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Research Article

Modeling the Combined Effect of Hepatitis B Infection and Heavy Alcohol Consumption on the Progression Dynamics of Liver Cirrhosis

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Liver cirrhosis is the liver scarring in human body which causes the liver organ failure to function its regular activities effectively and normally. In this paper, we proposed and analyzed the combined effect of hepatitis B virus (HBV) infection and heavy alcohol consumption on the progression dynamics of liver cirrhosis. In order to study the progression dynamics of cirrhosis and to describe the effect of alcohol intake variation on a chronic hepatitis B patients a deterministic model and a logistic function are considered, respectively. The detailed proof of the positivity, boundedness, and biological feasibility of the proposed model is presented. The disease endemic equilibrium point and the existence of bifurcation were investigated in detail. We established and proved the existence theorems for forward and backward bifurcations, respectively. Finally, we performed large scale numerical simulations to verify the analytic work and the result of the numerical simulations reveal that heavy alcohol consumption significantly accelerates the progression of liver cirrhosis in chronic hepatitis B infected individuals.

1. Introduction

Liver cirrhosis is a late stage of liver diseases where a healthy liver tissue is possibly transformed into scar tissue when forced to process alcohol or subjected to viral infections, which in turn makes the liver organ fail to function normally. It is characterized by high morbidity and mortality in the world where one million deaths are attributable to cirrhosis every year [1]. Liver cirrhosis is caused by alcohol abuse, chronic viral hepatitis (B and C), and nonalcohol fatty diseases [2]. Although liver cirrhosis has no signs until liver damage is extensive, acute infection individuals gradually develop symptoms such as easily bleeding, nausea, loss of appetite, and sudden weight loss.

The two main etiologic factors of liver cirrhosis include HBV infection and heavy alcohol consumption [3]. Between 350 and 400 million people are chronic carriers and 2 billion people are living with HBV infection in the world [4]. Hepatitis B, one of the major risk factors of liver cirrhosis which originates from hepatitis B virus, is more likely to occur among people with long term viral hepatitis. The HBV infection involves two phases: acute infection and chronic HBV carriers [5]. About 90% of acute infection individuals are capable of clearing HBV from their blood within 6 months [6, 7]. However, the chronic phase is the end-stage liver disease which results in liver inflammation and can lead to life-long illness. This contagious disease is spreading either vertically from infected mothers to her infants during delivery or horizontally through unsafe sexual practices, blood transfusion with another infected human, and exposures to infectious blood and body fluids [6, 8]. Liver cirrhosis is heavily prevalent in hepatocellular carcinoma (HCC) when compared with HBV patients [9], Liver cirrhosis development is higher in chronic HBV patients with high viral load than in those with low viral load [10].

Heavy alcohol consumption is another major risk factor of chronic liver cirrhosis development in which about 38% of people older than 15 years consume approximately more

than 17 litres of pure alcohol annually (see [4] and references therein). About 10%–20% of heavy drinkers of alcohol commonly develop cirrhosis after 10 or more years. Specifically, drinking 50 grams of pure alcohol daily for 10 to 20 years is the minimum amount of alcohol required to generate cirrhosis. Heavy alcohol consumption causes rapid progression of liver disease, weakens innate and adaptive immunity, and allows HBV to persist chronically [3]. Many studies reveal that there is no significant increase to cirrhosis for people who consume less than 50 grams of pure alcohol per day. Consumption of greater than 50 grams of pure alcohol per day for both males and females accelerates the progression of cirrhosis in chronic hepatitis B carriers and consumption of greater than 300 grams of alcohol per day is poisonous and lethal for a 60 kg weighing person [4, 5, 11, 12]. Moreover, alcohol abuse exponentially increases the risk for liver cirrhosis [10, 13].

Khatun and Biswas [2] clarified the transmission dynamics of liver cirrhosis from HBV and concluded that the disease can be controlled through vaccination and treatment using a mathematical model and optimal control strategy. Ganesan et al. [3] suggested that the combination of HBV infection and alcohol abuses can provide detrimental consequences in rapid end-stage liver disease. Iida-Ueno et al. [4] investigated the association between hepatitis B virus infection and alcohol consumption. The authors concluded that heavy alcohol consumption within chronic HBV infected patients significantly increases the progression of liver disease to cirrhosis, on average fivefold increased risk. Din et al. [5] formulated an epidemic model to investigate the viral dynamics of HBV by considering the impact of acutely infected individuals in the vertical transmission of HBV infection. The authors incorporated two time dependent controls in their model and concluded that effective implementation of the control strategies for the long-run is possible enough in order to eradicate HBV in the community. Khan et al. [6] developed a deterministic mathematical model to qualitatively analyze the impact of migration, vaccination, and hospitalization on the spread and control of HBV. The authors concluded that the migration, vaccination, and hospitalization are effective measures to predict the intervention strategies. Macías-Díaz et al. [7] presented a nonstandard numerical design to analyze a discrete three-dimensional HBV epidemic model. Mokdad et al. [8] suggested preventive measures to control and reduce liver cirrhosis risk factors should be urgently strengthened. Vonghia et al. [11] related binge drinking with body mass index and suggested that for a 60 kg person drinking 300 g of pure alcohol per day which is the lethal amount can kill the person or poison his blood. Yang et al. [9] studied the prevalence of cirrhosis in HBV and hepatocellular carcinoma (HCC) and the result shows that it was 88% and 97% among HBV and hepatitis C virus (HCV) patients, respectively. Khajji et al. [14] analyzed the impact of the addiction treatment centers on system stability and awareness creation programs on the drinkers.

Mathematical models are widely used and can be employed to study the dynamics behavior of infectious diseases such as HBV infection, liver cirrhosis, cholera, and so on. The studies on these infectious diseases highlight how to control the spread and predict its future damage on the lives and economies of the country. Interestingly, there is a large scale of mathematical models developed on the transmission dynamics and control mechanisms of HBV infection, alcohol drinking pattern, and liver cirrhosis reduction.

The authors in [14, 15] formulated a continuous and discrete mathematical model to study the dynamical behavior of alcohol drinking with the impact of private and public addiction treatment centers. Park et al. [16] discussed the factors associated with alcohol consumption in HBV carriers in Korea and identified high-risk alcohol consumption as consuming at least 60 g of alcohol on one occasion and 40 g of alcohol on more than one occasion for male and female, respectively. Ullah et al. [17] analyzed the dynamics of HBV transmission model with hospitalized class. Zou et al. [18] developed a deterministic model to analyze the impact of sexual transmission on the disease prevalence. Khan et al. [19] illustrated the merits of media coverage with the help of dynamical model for hepatitis B. Zhao et al. [20] studied the application of vaccination strategies in China against HBV infection and found that long term effective immunization is needed by providing higher vaccination coverage. Zhou et al. [21] compared excessive drinking and moderate alcohol consumption and concluded that alcohol abuse in patients with chronic HBV infection increases liver inflammation which finally accelerates the progression of liver cirrhosis while moderate alcohol consumption has no significant effect on its progression.

Even though there is a safe and effective vaccine available for HBV, HBV related mortality and morbidity are still there in the top list and the progression of liver cirrhosis is increasing in the world. The efficacy of drugs aimed at breaking the progression of liver fibrosis was studied by Friedman and Hao [22] by developing a mathematical model of liver cirrhosis. Hence, we will formulate a deterministic model along with logistic alcohol intake variation to investigate the combined effect of HBV infection and heavy alcohol consumption on the progression dynamics of chronic liver cirrhosis, which is not considered by any scholar yet, to the best of the knowledge of the authors.

This article is organized as follows. Section 2 is devoted to model formulation and presents the fundamental properties of the model. In Section 3, positivity of the solution, boundedness of the feasible region, disease free-equilibrium, and the existence of disease endemic equilibrium will be presented and the stabilities of disease free-equilibrium (DFE) and endemic equilibrium (EE) are checked in Section 4. In Section 5, we will analyze the bifurcation phenomena and prove the existence of forward and backward bifurcation of the model. In Section 6, the local sensitivity analysis of the model will be calculated and its biological interpretation will be provided. Section 7 is devoted to explore the simulation of the liver cirrhosis model. Finally, conclusion of the overall work is presented in Section 8.

