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Optimal control strategies for preventing hepatitis B infection and reducing chronic liver cirrhosis incidence

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ABSTRACT

Advanced liver cirrhosis has become life-threatening among 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. Among liver diseases, viral hepatitis is the major risk factor for chronic cirrhosis development. The present paper demonstrates a compartmental model of chronic disease liver cirrhosis describing the transmission dynamics of this disease. Applying the Pontryagin's maximum principle, the optimal control policies such as vaccination for hepatitis B virus and treatment of other causes of cirrhosis are adopted as control measures. The target of this study is to minimize the number of infected and liver cirrhotic individuals as well as the associated cost of the control. For this purpose, the optimal control strategies are employed according to the underlying causes behind this disease. Our goal is to find the strategy of preventing hepatitis B infection which is considered one of the leading causes of cirrhosis and consequently, reduction of the chronic cirrhosis incidence. Efficiency analysis is also performed to observe the effective control among the two control strategies. The model is investigated both analytically and numerically and the numerical simulations are carried out to illustrate the analytical findings. The analysis reveals that both the vaccination and treatment could be the most fruitful way to reduce the incidence of chronic liver cirrhosis.

1. Introduction

Any kind of liver disease acts as a source for cirrhosis of the liver. Liver cirrhosis has become a significant health problem worldwide as it leads to 1.34 million deaths every year (World Health Organization (WHO), 2017). In liver cirrhosis, the healthy liver tissue is transformed into scar tissue which substantially blocks the normal blood flow in the liver. Finally, the liver ploddingly deteriorates and is unable to function normally due to chronic or long-lasting injury. A unique characteristic of the liver is to regenerate or regrow and this also becomes stopped due to liver cirrhosis. Cirrhosis is caused by many forms of liver diseases and conditions like viral infections (hepatitis B and C virus) and chronic alcoholism. Viral hepatitis is considered a major risk factor for the progression of chronic cirrhosis. Cirrhosis is more likely to occur among people having long-term viral infections. A result in (Yang et al., 2011) showed that cirrhosis was present in 94% of patients having hepatitis B

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and 97% of patients having hepatitis C in the study. However, each year viral hepatitis B and hepatitis C affect 325 million people causing 1.4 million deaths all over the world. There is no vaccination available for viral Hepatitis C, while hepatitis B can be precluded by vaccines. These vaccines are safe, accessible and efficacious. Hepatitis B is a potentially life-threatening liver infection which is caused by the hepatitis B virus (HBV). It keeps people at high risk of causing cirrhosis and thus enhances the possibility of death (World Health Organization (WHO), 2017). Hepatitis B is transmitted both vertically (from mother to child during birth) and horizontally (exposure to infectious blood and body fluids). Sexual contact, blood transfusion with another infected human, the use of contaminated injection and razors, and also the reuse of needles and syringes etc. are the forms of horizontal transmission for the hepatitis B development. The long-time progression of this infection in the body causes chronic cirrhosis. Moreover, advanced cirrhosis is a fatal condition where the treatment options are very limited. So it is essential to find out control measures of this chronic liver disease. For this purpose, optimal control theory has been applied to discuss the optimal control strategy to prevent hepatitis B and hence consequently to reduce the chronic cirrhosis transmission.

There is a large body of work to develop mathematical models and optimal control policies of infectious diseases. Biswas et al. (Biswas, Paiva, & de Pinho, 2014) (see also Biswas (Biswas, 2014a,b; Biswas, 2013a,b; Biswas, 2012a,b,c; Biswas, Haque, Mallick, 2019)), Khatun and Biswas (Khatun & Biswas, 2018; Khatun, Biswas, 2019) investigated and analyzed the treatment of most devastating diseases in which mathematical modeling and optimal control strategy was the key tool. Several other mathematical models of liver cirrhosis have been presented as well. Celechovska (2004) studied a simple mathematical model of the liver by applying Bellman's quasilinearization method. The liver fibrosis stage could be examined with the help of MR Elastography (Non-invasive). The detailed using a mathematical model was presented by Huwart et al. (Huwart, Peeters, Sinkus, Annet, Salameh, Beek, Horsmans, Beers, 2006). Kumar et al. (Kumar, Upadhyay, Agrawal, Pandey, 2017) also presented a mathematical model showing that hematocrit is inversely proportional to blood pressure drop. Remien et al. (Remien, Adler, Waddoups, Box, & Sussman, 2012) used a set of differential equations to develop a mathematical model for describing the acute liver injury caused by the overdose of acetaminophen. Furthermore, Friedman (Friedman) analyzed a mathematical model of liver cirrhosis to explore the efficacy of the drugs aimed at obstructing the progression of liver fibrosis. Wang et al. (Wang, Liang, Jhou, & Shi, 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. Pratt et al. (Pratt, Wattis & Salter, 2015) developed a mathematical model showing that the interaction of carbohydrates and lipids through digestion and absorption is relevant to storage and oxidation of the body. 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, Akbari, Heydari & Heydari, 2014). Readers can follow to ((Adams, 2011; Greena, Watersa, Shakesheff & Byrne, 2009; Dahari et al., 2011; Dontwi, Frempong, Bentil, Adetunde, & Owusu-Ansah, 2010; Hao, Rovin, & Friedman, 2014; Momoh, Ibrahim, Madu, & Asogwa, 2012; Sahani & Biswas, 2017; Wiegand & Berg, 2013; Yusuf & Benyah, 2012; Zoua, Zhanga, & Ruan, 2010) and the references within) for more details on liver diseases and some recent developments on mathematical modeling as well as control strategies.

In this paper, we present a mathematical model to clarify the transmission dynamics of chronic liver cirrhosis from hepatitis B infection, which can be controlled by vaccination as well as treatment. In this study, we analyze the mathematical model of liver cirrhosis and also apply optimal control theory considering two control variables for the prevention and minimization of the disease. Finally, we perform numerical simulations to interpret the outcomes and also to show the effectiveness of vaccination in preventing the hepatitis B infections and the proper treatment for controlling the chronic liver cirrhosis. In the numerical analysis section Efficiency index is also carried out to find out which control is more effective than the other. The main aim of this work is to minimize the infected and liver cirrhotic individuals using vaccination and treatment as control and also the associated cost of the implementation of the two control measures.

2. Current status of liver cirrhosis

Cirrhosis of liver has become life-threatening for the people irrespective of developed, developing and under-developing countries throughout the world. Liver cirrhosis is developed from long term progression of viral diseases (hepatitis B and hepatitis C), alcoholic disease, fatty liver disease or other liver diseases (see detail in Fig. 1) which were not diagnosed before

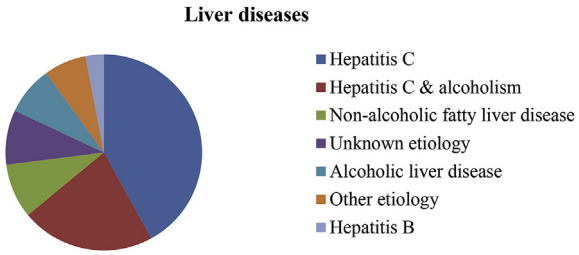

Fig. 1. Pie-chart showing different types of liver diseases which ultimately lead the liver to cirrhosis.

in the body. It is the result of continuous damages of the liver by these diseases. Among these diseases, hepatitis B infection is the most prominent for the chronic liver cirrhosis development. Because every year this disease affects millions of people all over the world and consequently leads to chronic cirrhosis. According to the world health organization (WHO), about 257 million people were affected worldwide by this infection in 2015 and this incidence rate is shown in Fig. 2. Fig. 3 shows the number of hepatitis B infection-related death rates from 2000 to 2016 in the world (Global Health Estimates). However, liver cirrhosis occurs all most all the countries in Asia. In 2016, a remarkable number of people (Male 111.4 and Female 47.3) died from liver cirrhosis in Myanmar. Fig. 4 exhibits the number of liver cirrhosis related death rates in Asia in the year 2016 (World Health Organization (WHO), 2017). Cirrhosis affected about 2.8 million people and resulted in 1.3 million deaths in 2015. In 1995, it affected about 33.63 million people worldwide. Since then, it has been enhanced considerably. Fig. 5 presents the number of the incidence rate of liver cirrhosis from the year 1995–2016 (Global burden of disease, 2018). Among the four countries (China, India, United States, Bangladesh), the liver cirrhosis incidence rate is very high in India. The populations of India are affected by liver cirrhosis more frequently while liver cirrhosis incidence rate is low in Bangladesh comprises to other three countries in the world.

