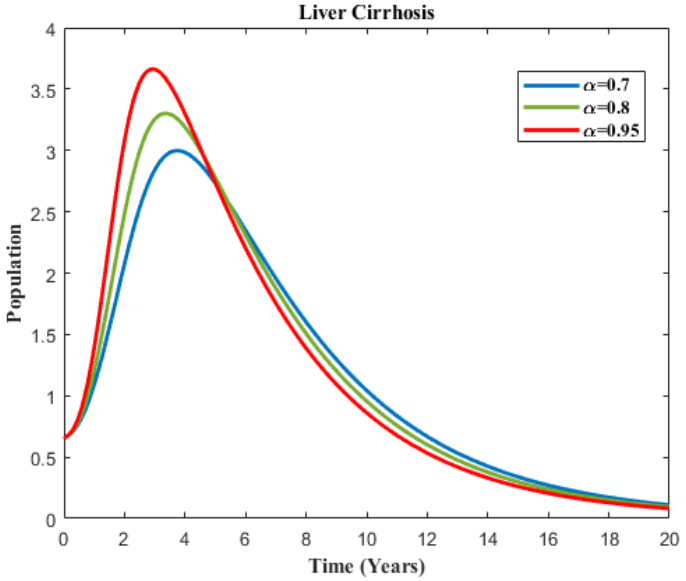

Figure 2. Variation of the liver cirrhosis population for different values of α.

Figure 1 shows the variation of the infected population with time 20 years for different parameter values of the model (1). Here we observe that the infected population decreases more rapidly than before as the infection rate β increases. Figure 2 shows the variation of the cirrhotic population with time 20 years for different parameter values of the model (1). Here we observe that the liver cirrhosis population increases as the transmission rate α increases.

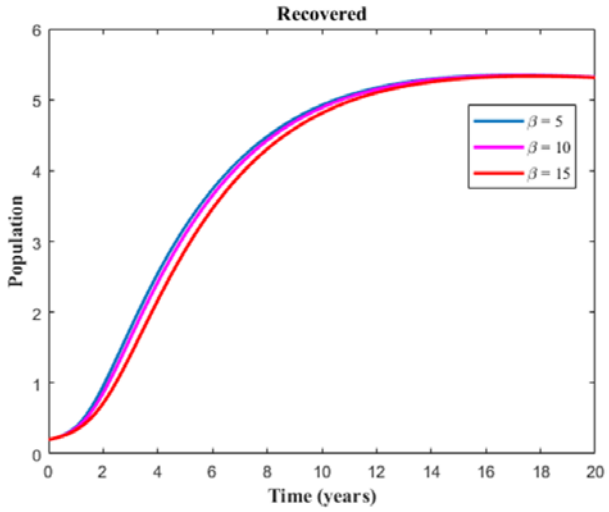

Figure 3. Variation of recovered populations for different values of acute infection rate β.

Figure 3 shows the variation of the recovered populations with time 20 years for different parameter values of the model (1). Here we observe that the liver cirrhosis population increases as the transmission rate β increases.