2. Model Formulation

Here, we develop a deterministic mathematical model that consists of four ordinary differential equations along with a logistic model with alcohol consumption variation to study the progression dynamics of chronic liver cirrhosis. We partitioned the whole population into four compartments: the susceptible individuals $S(t)$, the acutely infected individuals $I(t)$, the liver cirrhotic individuals $C(t)$, and the recovered individuals $R(t)$ with $N(t) = S(t) + I(t) + C(t) + R(t)$.

Susceptible individuals $S(t)$ are individuals who are not yet infected with the disease at time t. The susceptible population do not have an immunity against a potential infection. This class is generated by the recruitment rate Λ and decreased by disease transmission coefficient $\beta(A)$, where $A(t)$ is the amount of pure alcohol consumed in grams per day. Further, it is decreased by the natural death rate μ. Hence, the above hypotheses lead to a differential equation of the susceptible population at time t

$$\frac{d}{dt}S(t) = \Lambda - \beta(A)(I(t) + \gamma C(t))S(t) - (\mu + \nu)S(t). \quad (1)$$

The parameters ν and γ represent the vaccination rate of newborn infants and the rate of relative infectiousness of cirrhosis over acute infection, respectively. All population classes are subjected to the natural death rate μ.

The acutely infected populations $I(t)$ are individuals who are currently infected with the disease, develop strong enough immunity to clear the disease from the body, and are capable of spreading the disease to those in the susceptible phase. This class is generated by the transmission coefficient $\beta(A)$ and it is decreased by a spontaneous recovery rate η, a cirrhosis progression rate σ, and natural and disease related death rates μ and μ_1, respectively. The acute infection compartment is given by the following differential equation:

$$\frac{d}{dt}I(t) = \beta(A)(I(t) + \gamma C(t))S(t) - (\mu + \mu_1 + \eta + \sigma)C(t). \quad (2)$$

Liver cirrhotic individuals $C(t)$ are asymptomatic infection individuals who are infected with the end-stage liver disease and can transmit the disease at any time t. The cirrhotic compartment is increased by a cirrhosis progression rate σ and a proportion q, $(0 < q \leq 1)$ of relapse rate. It is decreased by a cirrhosis recovery rate δ and natural and disease related death rates μ and μ_2, respectively. The differential equation governing the liver cirrhosis compartment is given by

$$\frac{d}{dt}C(t) = (\sigma + q\eta)I(t) - (\mu + \mu_2 + \delta)C(t). \quad (3)$$

Finally, the recovered population $R(t)$ is generated by cirrhosis recovery rate δ and a spontaneous acute recovery rate η. This class is further decreased by natural death rate μ. Hence, the recovery class is governed by the following equation:

$$\frac{d}{dt}R(t) = \nu S(t) + (1 - q)\eta I(t) + \delta C(t) - \mu R(t). \quad (4)$$

Moreover, we assumed the variation in the amount of pure alcohol consumption of young adults is supposed to be given by a logistic model with an alcohol consumption growth rate r. The rate of change of alcohol consumption at any time t is given by

$$\frac{d}{dt}A(t) = r(A(t) - A_0)\left(1 - \frac{A(t)}{A_{\max}}\right), \quad (5)$$

where A_0 represents a minimum amount of pure alcohol consumed and $A_{\max}$ represents a maximum amount of pure alcohol consumed in grams. Furthermore, we considered the following assumptions to enhance the model formulation for the progression dynamics of chronic liver cirrhosis.

(i) All state variables are nonnegative and known quantities.

(ii) The transmission coefficient depends on the variation of alcohol consumption of HBV infection patient.

$$\beta(A) = \beta_0 + \beta_1\left(\frac{A(t) - A_0}{A_{\max}}\right). \quad (6)$$

β_0 is the mean transmission rate of liver cirrhosis and β_1 is the incremental rate of pure alcohol consumption.

(iii) Individuals aged above 15 years are considered.

(iv) The average amount of alcohol consumption for male and female is the same.

(v) Alcohol consumption with meal is taken into account.

Figure 1 represents the transfer diagram for chronic liver cirrhosis.

$$\begin{cases} \dfrac{d}{dt}S(t) = \Lambda - \beta(A)(I(t) + \gamma C(t))S(t) - (\mu + \nu)S(t), \\ \dfrac{d}{dt}I(t) = \beta(A)(I(t) + \gamma C(t))S(t) - (\mu + \mu_1 + \eta + \sigma)I(t), \\ \dfrac{d}{dt}C(t) = (\sigma + q\eta)I(t) - (\mu + \mu_2 + \delta)C(t), \\ \dfrac{d}{dt}R(t) = \nu S(t) + (1 - q)\eta I(t) + \delta C(t) - \mu R(t), \\ \dfrac{d}{dt}A(t) = r(A(t) - A_0)\left(1 - \dfrac{A(t)}{A_{\max}}\right). \end{cases} \quad (7)$$

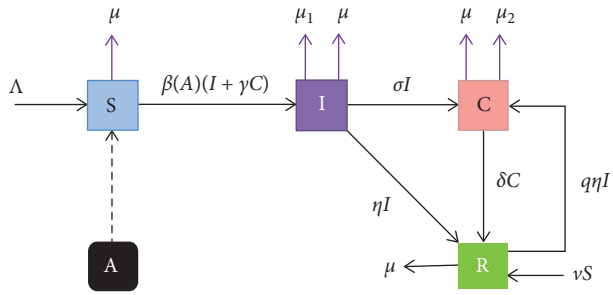

Figure 1: Transfer diagram of liver cirrhosis. Hence, combining equations (1)–(5) above together with the assumptions (i)–(v), finally, we obtain the following system of differential equations for the progression dynamics of liver cirrhosis.

This is done along with the subsidiary condition

$$\begin{aligned} S(0) &= S_0 \geq 0, \\ I(0) &= I_0 > 0, \\ C(0) &= C_0 > 0, \\ R(0) &= R_0 > 0, \\ A(0) &\geq 0. \end{aligned} \tag{8}$$

3. Model Analysis

In this section, we present the solution of the model under discussion and affirm that the solution is nonnegative for long time in future.

3.1. Positivity and Boundedness of Solution

Theorem 1. *The solution* $G(t) = (S(t), I(t), C(t), R(t), A(t))$ *is nonnegative for all* $t > 0$ *if the initial data of system (7) in the form* $G(0) = (S(0), I(0), C(0), R(0), A(0))$ *is nonnegative.*

Proof. To show the positivity of the state $S(t), I(t), C(t), R(t)$, and $A(t)$, we first present the solution of the first equation of system (7).

$$\frac{d}{dt}S(t) + \beta(A)(I(t) + \gamma C(t))S(t) + (\mu + \nu)S(t) = \Lambda. \tag{9}$$

Integration of (9) with respect t yields

$$S(t) = e^{\left(-(\mu+\nu)t + \int_0^t \beta(A)(I(x)+\gamma C(x))\mathrm{d}x\right)}\left\{S_0 + \int_0^t \Lambda\left(e^{\left((\mu+\nu)t + \int_0^t \beta(A)(I(u)+\gamma C(u))\mathrm{d}u\right)}\right)\mathrm{d}t\right\} \geq 0. \tag{10}$$

From equation (10), we observe that $S(t)$ is nonnegative for all $t > 0$. In a similar procedure, one can verify that $I(t), C(t), R(t)$, and $A(t)$ are nonnegative for $t > 0$. □

Theorem 2. *The closed set*

$$\Omega = \left\{(S, I, C, R) \in \mathbb{R}_+^4 : 0 < N(S, I, C, R) \leq \frac{\Lambda}{\mu}\right\}. \tag{11}$$

It is biologically feasible region of the initial value problems (7) and (8).