3. Mathematical model

Mathematical modeling is playing an incredible role for providing quantitative insights into the mechanisms of various diseases which lead to design better prediction, management and control policies. To analyze and control liver cirrhosis progression in the present study, we develop a mathematical model introducing two control variables. Firstly, we construct a model considering the feature of liver cirrhosis transmission and then we apply optimal control theory to minimize the progression or complications of the chronic disease liver cirrhosis. Let $N(t)$ be the total number of population. The individuals who are not affected by infections like hepatitis B virus (HBV), hepatitis C virus (HCV). 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 progression 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 such as hepatitis B (HBV) and hepatitis C (HCV) which were not diagnosed before in the body. These infections have a development period within the liver of the body. This incubation period of the infections usually ranges from approximately 10 to 15 years. So considering this, we create another compartment called exposed individuals denoted by $E(t)$.

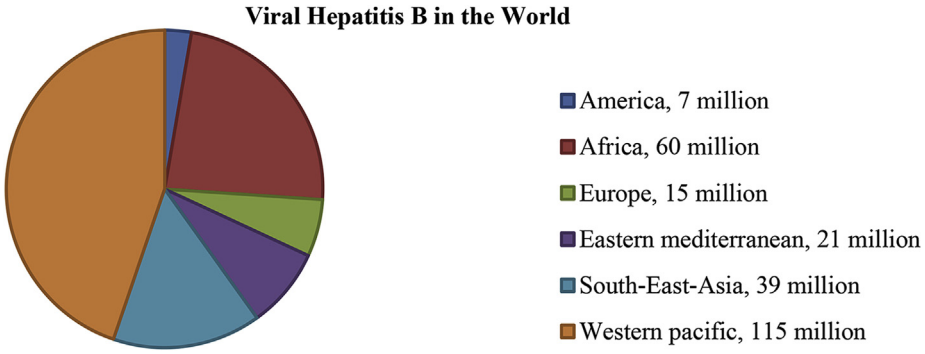

Fig. 2. The number of hepatitis B incidence in the world in 2015. About 257 million people were affected worldwide by this infection that year.

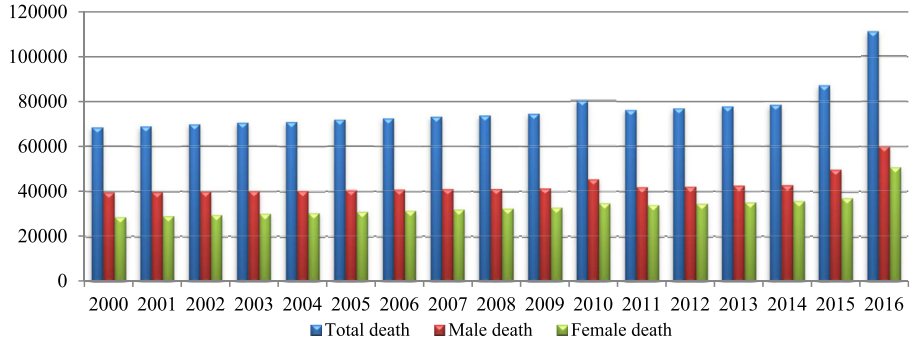

Fig. 3. The number of hepatitis B infection-related death rates from 2000 to 2016 in the world.

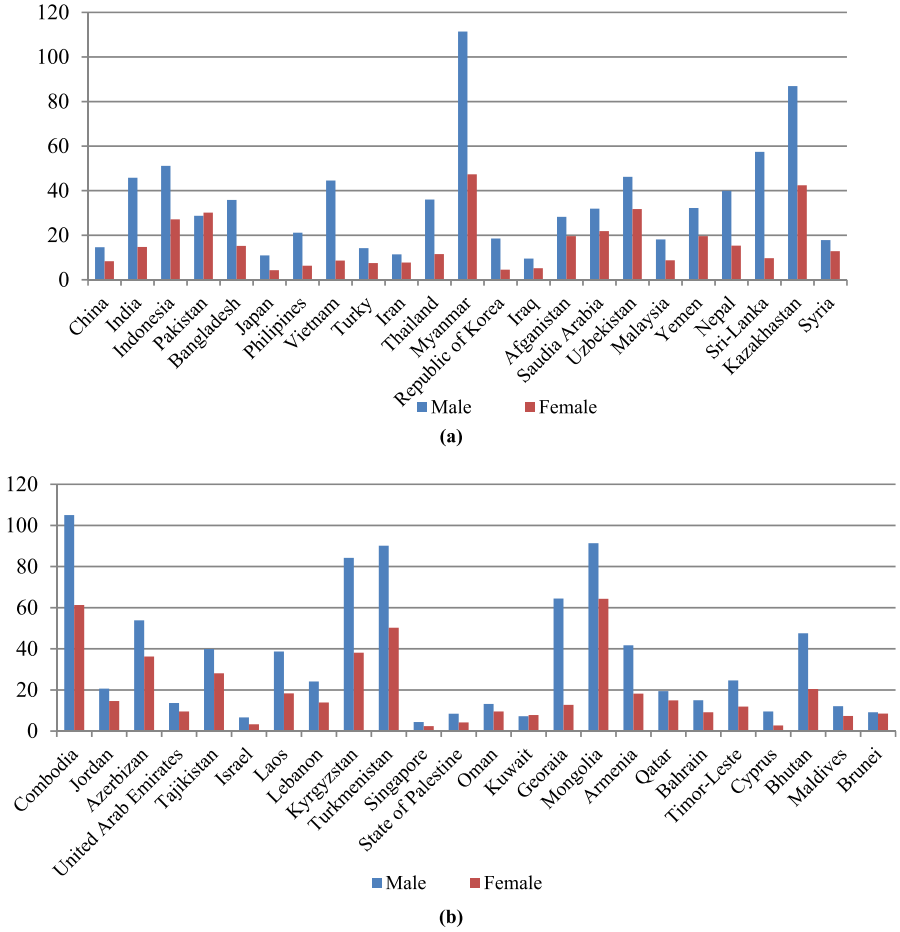

Fig. 4. (a) Number of liver cirrhosis related death rates in Asia (China to Syria) in the year 2016; (b) Number of. liver cirrhosis related death rates in Asia (Combodia to Brunei) in the year 2016.

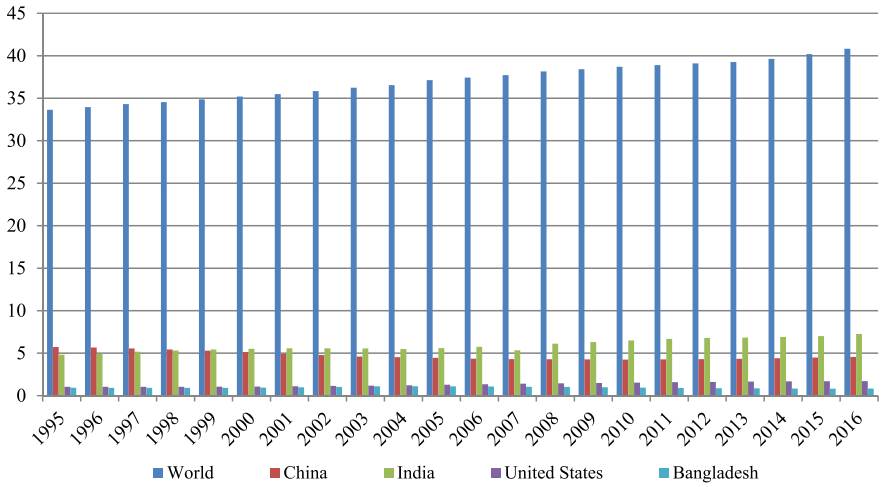

Fig. 5. The number of incidence of liver cirrhosis (world, China, India, United States, Bangladesh) from 1995 to 2016.

Here, $E(t)$ is the number of infected individuals who are not infectious at time t. There are also some individuals $I(t)$ who are affected by infections (hepatitis B or hepatitis C) and can transmit at any time. When these infections remain undiagnosed for a long time, they become horrible. Long-time progression of these infections leads to cause of liver cirrhosis. Now we consider the individuals $L_C(t)$ who are affected by liver cirrhosis. The individuals who have recovered and have the immunity from liver cirrhosis are denoted by $R(t)$. Fig. 6 shows the flowchart of the compartmental model of liver cirrhosis.