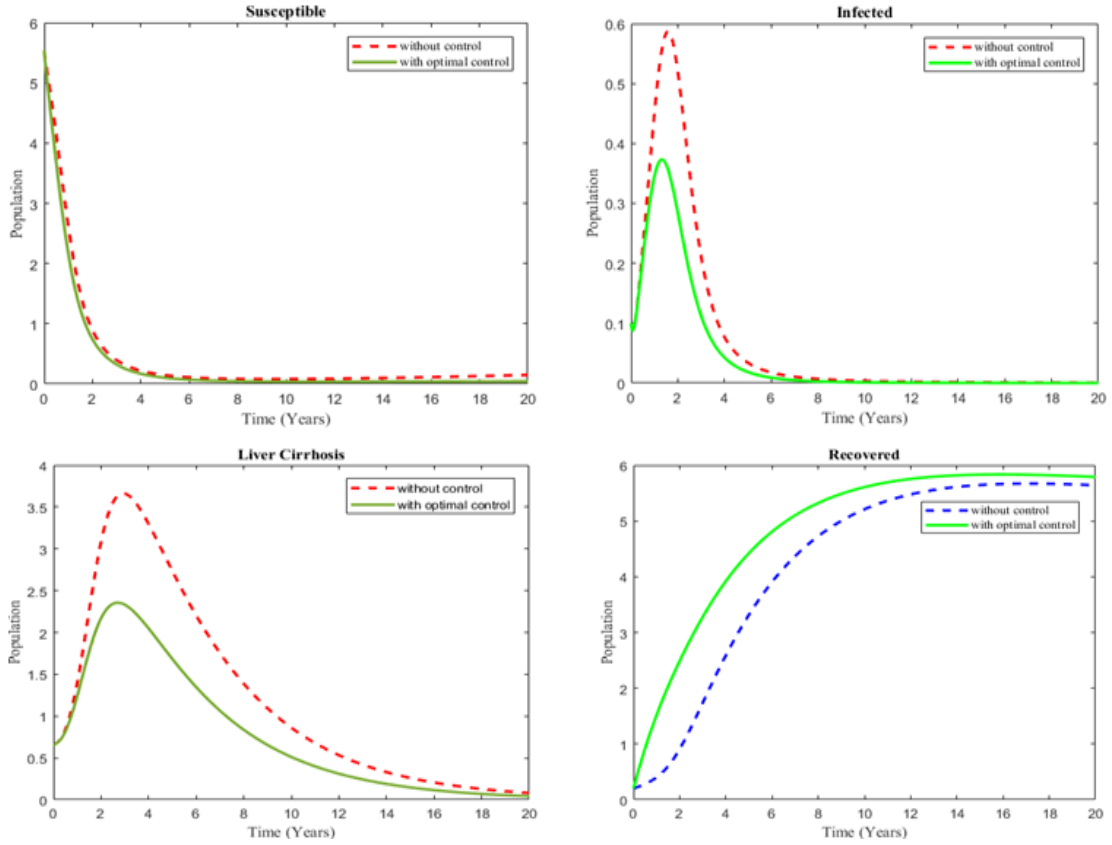

Figure 4. The dynamic behavior of populations using vaccination (u_1) and treatment (u_2) as optimal control measures.

From Figure 4, we observe the effects of control measure (vaccination and treatment) on the susceptible, infected, liver cirrhosis and recovered population for 20 years timeline. It has been noticed that, the control measure slightly influences the susceptible population, but significantly controls the infected, liver cirrhosis and recovered population. As expected, both the infected and liver cirrhosis population has increased in the absence of vaccination and treatment than the population with having the control measure. On the contrary, the number of recovered population increases when vaccination and treatment control is applied compared to the population without optimal control.

6. Conclusions

Liver cirrhosis is a major cause of illness and death worldwide. It affects millions of patients all over the world. Liver cirrhosis occurs throughout the world irrespective of age, sex, region and race. It is time to get rid of this fatal disease. Investigating the model (1) and optimal control model (16), we can conclude that the combination of vaccination and treatment control for the population will be more effective way of controlling liver cirrhosis. Finally, our model help to identify the causes of liver cirrhosis and control them accordingly and thus can contribute to the public health worldwide.

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Biographies

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Dr. Haider Ali Biswas is currently affiliated with Khulna University, Bangladesh as a Professor of Mathematics under Science Engineering and Technology School. Prof. Biswas obtained his B. Sc. (Honors) in Mathematics and M.Sc in Applied Mathematics in the year 1993 and 1994 respectively from the University of Chittagong, Bangladesh, M Phil in Mathematics in the year 2008 from the University of Rajshahi, Bangladesh and PhD in Electrical and Computer Engineering from the University of Porto, Portugal in 2013. He has more than 18 years teaching and research experience in the graduate and postgraduate levels at different public universities in Bangladesh. He published three books, one chapters and more than 70 research papers in the peer reviewed journals and international conferences. His present research interests include Optimal Control with State Constraints, Nonsmooth Analysis, Mathematical Modeling and Simulation, Mathematical Biology and Biomedicine, Epidemiology of Infectious Diseases. Recently Professor Biswas has been nominated the Member of the Council of Asian Science Editors (CASE) for 2017-2020 and the Associate Member of the Organization for Women in Science for the Developing World (OWSD) since 2017.