Proof. For the sake of convenience, we let $r_1 = \mu + \nu, r_2 = \mu + \mu_1 + \eta + \sigma, r_3 = \mu + \mu_2 + \delta$ throughout this paper. Recall that the total population $N(t)$ at any time t is given by

$$N(t) = S(t) + I(t) + C(t) + R(t). \tag{12}$$

Differentiation of equation (12) with respect t gives

$$\frac{dN}{dt} = \Lambda - \mu N - \mu_1 I - \mu_2 C. \tag{13}$$

Simplification of equation (13) in the absence of infectious yields

$$\frac{dN}{dt} \leq \Lambda - \mu N. \tag{14}$$

After a slight arrangement and integration of equation (14) with respect to t we obtain

$$0 < N \leq \frac{\Lambda}{\mu} + \left(N(0) - \frac{\Lambda}{\mu}\right)e^{-\mu t}. \tag{15}$$

By taking limit as $t \longrightarrow \infty$ on the inequality in equation (15) we obtain

$$N(t) \leq \frac{\Lambda}{\mu}. \tag{16}$$

Hence, each solution of the initial value problems (7) and (8) remains in equation (11) for all $t > 0$. □

3.2. Basic Reproduction Number ($\mathscr{R}_0$). To calculate the expression for basic reproduction number ($\mathscr{R}_0$), we want to determine the DFE of system (7). For this purpose, we set the right hand side (RHS) of system (7) equal to zero and substitute $S(t) = S_0 > 0, I(t) = I_0 = 0, C(t) = C_0 = 0, R(t) = R_0 = 0$, and $A(t) = [A_0, A_{\max}]$. Thus,

$$\begin{aligned} \varepsilon_{01} &= \left(\frac{\Lambda}{r_1}, 0, 0, 0, A_0\right), \\ \text{or}\varepsilon_{02} &= \left(\frac{\Lambda}{r_1}, 0, 0, 0, A_{\max}\right). \end{aligned} \tag{17}$$

Therefore, $\varepsilon_0 = \{\varepsilon_{01}, \varepsilon_{02}\}$ is the set of DFE point of system (7). By using DFE, we can calculate the basic reproduction number ($\mathscr{R}_0$). We follow the work of Watmough and Driessche method [23] to calculate $\mathscr{R}_0$. Consider the system $(dx/dt) = (\mathscr{F} - \mathscr{V})x$, where the transmission matrix $\mathscr{F}$ is given by

$$\mathscr{F} = \begin{pmatrix} \beta(A)S_0 & \gamma\beta(A)S_0 \\ 0 & 0 \end{pmatrix}, \tag{18}$$

and the transition matrix $\mathscr{V}$ is given by

$$\mathscr{V} = \begin{pmatrix} r_2 & 0 \\ -(\sigma + q\eta) & r_3 \end{pmatrix}. \tag{19}$$

Hence, the next generation matrix calculated from equations (18) and (19) becomes

$$\mathscr{F}\mathscr{V}^{-1} = \begin{pmatrix} \dfrac{\beta(A)S_0}{r_2} + \dfrac{\gamma\beta(A)(\sigma + q\eta)S_0}{r_2 r_3} & \dfrac{\gamma\beta(A)S_0}{r_3} \\ 0 & 0 \end{pmatrix}. \tag{20}$$

Now, the dominant eigenvalue $\rho(\mathscr{F}\mathscr{V}^{-1})$ represents ($\mathscr{R}_0$) of system (7) which is given by

$$\begin{aligned} \mathscr{R}_0 &= \frac{\beta(A)S_0}{r_2} + \frac{\gamma\beta(A)(\sigma + q\eta)S_0}{r_2 r_3} \\ &= \frac{\Lambda\beta(A)(\mu + \mu_2 + \delta + \gamma(\sigma + q\eta))}{(\mu + \nu)(\mu + \mu_1 + \eta + \sigma)(\mu + \mu_2 + \delta)}. \end{aligned} \tag{21}$$

From equation (21), we calculate two different expressions for $\mathscr{R}_0$. The expression for the first basic reproduction number $\mathscr{R}_{01}$ is calculated when a chronic hepatitis B patient consumes a minimum amount of alcohol (i.e., $A(t) = A_0$).

$$\mathscr{R}_{01} = \frac{\Lambda\beta_0(\mu + \mu_2 + \delta + \gamma(\sigma + q\eta))}{(\mu + \nu)(\mu + \mu_1 + \eta + \sigma)(\mu + \mu_2 + \delta)}. \tag{22}$$

The expression for the second basic reproduction number $\mathscr{R}_{02}$ of system (7) is calculated when a chronic hepatitis B carrier consumes maximum amount of alcohol (i.e., $A(t) = A_{\max}$).

$$\mathscr{R}_{02} = \mathscr{R}_{01} + \frac{\Lambda k\beta_1(\mu + \mu_2 + \delta + \gamma(\sigma + q\eta))}{(\mu + \nu)(\mu + \mu_1 + \eta + \sigma)(\mu + \mu_2 + \delta)}, \tag{23}$$

where $k = ((A(t) - A_0)/A_{\max})$. We observe that $0 < \mathscr{R}_{01} < \mathscr{R}_{02}$ and rewrite it as $\mathscr{R}_0 = \{\mathscr{R}_{01}, \mathscr{R}_{02}\}$ in compact form.

3.3. Existence of Endemic Equilibrium. In this current section, we investigate the disease endemic equilibrium of system (7). One interesting idea behind the endemic equilibrium is that it is used to determine the persistence of liver cirrhosis in the population. Let us denote the steady state solution of system (7) by $\varepsilon^* = \{S^*(t), I^*(t), C^*(t), R^*(t)\}$ where $A^*(t) \in [A_0, A_{\max}]$. Thus, the reduced part of system (7) will take the form

$$\begin{cases} 0 = \Lambda - \beta(A^*)(I^*(t) + \gamma C^*(t))S^*(t) - (\mu + \nu)S^*(t), \\ 0 = \beta(A^*)(I^*(t) + \gamma C^*(t))S^*(t) - (\mu + \mu_1 + \eta + \sigma)I^*(t), \\ 0 = (\sigma + q\eta)I^*(t) - (\mu + \mu_2 + \delta)C^*(t), \\ 0 = \nu S^*(t) + (1 - q)\eta I^*(t) + \delta C^*(t) - \mu R^*(t), \\ 0 = r(A^*(t) - A_0)\left(1 - \dfrac{A^*(t)}{A_{\max}}\right). \end{cases} \tag{24}$$

Hence, after a tiresome calculation we worked out the first endemic equilibrium ε_1^* from equation (24) which is given by

$$\begin{aligned} S^*(t) &= \frac{(\mu + \mu_1 + \eta + \sigma)(\mu + \mu_2 + \delta)}{\beta_0(\mu + \mu_2 + \delta + \gamma(\sigma + q\eta))}, \\ I^*(t) &= \frac{(\mu + \nu)(\mu + \mu_2 + \delta)(\mathscr{R}_{01} - 1)}{\beta_0(\mu + \mu_2 + \delta + \gamma(\sigma + q\eta))}, \\ C^*(t) &= \frac{(\mu + \nu)(\sigma + q\eta)(\mathscr{R}_{01} - 1)}{\beta_0(\mu + \mu_2 + \delta + \gamma(\sigma + q\eta))}, \\ R^*(t) &= \frac{1}{(\mu + \nu)}[\nu S^* + (1 - q)\eta I^* + \delta C^*], \end{aligned} \tag{25}$$

where $A^*(t) = A_0$. Hence, the existence of the first endemic equilibrium $\mathscr{E}_1^*$ in equation (25) depends on $\mathscr{R}_{01}$. This implies that there is at least one positive endemic equilibrium point if and only if $\mathscr{R}_{01} > 1$.