This flowchart leads to the following set of nonlinear ordinary differential equations (NODEs):

$$\begin{aligned}
\frac{dS}{dt} &= r - \alpha(I + \sigma L_c)S - \mu_0 S - u_1 S \\
\frac{dE}{dt} &= \alpha(I + \sigma L_c)S - (\mu_0 + \beta)E \\
\frac{dI}{dt} &= \beta E - \mu_0 I - (\mu + \gamma)I \\
\frac{dL_c}{dt} &= \mu I + p\gamma I - (\mu_0 + \delta + \varepsilon)L_c - u_2 L_c \\
\frac{dR}{dt} &= \delta L_c - \mu_0 R + \gamma I - p\gamma I + u_1 S + u_2 L_c
\end{aligned} \tag{1}$$

with the initial condition $S(0) > 0, E(0) \geq 0, I(0) \geq 0, L_c(0) \geq 0, \quad R(0) \geq 0$.

In the above model (1), we have assumed that a stable population with per capita birth rate r and per capita death rate μ_0. α is the transmission rate and σ is the infectiousness of carriers relative to acute infections. β is the acute infection rate of exposed individuals and γ is the spontaneous recovery rate of infected individuals. Here, the parameter μ is the rate at which the infected individuals get cirrhotic, δ is the recovery rate of cirrhotic individuals, and ε is the disease-induced death rate. Furthermore, $p\gamma$ is the rate at which the infections of cirrhosis relapse in the liver cirrhotic individuals after being recovered.

Here, we have considered two control variables $(u_1,\ u_2)$: (i) before infection, vaccinations of hepatitis B so that the infections can be prevented and (ii) after infection, treatment based on causes from which liver cirrhosis has developed. So that $u_1(t)$ and $u_2(t)$ denotes the vaccination and the treatment control respectively.

Now, model (1) is an optimal control model, and the set of control variables $(u_1(t),\ u_2(t)) \in U$ is Lebesgue measurable, where

$$U = \{(u_1(t),\ u_2(t)) :\ 0 \leq a_i \leq u_i(t) \leq b_i \leq 1,\ i = 1, 2\},\ \ \forall t \in [0,\ T]$$

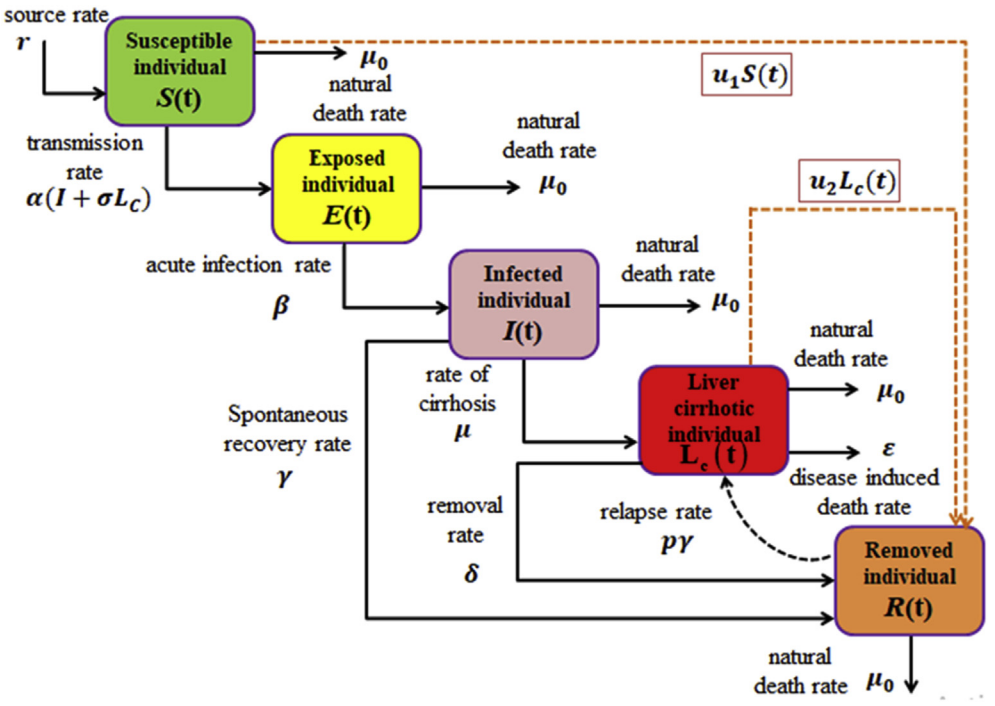

Fig. 6. Flow diagram of the compartmental model of liver cirrhosis transmission with optimal control.

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Considering these two control variables, the performance index is given by

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

We can reformulate model (1) as an optimal control problem with the performance index (2) as

$$(P_c)\ \begin{cases} \text{Minimize } J(x,u) = \int_0^T L(t,x(t),u(t))\ dt \\ \text{subject to} \\ \dot{x}(t) = f(x(t)) + g(x(t))u(t),\quad \forall t \in [0,\ T] \\ u(t) \in U(t),\quad \forall t \in [0,\ T] \\ x(0) = x_0 \end{cases} \tag{3}$$

where, $x(t) = \begin{pmatrix} S(t) \\ E(t) \\ I(t) \\ L_c(t) \\ R(t) \end{pmatrix}$, $g(x) = \begin{pmatrix} -S & 0 \\ 0 & 0 \\ 0 & 0 \\ 0 & -L_c \\ S & L_c \end{pmatrix}$, $f(x) = \begin{pmatrix} r - \alpha(I + \sigma L_c)S - \mu_0 S \\ \alpha(I + \sigma L_c)S - (\mu_0 + \beta)E \\ \beta E - \mu_0 I - (\mu + \gamma)I \\ \mu I + p\gamma I - (\mu_0 + \delta + \varepsilon)L_c \\ \delta L_c + (1-p)\gamma I - \mu_0 R \end{pmatrix}$, $u(t) = \begin{pmatrix} u_1(t) \\ u_2(t) \end{pmatrix}$ and the integrand of the performance index is denoted by

$$L(x,\ u) = I(t) + L_c(t) + \frac{A}{2}u_1^2 + \frac{B}{2}u_2^2 \tag{4}$$

4. Existence of the optimal control

In order to prove the existence of the optimal control, we have to show the existence of the state and the existence of the objective functional.

4.1. Existence of the state variable

The state equation (1) with the initial condition can be written in the following form as

$$\begin{aligned} S' &= r - \alpha(I + \sigma L_c - \mu_0)S + (0)E(t) + (0)I(t) + (0)L_c(t) + (0)R(t) \\ E' &= \alpha(I + \sigma L_c)S - (\mu_0 + \beta)E + (0)I(t) + (0)L_c(t) + (0)R(t) \\ I' &= (0)S(t) + \beta E + (0)I(t) + (0)L_c(t) + (0)R(t) \\ L_c' &= (0)S(t) + (0)E(t) + (\mu + p\gamma)I - (\mu_0 + \delta + \varepsilon)L_c + (0)R(t) \\ R' &= (0)S(t) + (0)E(t) + (1-p)\gamma I + \delta L_c - \mu_0 R \end{aligned} \tag{5}$$

Let

$$N(t) = S(t) + E(t) + I(t) + L_c(t) + R(t)$$

So that,

$$N'(t) = S'(t) + E'(t) + I'(t) + L_c'(t) + R'(t) \tag{6}$$

Now putting the right hand sides of equation (5) into equation (6), we get

$$N'(t) = r - \varepsilon L_c - \mu_0 N(t) \Rightarrow N'(t) + \varepsilon L_c = r - \mu_0 N(t) \therefore N'(t) \le r - \mu_0 N(t)$$

So, we have $N(t) \le \frac{r}{\mu_0} + \left(N_0 - \frac{r}{\mu_0} \right) e^{-\mu_0 t} = V_1 \in \mathbb{R}_+$ and $\lim_{t \to \infty} \sup\ N(t) \le V_1$,which conclude $S(t), E(t), I(t), L_c(t), R(t) \le V_1$ as $t \to \infty$.