Similarly, the second endemic equilibrium ε_2^* when $A^*(t) = A_{\max}$ and $\beta(A^*) = \beta_0 + k\beta_1$ becomes

$$\begin{aligned} S^*(t) &= \frac{(\mu + \mu_1 + \eta + \sigma)(\mu + \mu_2 + \delta)}{(\beta_0 + k\beta_1)(\mu + \mu_2 + \delta + \gamma(\sigma + q\eta))}, \\ I^*(t) &= \frac{(\mu + \nu)(\mu + \mu_2 + \delta)(\mathscr{R}_{02} - 1)}{(\beta_0 + k\beta_1)(\mu + \mu_2 + \delta + \gamma(\sigma + q\eta))}, \\ C^*(t) &= \frac{(\mu + \nu)(\sigma + q\eta)(\mathscr{R}_{02} - 1)}{(\beta_0 + k\beta_1)(\mu + \mu_2 + \delta + \gamma(\sigma + q\eta))}, \\ R^*(t) &= \frac{1}{(\mu + \nu)}[\nu S^* + (1 - q)\eta I^* + \delta C^*]. \end{aligned} \tag{26}$$

Hence, the existence of $\mathscr{E}_2^*$ in equation (26) depends on $\mathscr{R}_{02}$. Therefore, the disease endemic equilibrium $\mathscr{E}^* = \{\mathscr{E}_1^*, \mathscr{E}_2^*\}$ of system (7) exists if $\mathscr{R}_{02} > \mathscr{R}_{01} > 1$.

4. Stability Analysis

To present the local and global asymptotic stability of the two equilibria of system (7), we use the Jacobian matrices at DFE and EE for local stability and the Lyapunov function for the global stability of both equilibria.

4.1. Local Stability Analyses

Theorem 3. *The disease free-equilibrium point, $\varepsilon_0 = \{\varepsilon_{01}, \varepsilon_{02}\}$, of system (7) is locally asymptotically stable if $\mathscr{R}_{01} < \mathscr{R}_{02} < 1$ and unstable otherwise.*

Proof. The desired Jacobian matrix evaluated at $\mathscr{E}_0$ when $A^*(t) \in [A_0, A_{\max}]$ becomes

$$J(\varepsilon_0) = \begin{pmatrix} -r_1 & -\beta(A^*)S_0 & -\gamma\beta(A^*)S_0 & 0 & 0 \\ 0 & \beta(A^*)S_0 - r_2 & \gamma\beta(A^*)S_0 & 0 & 0 \\ 0 & (\sigma + q\eta) & -r_3 & 0 & 0 \\ \nu & (1-q)\eta & \delta & -\mu & 0 \\ 0 & 0 & 0 & 0 & -r_5 \end{pmatrix}, \tag{27}$$

where $r_5 = ((2A^* - (A_0 + A_{\max}))/A_{\max})$.

The characteristic polynomial of equation (27) becomes

$$\psi(\lambda) = (\lambda + r_1)(\lambda + \mu)(\lambda + r_5)\left(\lambda^2 + a_1\lambda + a_2\right). \tag{28}$$

The first three eigenvalues of equation (28) are $\lambda = -r_1, \lambda = -\mu, \lambda = -r_5$. They are negative and the existence of the remaining eigenvalues is determined using the Routh-Hurwitz condition such that

$$\begin{aligned} a_1 &= r_2 + r_3 > 0, \\ a_2 &= r_1 r_2 r_3 (1 - \mathscr{R}_{02}) > 0, \end{aligned} \tag{29}$$

hold. Thus, the necessary condition for the Routh-Hurwitz criteria is satisfied whenever $\mathscr{R}_{02} < 1$. Therefore, the DFE $\mathscr{E}_0$ of system (7) is locally asymptotically stable if $\mathscr{R}_{01} < \mathscr{R}_{02} < 1$. □

Theorem 4. *The disease endemic equilibrium point, $\varepsilon^* = \{\varepsilon_1^*, \varepsilon_2^*\}$, of system (7) is locally asymptotically stable in Ω if $\mathscr{R}_{02} > \mathscr{R}_{01} > 1$ and unstable otherwise.*

Proof. We compute the desired Jacobian matrix $J(\varepsilon^*)$ calculated at $\mathscr{E}^*$ which becomes

$$J(\varepsilon^*) = \begin{pmatrix} -(\beta(A^*)I^* + \gamma\beta(A^*)C^* + r_1) & -\beta(A^*)S^* & -\gamma\beta(A^*)S^* & 0 & 0 \\ \beta(A^*)I^* + \eta\beta(A^*)C^* & \beta(A^*)S^* - r_2 & \gamma\beta(A^*)S^* & 0 & 0 \\ 0 & (\sigma + q\eta) & -r_{\cdot 3} & 0 & 0 \\ \nu & (1-q)\eta & \delta & -\mu & 0 \\ 0 & 0 & 0 & 0 & -r_5 \end{pmatrix}. \tag{30}$$

The first two roots of equation (30) are $\lambda = -\mu < 0$ and $\lambda = -r_5 < 0$ and the remaining roots can be calculated from the polynomial equation

$$\psi(\lambda) = \lambda^3 + a_1\lambda^2 + a_2\lambda + a_3. \tag{31}$$

The coefficient $a_i\,(i = 1, 2, 3)$ of equation (31) becomes

$$\begin{aligned} a_3 &= r_2 r_3 (\beta(A^*)I^* + \gamma\beta(A^*)C^* + r_1) - (r_1 r_3 \beta(A^*) + r_1\gamma\sigma\beta(A^*) + q\eta\gamma\beta(A^*)I^*)S^*, \\ a_2 &= r_2 r_3 (\beta(A^*)I^* + \gamma\beta(A^*)C^* + r_1) - r_1\beta(A^*)S^*, \\ a_1 &= r_1 + r_2 + r_3 + \beta(A^*)I^* + \gamma\beta(A^*)C^* - \beta(A^*)S^*. \end{aligned} \tag{32}$$

Hence, the values $a_i\,(i = 1, 2, 3)$ are positive terms if $\mathscr{R}_{02} > \mathscr{R}_{01} > 1$. The necessary and sufficient condition for the local asymptotic stability of $\mathscr{E}^*$ of system (7) holds if $H_i > 0$ of the third-order degree polynomial in equation (31) is satisfied for $i = 1, 2, 3$.

$$H_I = \det\begin{pmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ 0 & 0 & a_3 \end{pmatrix} > 0. \tag{33}$$

Clearly, H_I in equation (33) is positive if $\mathscr{R}_{02} > \mathscr{R}_{01} > 1$. Hence, the disease endemic equilibrium $\mathscr{E}^*$ of system (7) is locally asymptotically stable in the biological feasible region if $\mathscr{R}_{02} > \mathscr{R}_{01} > 1$. □

4.2. Global Stability Analysis. In the following part of work, we discuss the global behavior of both equilibria of system (7) using the well-known LaSalle's invariant principle [24] by developing an appropriate Lyapunov functions.

Theorem 5. *The disease free-equilibrium, $\mathscr{E}_0 = \{\mathscr{E}_{01}, \mathscr{E}_{02}\}$, of system (7) is globally asymptotically stable in Ω if $\mathscr{R}_{01} < \mathscr{R}_{02} < 1$.*

Proof. First we construct a suitable Lyapunov function of the form

$$V(t) = k_1\left(S(t) - S_0\right) + k_2 I(t) + k_3 C(t), \tag{34}$$

where k_i, $(i = 1, 2, 3)$ are nonnegative real numbers to be chosen later. Differentiating equation (34) with respect to t and simplifying the result yields

$$\frac{dV(t)}{dt} = k_1\frac{d(t)}{dt} + k_2\frac{d(t)}{dt} + k_3\frac{d(t)}{dt}. \tag{35}$$

Upon arrangement of equation (35) for $A^* = [A_0, A_{\max}]$, we obtain

$$\begin{aligned}\frac{dV(t)}{dt} &= k_1\left(\Lambda - \beta(A)\left(I + \eta C + r_1\right)S\right) \\ &\quad + k_2\left(\beta(I + \eta C)S - r_2 I\right) + k_3\left((\sigma + q\eta)I - r_3 C\right).\end{aligned} \tag{36}$$

Next, we choose $k_1 = r_1 = k_2$ and $k_3 = (\gamma\beta(A^*))/r_3$. Simplification of equation (35) yields

$$\begin{aligned}\frac{dV}{dt} &= -r_1^2\left(S(t) - S_0\right) - r_1 r_2\left(1 - R_{02}\right)I(t) \\ &\quad - \left(\beta\left(A^*\right)S_0 + \gamma\beta\left(A^*\right)C(t)S_0\right).\end{aligned} \tag{37}$$

Here, it is to be noted that $R_{02} < 1$ automatically implies that $R_{01} < 1$. Hence, $(dV/dt) < 0$ whenever $R_{01} < R_{02} < 1$. Also, $(dV/dt) = 0$ if and only if $S(t) = S^0, I(t) = 0$, and $C(t) = 0$. Therefore, the largest compact invariant in set $\{(S, I, C, R) \in \Omega\colon (dV/dt) = 0\}$ is the singleton $\mathscr{E}_0$. Therefore, we conclude that the point $\mathscr{E}_0$ is globally asymptotically stable in Ω if $R_{01} < R_{02} < 1$ using LaSalle's invariant principle [24]. □

Theorem 6. *The disease endemic equilibrium, $\mathscr{E}^* = \{\mathscr{E}_1^*, \mathscr{E}_2^*\}$, of system (7) is locally asymptotically stable in Ω if $\mathscr{R}_{02} > \mathscr{R}_{01} > 1$.*

Proof. To examine the global behavior of $\mathscr{E}^*$, we develop a Lyapunov function of the form (see [25])

$$\frac{1}{2}\left[\left(S - S^*\right) + \left(I - I^*\right) + \left(C - C^*\right) + \left(R - R^*\right)\right]^2. \tag{38}$$

By differentiating equation (37) along its trajectories with respect to t we obtain

$$\begin{aligned}\frac{dV}{dt} &= \left(\left(S - S^*\right) + \left(I - I^*\right) + \left(C - C^*\right) + \left(R - R^*\right)\right) \\ &\quad \times \frac{d}{dt}\left\{\left(S - S^*\right) + \left(I - I^*\right) + \left(C - C^*\right) + \left(R - R^*\right)\right\}.\end{aligned} \tag{39}$$

Further, it follows that

$$\begin{aligned}\frac{dV}{dt} &= \left((S + I + C + R) - \left(S^* + I^* + C^* + R^*\right)\right) \\ &\quad \times \left\{\frac{dS}{dt} + \frac{dI}{dt} + \frac{dC}{dt} + \frac{dR}{dt}\right\} \\ &= \left(N(t) - \left(S^* + I^* + C^* + R^*\right)\right) \times \left\{\frac{dN}{dt}\right\}.\end{aligned} \tag{40}$$

Without loss of generality $S^* + I^* + C^* + R^* \le (\Lambda/\mu)$, and substituting equations (12) and (14) in the above equation gives

$$\frac{dV}{dt} = \left(N(t) - \frac{\Lambda}{\mu}\right) \times \left\{\Lambda - \mu N(t)\right\}. \tag{41}$$

Upon simplification and rearrangement of equation (39) we obtain

$$\frac{dV}{dt} = \left(N(t) - \frac{\Lambda}{\mu}\right) \times \left\{-\mu\right\}\left(N(t) - \frac{\Lambda}{\mu}\right). \tag{42}$$

After simplification and a slight arrangement of equation (43) we obtain

$$\frac{dV}{dt} = -\mu\left(N(t) - \frac{\Lambda}{\mu}\right)^2. \tag{43}$$

Thus, $(dV/dt) \le 0$ when $\mathscr{R}_{02} > \mathscr{R}_{01} > 1$. Clearly, $(dV/dt) = 0$ if and only if $S = S^*, I = I^*, C = C^*$, and $R = R^*$. Hence, the largest compact set in $\{(S, I, C, R) \in \Omega\colon (dV/dt) = 0\}$ is the singleton $\varepsilon^* = \{\varepsilon_1^*, \varepsilon_2^*\}$, which is a disease endemic equilibrium. Therefore, by LaSalle's invariant principle [24], $\mathscr{E}^*$ is globally asymptotically stable in the biological feasible region when $\mathscr{R}_{02} > \mathscr{R}_{01} > 1$. □

5. Bifurcation Analysis

In this section, we investigate the bifurcation phenomena of system (7). We employ the center manifold theory presented

in [26] to discuss the existence of bifurcation. We establish the existence theorem for backward bifurcation and present detail proof. A backward bifurcation is maintained when stable DFE and stable EE coexist in a specified biological region. In our model, both forward bifurcation and backward bifurcation are sufficiently presented.

Let us denote $S(t) = x_1, I(t) = x_2, C(t) = x_3, R(t) = x_4$, and $A(t) = x_5$. Thus, in vector notation it becomes $\overrightarrow{x} = (x_1, x_2, x_3, x_4, x_5)$ and

$$\begin{cases} f_1 = \Lambda - \beta(A^*)(x_2 + \gamma x_3)x_1 - (\mu + \nu)x_1, \\ f_2 = \beta(A^*)(x_2 + \gamma x_3)x_1 - (\mu + \mu_1 + \eta + \sigma)x_2, \\ f_3 = (\sigma + q\eta)x_2 - (\mu + \mu_2 + \delta)x_3, \\ f_4 = \nu x_1 + (1-q)\eta\, x_2 + \delta x_3 - \mu x_5, \\ f_5 = r(x_5 - A_0)\left(1 - \dfrac{x_5}{A_{\max}}\right), \end{cases} \tag{44}$$

where $A^* = [A_0, A_{\max}]$.

Let $f_i (i = 1, \ldots, 5)$ be a continuous twice differential function defined on $\mathbb{R}^5 \times \mathbb{R}$. Thus, equation (44) can be written in the following dynamical system form

$$\frac{d\overrightarrow{x}}{dt} = f_i(\overrightarrow{x}). \tag{45}$$

Now setting $\mathscr{R}_0 = 1$ and solving the expression for the bifurcation parameter $\beta(A^*)$ and finally replacing the result by $\beta^*(A^*)$ yield

$$\beta^*(A^*) = \frac{r_2 r_3}{(r_3 + \gamma(\sigma + q\eta))S_0}. \tag{46}$$

The linearization matrix of equation (45) evaluated at the DFE $\mathscr{E}_0$ and $\beta^*(A^*)$ becomes

$$J^*(\varepsilon_0) = \begin{pmatrix} -r_1 & -\beta^*(A^*)S_0 & -\gamma\beta^*(A^*)S_0 & 0 & 0 \\ 0 & \beta^*(A^*)S_0 - r_2 & \gamma\beta^*(A^*)S_0 & 0 & 0 \\ 0 & (\sigma + q\eta) & -r_3 & 0 & 0 \\ \nu & (1-q)\eta & \delta & -\mu & 0 \\ 0 & 0 & 0 & 0 & -r_5 \end{pmatrix}. \tag{47}$$

The characteristic polynomial of equation (47) becomes

$$\psi(\lambda) = \lambda(\lambda + r_1)(\lambda + \mu)(\lambda + r_5)\left(\lambda + \frac{r_2\gamma(\sigma + q\eta)}{r_3 + \gamma(\sigma + q\eta)} + r_3\right). \tag{48}$$

We observe that equation (48) has four negative real part eigenvalues and one zero eigenvalue which assures us the existence of bifurcation phenomena for the proposed system (7).

Next, we will establish the existence of forward and backward bifurcations for the model under discussion.