Then, we can rewrite (5) in the following form:

$$\varphi_t = B\varphi + F(\varphi) \tag{7}$$

where $\varphi = \begin{bmatrix} S(t) \\ E(t) \\ I(t) \\ L_c(t) \\ R(t) \end{bmatrix}$, $\varphi_t = \begin{bmatrix} S'(t) \\ E'(t) \\ I'(t) \\ L_c{}'(t) \\ R'(t) \end{bmatrix}$, $F(\varphi) = \begin{bmatrix} -\alpha(I+\sigma L_c)S \\ \alpha(I+\sigma L_c)S \\ 0 \\ 0 \\ 0 \end{bmatrix}$ and

$$B = \begin{bmatrix} -\mu_0 & 0 & 0 & 0 & 0 \\ 0 & -(\mu_0+\beta) & 0 & 0 & 0 \\ 0 & \beta & -(\mu_0+\mu+\gamma) & 0 & 0 \\ 0 & 0 & (\mu+p\gamma) & -(\mu_0+\delta+\varepsilon) & 0 \\ 0 & 0 & (1-p)\gamma & \delta & -\mu_0 \end{bmatrix}.$$

Now

$$F(\varphi_1) - F(\varphi_2) = \begin{bmatrix} -\alpha(I_1+\sigma L_{c_1})S_1 \\ \alpha(I_1+\sigma L_{c_1})S_1 \\ 0 \\ 0 \\ 0 \end{bmatrix} - \begin{bmatrix} -\alpha(I_2+\sigma L_{c_2})S_2 \\ \alpha(I_2+\sigma L_{c_2})S_2 \\ 0 \\ 0 \\ 0 \end{bmatrix} \tag{8}$$

Equation (7) is a non-linear system with a bounded co-efficient.

We set

$$D(\varphi) = \varphi_t = B\varphi + F(\varphi)$$

For the existence of optimal control and optimality system, the boundedness of solution of the system for finite time is needed and we assume for $u \in U$, there exists a bounded solution.

$$|F(\varphi_1) - F(\varphi_2)| = |-\alpha(I_1+\sigma L_{c_1})S_1 + \alpha(I_2+\sigma L_{c_2})S_2| + |\alpha(I_1+\sigma L_{c_1})S_1 - \alpha(I_2+\sigma L_{c_2})S_2|$$

$$\leq 2\alpha(|S_1||I_1-I_2| + |S_1-S_2||I_2+\sigma L_{c_1}| + |\sigma S_2||L_{c_1}-L_{c_2}|)$$

$$\leq M|\varphi_1-\varphi_2|$$

where $M = 2gV_1$.

Also, we get $|D(\varphi_1) - D(\varphi_2)| \leq \|B\||\varphi_1-\varphi_2| + M|\varphi_1-\varphi_2| \leq V|\varphi_1-\varphi_2|$,where $V = \max\ (M,\ \|B\|) < \infty$.

Thus, it follows that the function D is uniformly Lipschitz continuous. From the definition of the control $U(t)$ and the restriction on $S, E, I, L_c,$ and $R \geq 0$, we see that a solution of the system (7) exists.

4.2. Existence of the objective functional

In order to prove the existence of the objective functional, we use the following theorem (Fleming, Rishel, 1975).

Theorem 1. *Let*

$$\overline{x}(t) = \begin{bmatrix} x_1(t) \\ \vdots \\ x_n(t) \end{bmatrix}$$

be a system of n state variables, and let $u(t)$ be a control variable with a set of admissible controls U, that satisfy the following differential equation $x_i'(t) = g(t, x_i(t), u(t))$ *for.* $i = 1, \ldots, n$

with associated performance index

$$J(u) = \int f(t, \overline{x}(t), u(t))\ dt$$

There exists an optimal control which minimizes $\bar{J}(u)$ if the following conditions are satisfied:

(i) F is non-empty.
(ii) The control set U must be closed and convex.
(iii) The right hand side of the state system is continuous, is bounded above by a linear combination of the control and state, and can be written as a linear function of u with coefficients defined by the time and the state.

(iv) The integrand of the objective functional is convex on U and is bounded below by $-C_2 + C_1(u)^{\eta}$, with $C_1 > 0$ and $\eta > 0$.

We define F as a class of $(S_0, E_0, I_0, L_{c_0}, R_0, u)$ such that u is a piecewise function on $[0, T]$ with values in U. To prove that F is nonempty, we will use a simplified version of an existence result in (Boyce, DiPrima, 2009), Theorem 7.1.1), which is stated below.

Theorem 2. *Let each of the functions $F_1, ..., F_n$ and the partial derivatives $\frac{\partial F_1}{\partial x_1}, ..., \frac{\partial F_1}{\partial x_n}, ..., \frac{\partial F_n}{\partial x_1}, ..., \frac{\partial F_n}{\partial x_n}$ be continuous in a region R of t, $x_1, x_2, ..., x_n$ space defined by $\alpha < t < \beta$, $\alpha_1 < x_1 < \beta_1, ..., \alpha_n < x_n < \beta_n$, and let the point $(t, x_1^0, x_2^0, ..., x_n^0)$ be in R. Then there is an interval $[t = t_0] < h$ in which there exists a unique solution $x_1 = \varphi_1(t), ..., x_n = \varphi_n(t)$ of the system of differential equations*

$$\begin{aligned} x_1{}' &= F_1(t, x_1, ..., x_n), \\ x_2{}' &= F_2(t, x_1, ..., x_n), \\ &\vdots \\ x_n{}' &= F_n(t, x_1, ..., x_n), \end{aligned} \tag{9}$$

That also satisfies the initial conditions

$$x_1(t_0) = x_1^0, \;\; x_2(t_0) = x_2^0, ..., x_n(t_0) = x_n^0 \tag{10}$$

Theorem 3. *Let $x_i = F_i(t, x_1, ..., x_n)$ for $i \in [1, \; n]$ be a system of n differential equations with initial conditions $x_i(t_0) = x_i{}^0$ for $i \in [1, \; n]$. If each of the functions $F_1, ..., F_n$ and the partial derivatives $\frac{\partial F_1}{\partial x_1}, ..., \frac{\partial F_1}{\partial x_n}, ..., \frac{\partial F_n}{\partial x_1}, ..., \frac{\partial F_n}{\partial x_n}$ are continuous in R^{n+1} space, then there exists a unique solution $x_1 = \sigma_1(t), ..., x_n = \sigma_n(t)$ that satisfies the initial conditions.*

With the help of the above two theorems (Theorem 2, Theorem 3) we try to prove the existence of the objective functional. We show that there exists an optimal control u^* that minimizes $J(u)$ over the control set U.

***Proof of* (i):** We consider

$$\begin{aligned} \dot{S} &= F_1(t, S, E, I, L_c, R), \\ \dot{E} &= F_2(t, S, E, I, L_c, R), \\ \dot{I} &= F_3(t, S, E, I, L_c, R), \\ \dot{L_c} &= F_4(t, S, E, I, L_c, R), \\ \dot{R} &= F_5(t, S, E, I, L_c, R), \end{aligned} \tag{11}$$

where F_1, F_2, F_3, F_4 and F_5 build up the right hand side of the equation (1). Let $u(t) = C$ for some constant C. F_1, F_2, F_3, F_4 and F_5 must be linear and they are also continuous everywhere. Moreover, the partial derivatives of F_1, F_2, F_3, F_4 and F_5 with respect to all states are constants and they are also continuous everywhere, so by the above Theorem 5.3, there exists a unique solution $S = \sigma_1(t), E = \sigma_2(t), I = \sigma_3(t), L_c = \sigma_4(t)$ *and* $R = \sigma_5(t)$ which satisfies the initial conditions. Therefore, the set of controls and corresponding state variables is non-empty. Hence, the condition (i) is satisfied.

***Proof of* (ii):** By definition, U is closed. We take two controls $(u_1, \; u_2) \in U$ and $\theta \in [0, \; 1]$ such that $0 \le \theta u_1 + (1 - \theta)u_2$. We also observe that $\theta u_1 \le \theta$ and $(1 - \theta)u_2 \le (1 - \theta)$. Then, $\theta u_1 + (1 - \theta)u_2 \le \theta + (1 - \theta) = 1$.

Hence, $0 \le \theta u_1 + (1 - \theta)u_2 \le 1$ *for all* $(u_1, \; u_2) \in U$ *and* $\theta \in [0, \; 1]$. So, U is convex and therefore, condition (ii) is satisfied.

Proof of (iii): If we consider,

$$F_1 \le r - u_1 S$$

$$F_2 \le K_1 E$$

$$F_3 \le \beta E - K_2 I$$

$$F_4 \le K_3 I - P_1 L_c - u_2 L_c$$

$$F_5 \le \delta L_c + P_2 I + u_1 S + u_2 L_c$$

Then, the system (11) can be written as $\overline{F}(t, \; \overline{X}, \; u) \le \overline{m}\left(t, \; \begin{bmatrix} S \\ E \\ I \\ L_c \\ R \end{bmatrix}\right)\overline{X} + \; \overline{n}\left(t, \; \begin{bmatrix} S \\ E \\ I \\ L_c \\ R \end{bmatrix}\right)u(t)$, where

$$\overline{m}\left(t,\begin{bmatrix}S\\E\\I\\L_c\\R\end{bmatrix}\right)=\begin{bmatrix}0&0&0&0&0\\0&K_1&0&0&0\\0&\beta&-K_2&0&0\\0&0&K_3&-P_1&0\\0&0&P_2&\delta&0\end{bmatrix}\text{ and }\overline{n}\left(t,\begin{bmatrix}S\\E\\I\\L_c\\R\end{bmatrix}\right)=\begin{bmatrix}-S&0\\0&0\\0&0\\0&-L_c\\S&L_c\end{bmatrix},$$

which gives a linear function of the control u defined by time and state variables. Then, we can find out the bound of the right hand side. It is noted that all parameters are constant and greater than or equal to zero. Therefore, we can write.