Theorem 7. *The proposed model (7) exhibits a forward bifurcation at $\mathscr{R}_{01} = 1$ if $\mathscr{R}_{01} < 1$.*

Proof. We investigate the bifurcation phenomenon for the transmission of liver cirrhosis of the model under discussion. We set $\mathscr{R}_{01} = 1$ and calculate the bifurcation parameter β_0 and consequently replace it with β_0^*. Thus,

$$\beta_0^* = \frac{r_2 r_3}{(r_3 + \gamma(\sigma + q\eta))S_0}. \tag{49}$$

Let us represent the right eigenvector $w = (w_1, w_2, w_3, w_4, w_5)^T$ corresponding to a zero eigenvalue (i.e., $\lambda = 0$),

$$J^* w = \begin{pmatrix} -r_1 & -\dfrac{r_2 r_3}{(r_3 + \gamma(\sigma + q\eta))} & -\dfrac{\gamma r_2 r_3}{(r_3 + \gamma(\sigma + q\eta))} & 0 & 0 \\ 0 & \dfrac{r_2 r_3}{(r_3 + \gamma(\sigma + q\eta))} - r_2 & \dfrac{\gamma r_2 r_3}{(r_3 + \gamma(\sigma + q\eta))} & 0 & 0 \\ 0 & (\sigma + q\eta) & -r_3 & 0 & 0 \\ \nu & (1-q)\eta & \delta & -\mu & 0 \\ 0 & 0 & 0 & 0 & -r_5 \end{pmatrix} \begin{pmatrix} w_1 \\ w_2 \\ w_3 \\ w_4 \\ w_5 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}. \tag{50}$$

Simplification and rearrangement of equation (50) yields

$$
\begin{aligned}
w_1 &= -\frac{r_2}{r_1}w_2,\\
w_2 &= w_2 > 0,\\
w_3 &= \frac{\sigma + q\eta}{r_3}w_2,\\
w_4 &= \left(\frac{\sigma + q\eta + (1-q)\eta + r_3\delta}{r_1 r_3}\right)w_2,\\
w_5 &= 0.
\end{aligned}
\tag{51}
$$

Similarly, we represent the left eigenvector $v = (v_1, v_2, v_3, v_4, v_5)$ corresponding to a zero eigenvalue $\lambda = 0$.

$$
\left(J^{*T}\right)v = \begin{pmatrix}
-r_1 & 0 & 0 & \sigma & 0\\
-\dfrac{r_2 r_3}{\left(r_3 + \gamma(\sigma + q\eta)\right)} & \dfrac{r_2 r_3}{\left(r_3 + \gamma(\sigma + q\eta)\right)} - r_2 & (\sigma + q\eta) & (1-q)\eta & 0\\
-\dfrac{r_2 r_3 \gamma}{\left(r_3 + \gamma(\sigma + q\eta)\right)} & \dfrac{r_2 r_3 \gamma}{\left(r_3 + \gamma(\sigma + q\eta)\right)} & -r_{\cdot 3} & \delta & 0\\
0 & 0 & 0 & -\mu & 0\\
0 & 0 & 0 & 0 & -r_5
\end{pmatrix}
\begin{pmatrix} v_1\\ v_2\\ v_3\\ v_4\\ v_5 \end{pmatrix} = \begin{pmatrix} 0\\ 0\\ 0\\ 0\\ 0 \end{pmatrix}.
\tag{52}
$$

Simplifying and rearranging equation (52) gives

$$
v_1 = v_4 = v_5 = 0, v_2 = v_2 > 0, = v_3 = \frac{r_2\gamma}{\left(r_3 + \gamma(\sigma + q\eta)\right)}v_2.
\tag{53}
$$

We represent the kth component of $f_i (i = 1, \ldots, 5)$ in equation (44) to be $f_k (k = 1, \ldots, 5)$ with

$$
\begin{aligned}
b_1 &= \sum_{i,j,k=1}^{5} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j},\\
b_2 &= \sum_{j,k=1}^{5} v_k w_j \frac{\partial^2 f_k}{\partial x_j \partial \beta_0^*}.
\end{aligned}
\tag{54}
$$

We use the center manifold theory [26] to calculate the coefficients $b_i (i = 1, 2)$ in equation (54) to complete the bifurcation process by finding the nonzero partial derivatives of second order of $f_k (k = 1, \ldots, 5)$ with respect to $x_i (i = 1, \ldots, 5)$ around the disease free-equilibrium.

$$
\begin{aligned}
&\frac{\partial^2 f_1}{\partial x_3 \partial x_1} = -\gamma\beta_0^* = \frac{\partial^2 f_1}{\partial x_1 \partial x_3}, \frac{\partial^2 f_1}{\partial x_2 \partial x_1} = -\beta_0^*\\
&= \frac{\partial^2 f_1}{\partial x_1 \partial x_2} \frac{\partial^2 f_2}{\partial x_3 \partial x_1} = \gamma\beta_0^* = \frac{\partial^2 f_2}{\partial x_1 \partial x_3}, \frac{\partial^2 f_2}{\partial x_2 \partial x_1} = \beta_0^* = \frac{\partial^2 f_2}{\partial x_1 \partial x_2}.
\end{aligned}
\tag{55}
$$

Similarly, the second-order nonzero partial derivatives of $f_k (k = 1, \ldots, 5)$ with respect to $x_j (j = 1, \ldots, 5)$ and β_0^* become

$$
\frac{\partial^2 f_1}{\partial x_2 \partial \beta_0^*} = -S_0, \frac{\partial^2 f_1}{\partial x_3 \partial \beta_0^*} = -\gamma S_0, \frac{\partial^2 f_2}{\partial x_2 \partial \beta_0^*} = S_0, \frac{\partial^2 f_2}{\partial x_3 \partial \beta_0^*} = \gamma S_0.
\tag{56}
$$

Substitution of equations (51) and (55) into equation (54) yields

$$b_1 = -\frac{2r_2\beta_0^*\left(r_3+\gamma(\sigma+q\eta)\right)}{r_1r_3}v_2w_2^2 < 0. \tag{57}$$

Similarly, substitution of equations (53) and (56) into equation (54) yields

$$b_2 = \frac{\Lambda}{r_1r_3}\left(r_3+\gamma(\sigma+q\eta)\right)v_2w_2^2 < 0. \tag{58}$$

Hence, the local dynamics of system (7) exhibits forward bifurcation around the first disease free-equilibrium, $\mathscr{E}_{01}$, which implies that there is at least one positive endemic equilibrium at $\mathscr{R}_{01} = 1$ if $\mathscr{R}_{01} < 1$. □

Theorem 8. *The proposed model (7) undergoes a backward bifurcation at $\mathscr{R}_{02} = 1$ if $\mathscr{R}_{02} < 1$.*

Proof. By Setting $\mathscr{R}_{02} = 1$ and calculating for the bifurcation parameterβ_1, we obtain

$$\beta_1^* = \frac{r_2r_3\left(1-\mathscr{R}_{01}\right)}{k\left(r_3+\gamma(\sigma+q\eta)\right)S_0}, \tag{59}$$

where β_1 is replaced by β_1^*.

The right eigenvector $u = (u_1, u_2, u_3, u_4, u_5)^T$ corresponding to a zero eigenvalue (i.e., $\lambda = 0$) becomes

$$J^*u = \begin{pmatrix} -r_1 & -\frac{r_2r_3\left(1-\mathscr{R}_{01}\right)}{k\left(r_3+\gamma(\sigma+q\eta)\right)} & -\frac{\gamma r_2r_3\left(1-\mathscr{R}_{01}\right)}{k\left(r_3+\gamma(\sigma+q\eta)\right)} & 0 & 0 \\ 0 & \frac{r_2r_3\left(1-\mathscr{R}_{01}\right)}{k\left(r_3+\gamma(\sigma+q\eta)\right)} - r_2 & \frac{\gamma r_2r_3\left(1-\mathscr{R}_{01}\right)}{k\left(r_3+\gamma(\sigma+q\eta)\right)} & 0 & 0 \\ 0 & (\sigma+q\eta) & -r_{\cdot 3} & 0 & 0 \\ \nu & (1-q)\eta & \delta & -\mu & 0 \\ 0 & 0 & 0 & 0 & -r_5 \end{pmatrix}\begin{pmatrix} u_1 \\ u_2 \\ u_3 \\ u_4 \\ u_5 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}. \tag{60}$$

After simplification of equation (60) we obtain

$$u_1 = -\frac{r_2\left(1-\mathscr{R}_{01}\right)}{kr_1}u_2, u_2 = u_2 > 0, u_3 = \frac{(\sigma+q\eta)}{r_3}u_2, u_4 = \left(\frac{r_3(1-q)\eta+\delta(\sigma+q\eta)}{r_1r_3}\right)u_2, u_5 = 0. \tag{61}$$

Similarly, we represent the left eigenvector $v = (v_1, v_2, v_3, v_4, v_5)$ corresponding to a zero eigenvalue $\lambda = 0$.

$$\left(J^{*T}\right)v = \begin{pmatrix} -r_1 & 0 & 0 & \sigma & 0 \\ -\frac{r_2r_3\left(1-\mathscr{R}_{01}\right)}{\left(r_3+\gamma(\sigma+q\eta)\right)} & \frac{r_2r_3\left(1-\mathscr{R}_{01}\right)}{\left(r_3+\gamma(\sigma+q\eta)\right)} - r_2 & (\sigma+q\eta) & (1-q)\eta & 0 \\ -\frac{r_2r_3\gamma\left(1-\mathscr{R}_{01}\right)}{\left(r_3+\gamma(\sigma+q\eta)\right)} & \frac{r_2r_3\gamma\left(1-\mathscr{R}_{01}\right)}{\left(r_3+\gamma(\sigma+q\eta)\right)} & -r_{\cdot 3} & \delta & 0 \\ 0 & 0 & 0 & -\mu & 0 \\ 0 & 0 & 0 & 0 & -r_5 \end{pmatrix}\begin{pmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \\ v_5 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}. \tag{62}$$

Simplifying and rearranging equation (62) gives

$$v_1 = v_4 = v_5 = 0, = v_3 = \frac{r_2\gamma(1-\mathscr{R}_{01})}{(r_3+\gamma(\sigma+q\eta))}v_2, \tag{63}$$

where $v_2 > 0$ is arbitrary constant. Let us assume the kth component of f_i in equation (44) is $f_k(k = 1, \ldots, 5)$ with

$$c_1 = \sum_{i,j,k=1}^{5} v_k u_i u_j \frac{\partial^2 f_k}{\partial x_i \partial x_j},$$
$$c_2 = \sum_{j,k=1}^{5} v_k u_j \frac{\partial^2 f_k}{\partial x_j \partial \beta_1^*}. \tag{64}$$

We calculate the coefficients $c_i(i = 1, 2)$ in equation (64) after finding the nonzero partial derivatives of second order of $f_k(k = 1, \ldots, 5)$ with respect to $x_{i,j}(i, j = 1, \ldots, 5)$ at the disease free-equilibrium.

$$\frac{\partial^2 f_1}{\partial x_1 \partial x_3} = -\gamma\beta_1^* = \frac{\partial^2 f_1}{\partial x_3 \partial x_1}, \frac{\partial^2 f_1}{\partial x_2 \partial x_1} = -\beta_1^* = \frac{\partial^2 f_1}{\partial x_1 \partial x_2} \frac{\partial^2 f_2}{\partial x_3 \partial x_1}$$
$$= \gamma\beta_1^* = \frac{\partial^2 f_2}{\partial x_1 \partial x_3}, \frac{\partial^2 f_2}{\partial x_2 \partial x_1} = \beta_1^* = \frac{\partial^2 f_2}{\partial x_1 \partial x_2}. \tag{65}$$

Similarly, the second-order nonzero partial derivatives of f with respect to $x_j(j = 1, \ldots, 5)$ and β_1^* become

$$\frac{\partial^2 f_1}{\partial x_2 \partial \beta_1^*} = -S_0, \frac{\partial^2 f_1}{\partial x_3 \partial \beta_1^*} = -\gamma S_0, \frac{\partial^2 f_2}{\partial x_2 \partial \beta_1^*} = S_0, \frac{\partial^2 f_2}{\partial x_3 \partial \beta_1^*} = \gamma S_0. \tag{66}$$

Exploiting equations (61), (64), and (65) we obtain

$$c_1 = \frac{2\beta_1^*}{k r_1 r_3^2}(r_3 + \gamma(\sigma + q\eta))(\beta_0 S_0(r_3 + \gamma(\sigma + q\eta)) - r_2 r_3) v_2 u_2^2. \tag{67}$$

Plugging equations (63) and (66) into equation (64) yields

$$c_2 = \frac{\Lambda}{r_1 r_3}(r_3 + \gamma(\sigma + q\eta)) v_2 u_2. \tag{68}$$

Hence, the existence of the backward bifurcation around the second disease free-equilibrium $\mathscr{E}_{02}$ depends on the coefficient c_i. Thus, $c_i > 0$ if and only if $\beta_0 S_0(r_3 + \gamma(\sigma + q\eta)) > r_2 r_3$. Therefore, system (7) exhibits backward bifurcation at $\mathscr{R}_{02} = 1$ if $\mathscr{R}_{02} < 1$.

Further, let us assume that one of the two infected classes of system (7) is nonzero. Then, the solution of system (7) at disease endemic equilibrium will become

$$S^*(t) = \frac{\Lambda(\sigma + q\eta) - r_2 r_3 C^*(t)}{r_1(\sigma + q\eta)}, I^*(t) = \frac{r_3 C^*(t)}{(\sigma + q\eta)}. \tag{69}$$

Substituting the above equations $S^*(t)$ and $I^*(t)$ in the first equation of system (7) for $A^* = [A_0, A_{\max}]C^*(t) \neq 0$, we get

$$Q(C) = aC^2 + bC + c, \tag{70}$$

where

$$a = r_2 r_3 \left(\beta_0 + \beta_1 \left(\frac{A^*(t) - A_0}{A_{\max}}\right)\right)(r_3 + \gamma(\sigma + q\eta)),$$
$$b = r_1 r_2 r_3 (\sigma + q\eta)(1 - \mathscr{R}_0), c = r_1 \Lambda (\sigma + q\eta)^2 \tag{71}$$
$$- r_1 \Lambda (\sigma + q\eta)^2 (= 0).$$

Clearly, $a > 0$ and $b > 0$ if $\mathscr{R}_0 < 1$. Hence, the coefficients of the quadratic equation are positive but b may be negative. Existence of nonnegative solution of the above quadratic equation ultimately depends on the sign of b since a is positive term. This ultimately suggests that the steady state solution $\mathscr{E}^*$ of system (7) depends on $\mathscr{R}_0$ and setting $Q(C) = 0$ yields

$$C_1 = \frac{-b + \sqrt{b^2 - 4ac}}{2a}, C_2 = \frac{-b - \sqrt{b^2 - 4ac}}{2a}. \tag{72}$$

It is obvious to notice that if the term under the square root is negative (i.e., $b^2 < 4ac$), then (1) the above quadratic equation has no solution, and (2) there is no positive endemic equilibrium for system (7). Hence, there is a unique endemic equilibrium $\mathscr{E}^*$ in the biological feasible region Ω since $b < 0$ if $\mathscr{R}_{02} > \mathscr{R}_{01} > 1$. □

6. Local Sensitivity Analysis

In this section, we present the sensitivity analysis of the proposed model (7). It measures the relative contribution of each model parameter which is responsible for the transmission and prevalence of disease. Since the initial disease transmission is directly related to $\mathscr{R}_0$, then we perform a sensitivity analysis on $\mathscr{R}_0$ to identify the most critical parameters that assist us to break the spread of the disease. We use the normalized forward sensitivity index to measure the relative change of the model parameter to the disease control and spreading.