Since $\overline{S}$ and $\overline{L_c}$ are bounded and q includes the upper bound of the constant matrix. Hence, we see that the right hand side is bounded by a sum of the state and the control. Therefore, condition (iii) is satisfied.

Proof of (iv): Let us consider that the integrand of the objective functional be $f(u) = I(t) + L_c(t) + u^2$, where $\frac{A}{2}u_1^2 + \frac{B}{2}u_2^2 = u^2$ (let). Here, the two controls $(u_1,\ u_2) \in U$ and $0 < \omega < 1$.

Then, we can write

$$u_1^2 - 2u_1u_2 + u_2^2 = (u_1 - u_2)^2 \geq 0$$

$$\Rightarrow u_1^2 + u_2^2 \geq 2u_1u_2 \Rightarrow \omega(1-\omega)u_1^2 + \omega(1-\omega)u_2^2 \geq 2\omega(1-\omega)u_1u_2 \therefore \omega f(u_1) + (1-\omega)f(u_2) \geq f(\omega u_1 + (1-\omega)u_2)$$

which implies that $f(u)$ is convex on U.

Now, we will show that

$$J(u) \geq -C_2 + C_1(u)^{\eta} \text{ with } \eta > 0\ C_1 \geq 0$$

Here, $J(u) = I(t) + L_c(t) + \frac{A}{2}u_1^2 + \frac{B}{2}u_2^2\ J(u) = I(t) + L_c(t) + u^2$ [since $\frac{A}{2}u_1^2 + \frac{B}{2}u_2^2 = u^2$]

$$J(u) \geq -[I(t) + L_c(t)] + u^2$$

$$= -C_2 + C_1u^2$$

where $C_2 > 0$ which depends on upper bounds of $I(t),\ L_c(t)$. We can also see that $\eta = 2 > 1, C_1 > 0$. Therefore, the condition (iv) is also satisfied. From the above discussion, the existence of the objective functional has been established.

5. Characterization of the optimal control

In order to derive the necessary conditions for this optimal control, we apply Pontryagin's Maximum Principle to the Hamiltonian (H). Using Pontryagin's Maximum Principle, to find the optimal vaccination and treatment term the standard Hamiltonian function H w.r.t $(u_1,\ u_2)$can be defined as follows:

$$H(t,\ x(t),\ u(t),\ p(t),\ \lambda(t)) = \langle p(t),\ f(x(t)) + g(x(t))u(t)\rangle - \lambda L(x(t), u(t)), \quad \lambda \in \mathbb{R}$$

where $p = (p_S,\ p_E,\ p_I,\ p_{L_c},\ p_R) \in \mathbb{R}^5$ denotes the adjoint variables.

Suppose that the pair (x^*, u^*) is the optimal solution of the above optimal control problem. Then, the maximum principle asserts the existence of a scalar $\lambda_0 \geq 0$, an absolutely continuous function $p(t)$, such that the following conditions are satisfied:

i. $\max\{|p(t)| :\ t \in [0,\ T]\} + \lambda_0 > 0$;
ii. $\dot{p}(t) = \lambda L_x[t] - \langle p[t],\ f_x[t] + g_x[t]u^*(t)\rangle$;
iii. $p(t) = (0,\ 0)$;
iv. $H(x^*(t),\ u^*(t),\ p(t)) = \max_u\{H(x^*(t),\ p(t),\ u(t))\}$, where $a_1 \leq u_1 \leq b_1, a_2 \leq u_2 \leq b_2$,

where time argument $[t]$ denotes the evaluation along with the optimal solution.

Then, from equation (ii) adjoint equations in normal form (i.e. $\lambda = 1$) are explicitly given by

$$p_S{}' = -\frac{\partial H}{\partial S} = -p_S\{-\alpha(I + \sigma L_c) - \mu_0 - u_1\} - p_E\{\alpha(I + \sigma L_c)\} - u_1p_R$$

$$= \alpha(I + \sigma L_c)(p_S - p_E) + p_S(\mu_0 + u_1) - u_1p_R$$

$$p_E' = -\frac{\partial H}{\partial E} = p_E(\mu_0+\beta) - \beta p_I$$

$$= p_E\mu_0 + \beta(p_E - p_I)$$

$$p_I' = -\frac{\partial H}{\partial I} = 1 + \alpha p_S S - \alpha p_E S + \mu_0 p_I + (\mu+\gamma)p_I - (1-p)\gamma p_{L_c} - (\mu+p\gamma)p_R$$

$$= 1 + \alpha S(p_S - p_E) + (\mu_0+\mu+\gamma)p_I - (1-p)\gamma p_{L_c} - (\mu+p\gamma)p_R$$

$$p'_{L_c} = -\frac{\partial H}{\partial L_c} = 1 + \alpha\sigma p_S S - \alpha\sigma p_E S + (\mu_0+\delta+\varepsilon)p_{L_c} + u_2 p_{L_c} - (\delta+u_2)p_R$$

$$= 1 + \alpha\sigma S(p_S - p_E) + (\mu_0+\delta+\varepsilon+u_2)p_{L_c} - (\delta+u_2)p_R$$

$$p_R' = -\frac{\partial H}{\partial R} = \mu_0 p_R$$

with transversality condition $p_i(T) = 0,\ i = 1,\ 2,\ 3,\ 4$ and 5.

Now, by applying Pontryagin's Maximum Principle (Lenhart and Workman, 2007) we have the following theorem and proving Theorem 4, we show the existence of controls.

Theorem 4. There exists optimal control (u_1^*, u_2^*) that minimizes the objective function J over U given by $u_1^* = \max_{[0,\ T]}\left\{0, \min\left(1, \frac{(p_S-p_R)S^*}{A}\right)\right\}$ and $u_2^* = \max_{[0,\ T]}\left\{0, \min\left(1, \frac{(p_{L_c}-p_R){L_c}^*}{B}\right)\right\}$.

Proof: By optimality conditions, we have.

$$\frac{\partial H}{\partial u_1} = Au_1 - p_S S + p_R S = 0 \Rightarrow u_1 = \frac{(p_S - p_R)S}{A} = \bar{u}_1;$$

$$\frac{\partial H}{\partial u_2} = Bu_2 + p_R L_c - p_{L_c} L_c = 0 \Rightarrow u_2 = \frac{(p_{L_c} - p_R)L_c}{B} = \bar{u}_2;$$

According to the property of U, the two controls (u_1^*, u_2^*) are bounded with upper bound 1 and lower bound 0. Therefore,

$$u_1^*(t) = \begin{cases} 0 & \text{if } \bar{u}_1 \le 0 \\ \frac{(p_S-p_R)S}{A} & \text{if } 0 < \bar{u}_1 < 1 \\ 1 & \text{if } \bar{u}_1 \ge 1. \end{cases}$$

This can be written in compact form as

$$u_1^* = \max_{[0,\ T]}\left\{0, \min\left(1, \frac{(p_S - p_R)S}{A}\right)\right\}$$

Similarly,

$$u_2^*(t) = \begin{cases} 0 & \text{if } \bar{u}_2 \le 0 \\ \frac{(p_{L_c}-p_R)L_c}{B} & \text{if } 0 < \bar{u}_2 < 1 \\ 1 & \text{if } \bar{u}_2 \ge 1. \end{cases}$$

In the same way, this can be written in compact form as

$$u_2^* = \max_{[0,\ T]}\left\{0, \min\left(1,\ \frac{(p_{L_c} - p_R)L_c}{B}\right)\right\}$$

Thus, we get optimal solutions as

$$(u_1^*, u_2^*) = \left(\max_{[0,\ T]}\left\{0, \min\left(1,\ \frac{(p_S - p_R)S}{A}\right)\right\},\ \max_{[0,\ T]}\left\{0, \min\left(1,\ \frac{(p_{L_c} - p_R)L_c}{B}\right)\right\}\right)$$

Hence completes the proof.

6. Numerical results and discussion

In the present section, numerical simulations of the optimal control model (3) have been performed using ODE-45 solver written in MATLAB programming. We use a set of logical parameter values. Graphical results are displayed using the initial values: $S = 5.54E = 0, I = 0.1, L_C = 0.3, R = 0.2$ and all the parameters showed in Table 1. The simulations are performed with time 20 years. Firstly, the optimal control model is simulated. For the simulations of the optimal control model (3), we first solve the optimality systems when no treatment is employed. So that we take the control variable $u_1 \neq 0$ (i.e. treatment control, $u_2 = 0$). The simulation results in the absence of treatment are shown in Figs. 7–11. Also, we run the program of the optimal control model (3) when no vaccination strategy is employed. Hence we take the control variable $u_2 \neq 0$ (i.e. vaccination control, $u_1 = 0$) and the simulations are presented in Figs. 12–16.

Again numerical simulations of the optimal system (3) are performed considering both the two controls: vaccination control (i.e.$u_1 \neq 0$) and treatment control (i.e. $u_2 \neq 0$) and also the results are shown in Figs. 17–21. Considering the vaccination and treatment controls at a great extent (i.e. $u_1 = 1,\ u_2 = 1$), we draw Figs. 22–26. Furthermore, we determine the efficiency index of the model by using MATLAB programming. For this purpose, we calculate, $E.I. = \left(1 - \frac{A^c}{A^0}\right) \times 100$ and the detailed about A^c and A^0 are given in (Ghosh, Ghosh, Biswas, Sarkar, 2019). Here the best strategy will be the one whom efficiency index will be bigger than the other. $A = \int_0^{20} L_c(t)\ dt$ represents the cumulated number of liver cirrhotic individuals during the time interval [0, 20]. We evaluate the value of integration and we have $A^0 = 2.4551$. The values of A^c and efficiency index (E.I.) for STR-1 and STR-2 are given in Table 2.

Table 2 shows that STR-2 is the best strategy among STR-1 and STR-2, which permits to reduce the number of incident cases. Thus, treatment is more effective than vaccination to minimize the disease (liver cirrhosis) transmission.

Figs. 7–11 represent the effects of vaccination as a control measure on the susceptible, exposed, infected, liver cirrhotic and recovered individuals for 20 years timeline. It has been noticed that the control measure slightly influences the susceptible individuals, but significantly controls the exposed, infected, liver cirrhotic and recovered individuals. As expected, both the infected and liver cirrhotic individuals have increased in the absence of vaccination than the individuals with having the control measure. On the contrary, the number of recovered individuals increases when vaccination control is applied compared to the individuals without optimal control.

From Figs. 12–16, we observe the effects of treatment as a control measure on the susceptible, exposed, infected, liver cirrhotic and recovered individuals for 20 years timeline. It has been seen that the control measure significantly influences the susceptible, exposed, infected, liver cirrhotic and recovered individuals. Here, both the infected and liver cirrhotic individuals have decreased noticeably for the presence of treatment control than the individuals without having the control measure.

Table 1
Parameter specifications of model (3).

Descriptions	Parameters	Values
Source rate of susceptible population	r	0.0121
Natural population death rate	μ_0	0.95
Transmission rate	α	0.16
Infectiousness of liver cirrhosis relative to acute infections	σ	0.00693
Acute infection rate	β	6 (per year)
Spontaneous recovery rate	γ	0.25
Rate of moving from infection to liver cirrhosis	μ	4 (per year)
Recovered rate from liver cirrhosis	δ	0.03
Disease induced death rate	ε	0.02
Rate of moving from recover to liver cirrhosis carriers	p	0.25

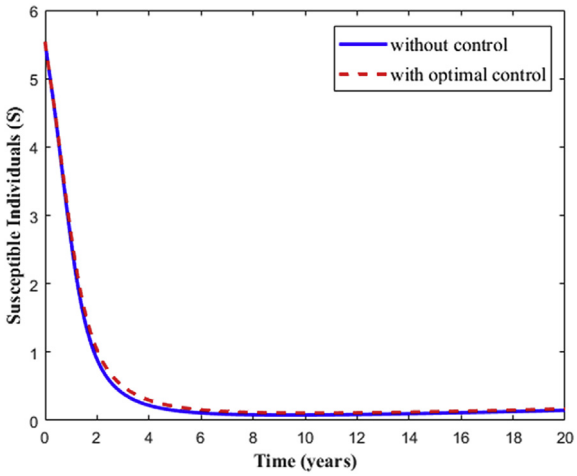

Fig. 7. Dynamics of susceptible individuals when only vaccination control (u_1) is employed as optimal control.

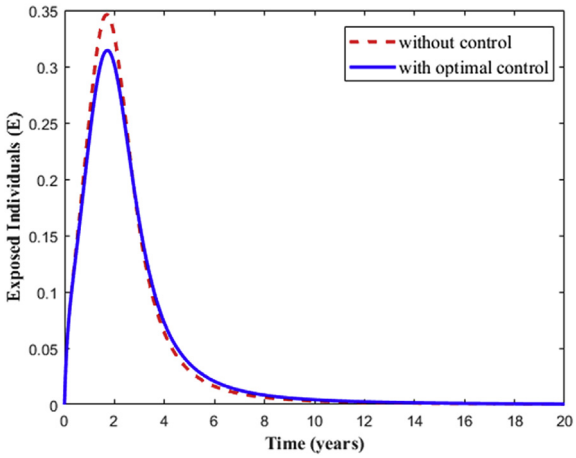

Fig. 8. Dynamics of exposed individuals when only vaccination control (u_1) is employed as optimal control.

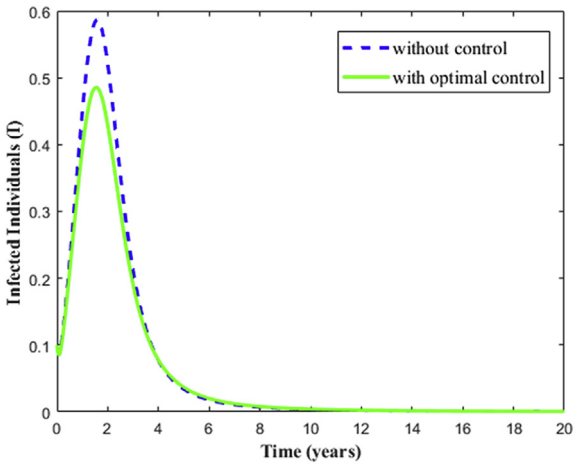

Fig. 9. Dynamics of infected individuals when only vaccination control (u_1) is employed as optimal control.

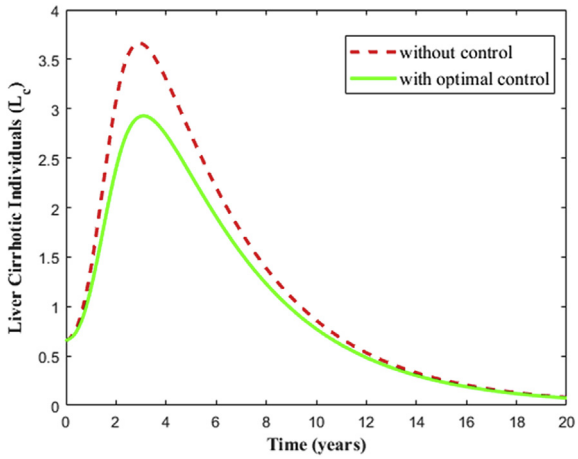

Fig. 10. Dynamics of liver cirrhotic individuals when only vaccination control (u_1) is employed as optimal control.

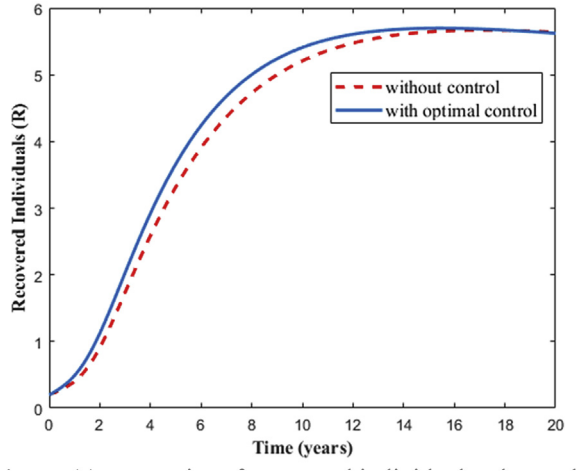

Fig. 11. Dynamics of recovered individuals when only vaccination control (u_1) is employed as optimal control.

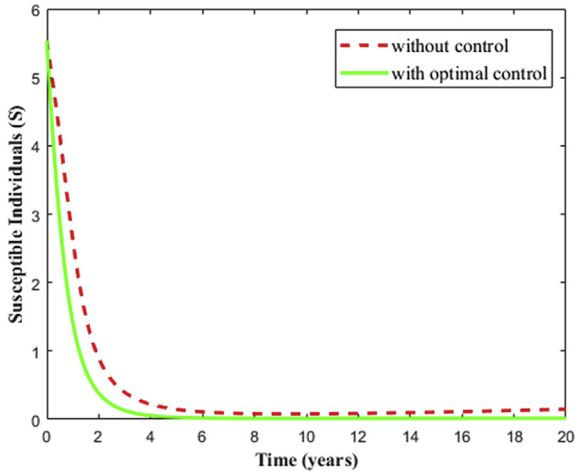

Fig. 12. Dynamics of susceptible individuals when only treatment control (u_2) is employed as optimal control.

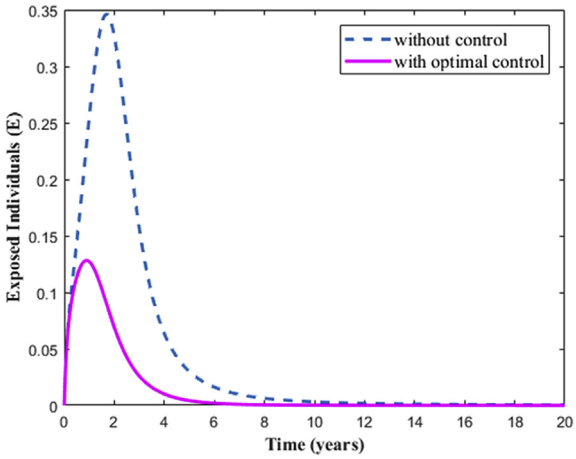

Fig. 13. Dynamics of exposed individuals when only treatment control (u_2) is employed as optimal control.

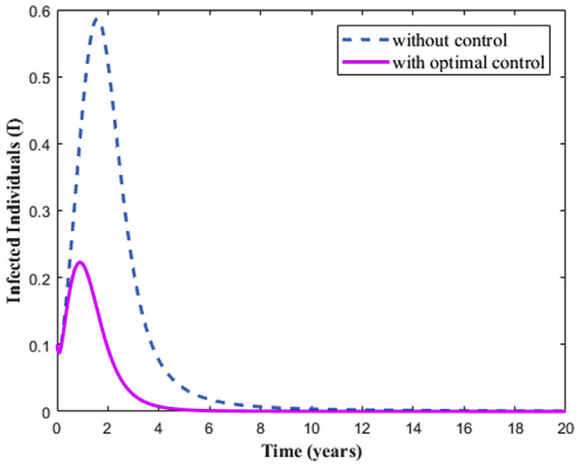

Fig. 14. Dynamics of infected individuals when only treatment control (u_2) is employed as optimal control.

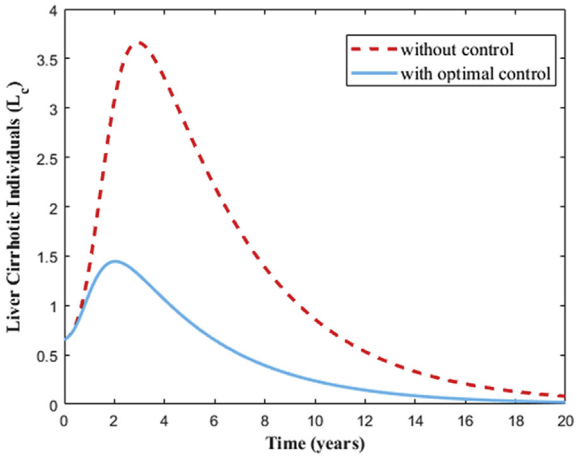

Fig. 15. Dynamics of liver cirrhotic individuals when only treatment control (u_2) is employed as optimal control.

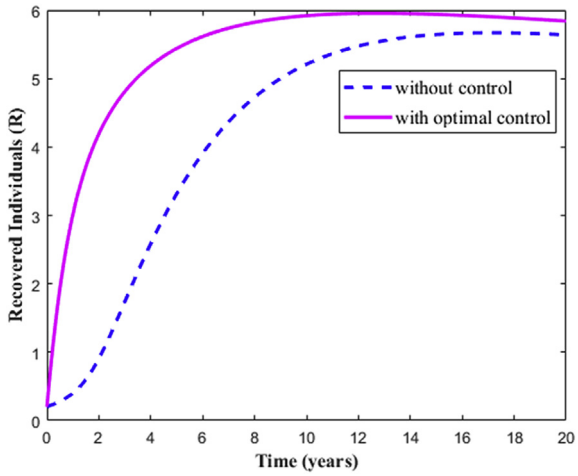

Fig. 16. Dynamics of recovered individuals when only treatment control (u_2) is employed as optimal control.

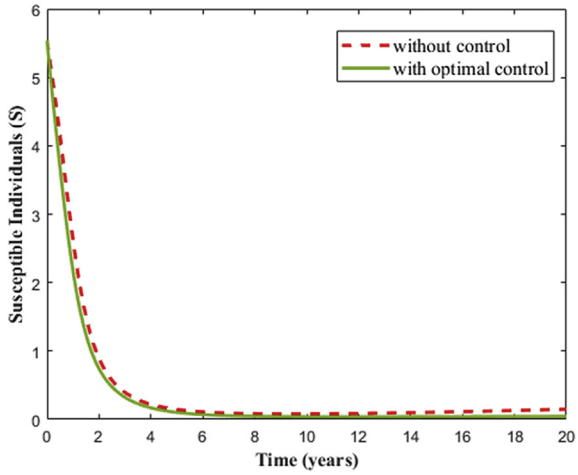

Fig. 17. Dynamics of susceptible individuals when both vaccination (u_1) and treatment control (u_2) are employed as optimal control.

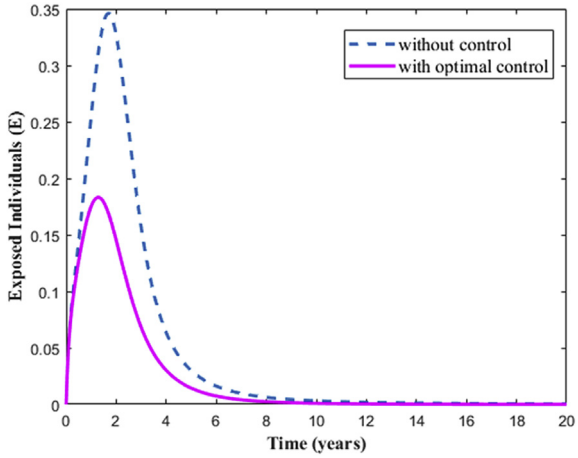

Fig. 18. Dynamics of exposed individuals when both vaccination (u_1) and treatment control (u_2) are employed as optimal control.

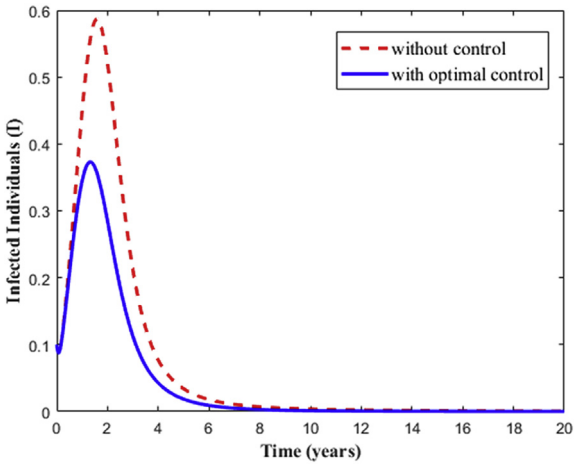

Fig. 19. Dynamics of infected individuals when both vaccination (u_1) and treatment control (u_2) are employed as optimal control.

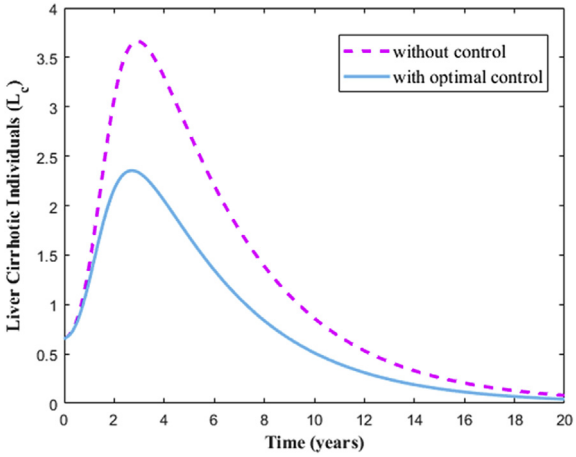

Fig. 20. Dynamics of liver cirrhotic individuals when both vaccination (u_1) and treatment control (u_2) are employed as optimal control.

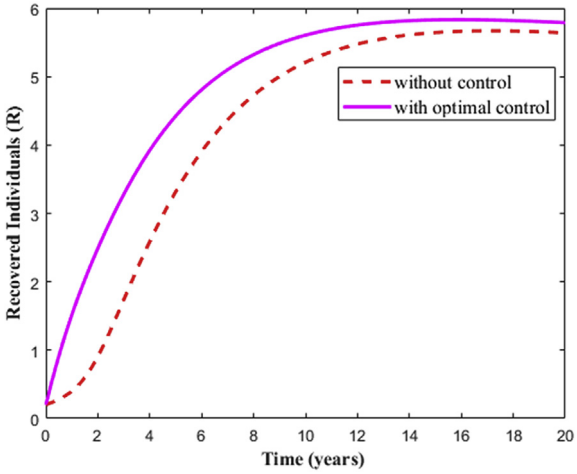

Fig. 21. Dynamics of recovered individuals when both vaccination (u_1) and treatment control (u_2) are employed as optimal control.

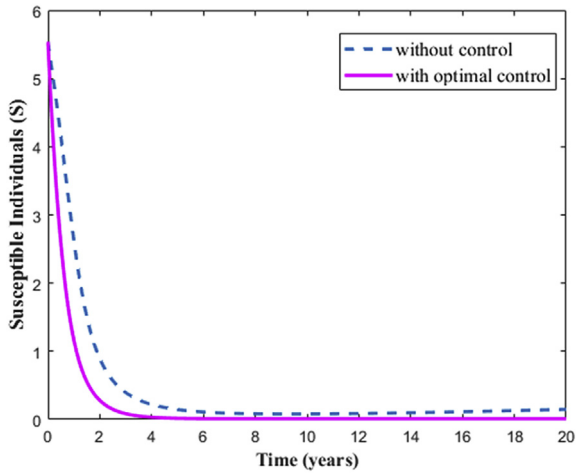

Fig. 22. Dynamics of susceptible individuals when the maximum level of both vaccination (u_1) and treatment control (u_2) are employed as optimal control.

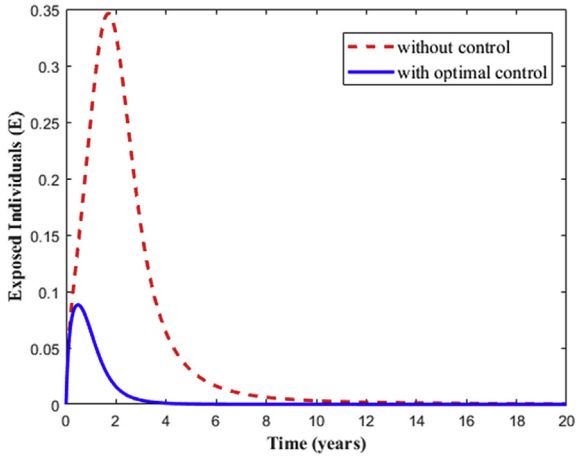

Fig. 23. Dynamics of exposed individuals when the maximum level of both vaccination (u_1) and treatment control (u_2) are employed as optimal control.

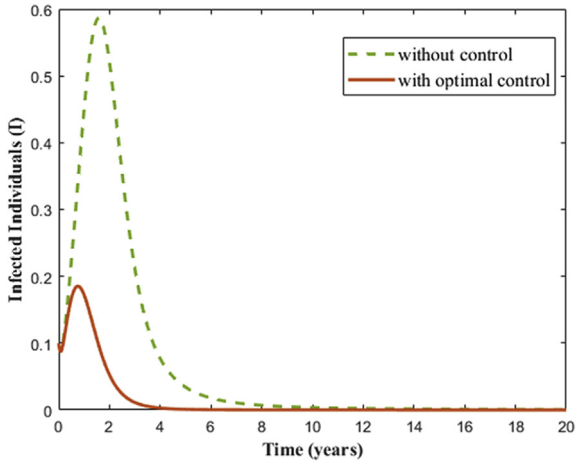

Fig. 24. Dynamics of infected individuals when the maximum level of both vaccination (u_1) and treatment control (u_2) are employed as optimal control.

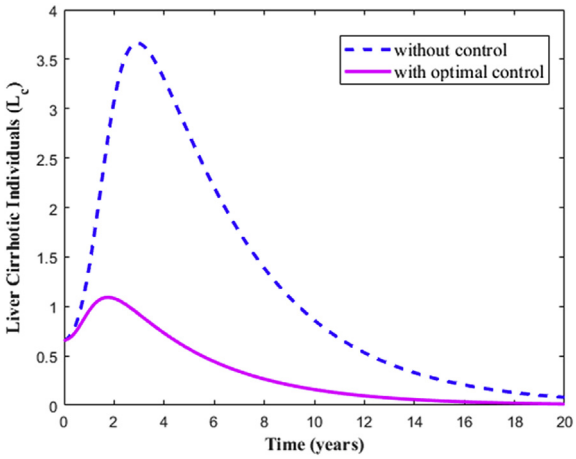

Fig. 25. Dynamics of liver cirrhotic individuals when the maximum level of both vaccination (u_1) and treatment control (u_2) are employed as optimal control.

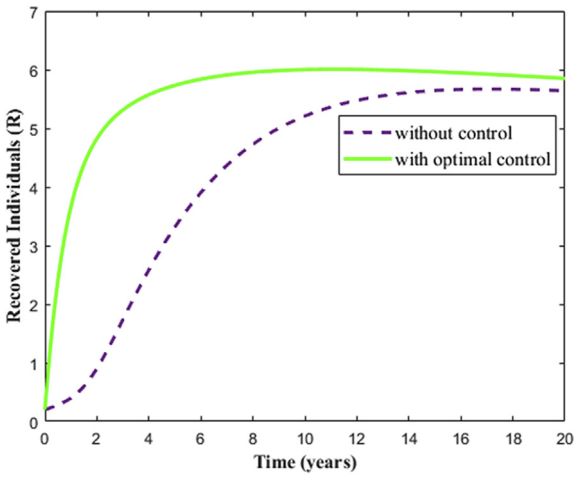

Fig. 26. Dynamics of recovered individuals when the maximum level of both vaccination (u_1) and treatment control (u_2) are employed as optimal control.

Table 2
Calculation of efficiency index.

Strategy	$\mathbf{A^c}$	E.I.
STR-1	2.4319	0.9474
STR-2	1.5208	38.0551

Again, the number of recovered individuals increases when treatment control is applied compared to the individuals without optimal control.

Figs. 17–21 show the effects of control measures (vaccination and treatment) on the susceptible, exposed, infected, liver cirrhotic and recovered individuals for 20 years timeline. It has been observed that the control measure slightly influences the susceptible population, but significantly controls the exposed, infected, liver cirrhotic and recovered individuals. As anticipated, both the infected and liver cirrhotic individuals have decreased for the presence of control measure than the individuals without having the control measure. In contrast, the number of recovered individuals increases when the control measure is applied compared to the individuals without optimal control.

Figs. 22–26 exhibit the effects of the maximum level of the control measures (vaccination and treatment) on the susceptible, exposed, infected, liver cirrhotic and recovered individuals for 20 years timeline at an extreme level of the control measure. It has been noted that the control measure significantly controls the susceptible, exposed, infected, liver cirrhotic and recovered individuals. As presumed, both the infected and liver cirrhotic individuals have increased for the absence of control measure than the individuals with having the control measure at their extreme level. Conversely, the number of recovered individuals increases when the control measure is applied compared to the individuals without optimal control.

7. Conclusions

In this paper, an optimal control model has been formulated considering two control variables by using the most well-known Pontryagin's maximum principle. Numerical simulations have been performed to illustrate the analytic results. After investigation, it has been observed that the optimal vaccination and treatment are much more effective for reducing the number of exposed, infected and liver cirrhotic individuals, to maximize the recovered individuals and also to minimize the cost of the two control measures. Since there are vaccination strategies available for hepatitis B infection (which ultimately leads to chronic disease liver cirrhosis) so from the simulations, it has been established that the optimal combination of vaccination and treatment is effective to control the disease progression. So to reduce the infections, hepatitis B virus vaccination should be started immediately after newborn birth. Eventually, liver cirrhosis is a significant 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.

Declaration of competing interest

The authors have no conflict of interest to declare.

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