Definition 1. A normalized forward local sensitivity index of $\mathscr{R}_0$ of system (7), depending on the differentiability with respect to a model parameter q, is given by

$$\Psi_q^{\mathscr{R}_0} = \frac{\partial \mathscr{R}_0}{\partial q} \times \frac{q}{\mathscr{R}_0}. \tag{73}$$

By applying equation (73) we calculate the sensitivity analysis of $\mathscr{R}_{01}$ and $\mathscr{R}_{02}$ with respect to the model parameters. For instance, the sensitivity indices of $\mathscr{R}_{01}$ and $\mathscr{R}_{02}$ with respect to β_0 are given by

$$\Psi_{\beta_0}^{\mathscr{R}_{01}} = \frac{\partial R_{01}}{\partial \beta_0} \times \frac{\beta_0}{\mathscr{R}_{01}} = \left(\frac{\Lambda\left(r_3 + \gamma(\sigma + q\eta)\right)}{r_1 r_2 r_3}\right)\left(\frac{r_1 r_2 r_3 \beta_0}{\Lambda\beta_0\left(r_3 + \gamma(\sigma + q\eta)\right)}\right) = +1.000,$$
$$\Psi_{\beta_0}^{\mathscr{R}_{02}} = \frac{\partial R_{02}}{\partial \beta_0} \times \frac{\beta_0}{\mathscr{R}_{02}} = \left(\frac{\Lambda\left(r_3 + \gamma(\sigma + q\eta)\right)}{r_1 r_2 r_3}\right)\left(\frac{r_1 r_2 r_3 \beta_0}{\Lambda\left(\beta_0 + k\beta_1\right)\left(r_3 + \gamma(\sigma + q\eta)\right)}\right) = 0.4808. \tag{74}$$

The sensitivity indices of the remaining basic model parameters evaluated at the parameter's value are presented in Table 1.

Table 1 presents the sensitivity indices of each model parameter with respect to the basic reproduction numbers $\mathscr{R}_{01}$ and $\mathscr{R}_{02}$. From observation of Table 1, we noticed some parameters have positive sign and some other parameters have negative sign. This helps us to give the biological interpretation of each model parameter in $\mathscr{R}_{01}$ and $\mathscr{R}_{02}$. Parameters with positive sign have positive impact on $\mathscr{R}_{01}$ and $\mathscr{R}_{02}$. On the contrary, parameters with negative sign have negative impact on $\mathscr{R}_{01}$ and $\mathscr{R}_{02}$. For instances, parameters such as $\beta_0, \beta_1, \Lambda$, and γ have positive signs and have direct relationship with $\mathscr{R}_{01}$ or $\mathscr{R}_{02}$. Biologically, this means the increase (or decrease) of the parameter's value automatically increases (or decreases) $\mathscr{R}_{01}$ and $\mathscr{R}_{02}$. Likewise, parameters such as $\sigma, \mu, \eta, \mu_1, \delta, q$, and μ_2 have negative signs and are inversely related to the basic reproduction numbers. This also mean that the increase (or decrease) of the parameter's value directly decreases (or increases) $\mathscr{R}_{01}$ and $\mathscr{R}_{02}$. We observe that the sensitivity indices enable us to determine the various factors of disease transmission and its control. These indices also allow us to find the most essential parameters that strongly affect the basic reproduction numbers $\mathscr{R}_{01}$ and $\mathscr{R}_{02}$. For example, if one can increase the parameter β_0 by 10%, then $\mathscr{R}_{01}$ will increase by 10% and $\mathscr{R}_{02}$ will also increase by 4.81%. On the other hand, if one can increase the parameter σ by 10%, so $\mathscr{R}_{01}$ and $\mathscr{R}_{02}$ will decrease by 42.98%.

The influence of parameters γ, β_0, and β_1 is clearly depicted in Figures 2(a) and 2(b) as discussed above. If we increase the values of γ and β_0 only by keeping the value of other parameters constant, then the basic reproduction number $\mathscr{R}_0$ will increase. This implies that the parameters γ and β_0 are directly related to $\mathscr{R}_{02}$. Figure 3 shows the diagrammatic representation of sensitivity indices of basic model parameters with their relative contribution on liver cirrhosis management. In Figure 3(b), the impact of β_1 is stronger than the impact of β_0 on $\mathscr{R}_{02}$ while β_1 has zero contribution on $\mathscr{R}_{01}$.

7. Simulation of the Liver Cirrhosis Model

We employed MATLAB programming of ODE45 solver built-in function to carry out the simulation of the proposed model (7). For the purpose of simulation, we considered a set of positive initial data 100, 40, 20, and 10 for the states in equation (7), $S(t), I(t), C(t), R(t)$, respectively. We assumed a period of 0–60 years as time interval. The values of the parameters are given in Table 2. The majority of the parameter's value are taken from published journals and the remaining parameter's values are assumed in biologically feasible ways.

The plots in Figure 4 represent the dynamic behavior of susceptible, acute infection, liver cirrhotic, and recovered individuals. It can be observed that the susceptible population decrease while the acute infection and liver cirrhotic individuals increase for over 15 years and start falling sharply to zero afterward. In both figures, all trajectories are converging to $(0.8, 0, 0)$ when large amount of alcohol and low amount of alcohol are consumed, which verifies the local stability of DFE of system (7).

Figure 5 shows the impact of alcohol consumption on the progression dynamics of liver cirrhosis. As clearly seen from Figure 5(a) alcohol abuse in an HBV infected person accelerates the progression of liver cirrhosis. The number of acute infection individuals in Figure 5(a) and the number of liver cirrhotic individuals in Figure 5(b) increase for the first few years and then return to zero.

In Figures 6(a) and 6(b), the simulation result for the variation of the mean transmission rate is presented. Maximization of this rate resulted in maximization of acute infection and liver cirrhotic individuals. One has to minimize the increment rate of alcohol consumption parallel to the minimization policy for minimizing the transmission rate.

The plot in Figure 7 is a demonstration showing the variation in the parameters β_{0} and β_{1} which yield tremendous change in the number of acute infection and liver cirrhotic individuals. It shows that the increase in the mean transmission rate increases the liver cirrhotic population.

Figure 8 reveals chronic liver progression is directly related to the progression rates. It indicates that if we keep the other model parameters fixed and vary the progression rate alone, we apparently observe the reduction of acute infection and the increment of liver cirrhotic individuals.

Figure 9 demonstrates the the phase portrait of the state variables in the model. The number of acute infection individuals increases sharply for the first years whenever the number of susceptible population increases as depicted in Figure 9(a). Likewise, Figure 9(b) shows the number of liver cirrhotic individuals increases when the number of acutely infected population increases and after a while it experiences a recyclic manner. Figure 9(d) indicates the change in liver cirrhotic individuals when we vary alcohol consumption over a period of 20 years. It rises for the first few years and starts falling after a certain period of time.

Table 1: Sensitivity analysis of basic mode parameters in $\mathscr{R}_{01}$ and $\mathscr{R}_{02}$.

Parameter	Value (per year)	Source	$\Psi_{\beta_0}^{\mathscr{R}_{01}}$	$\Psi_{\beta_0}^{\mathscr{R}_{02}}$
μ	0.0300	[5]	−1.3938	−1.3938
β_0	0.0050	[5]	+1.0000	+0.4808
μ_1	0.0020	[5]	−0.0217	−0.0217
σ	0.2500	[2]	−0.4298	−0.4298
μ_2	0.0020	Assumed	−0.0038	−0.0038
γ	0.1600	[5]	+0.1193	+0.1193
q	0.2500	[2]	−0.7117	−0.7117
δ	0.0600	[5]	−0.0577	−0.0577
η	0.0500	[5]	−0.1556	−0.1556
β_1	0.0250	Assumed	—	+0.5192
ν	0.0200	[5]	−0.1156	−0.1156
Λ	0.0400	[5]	+1.0000	+1.0000

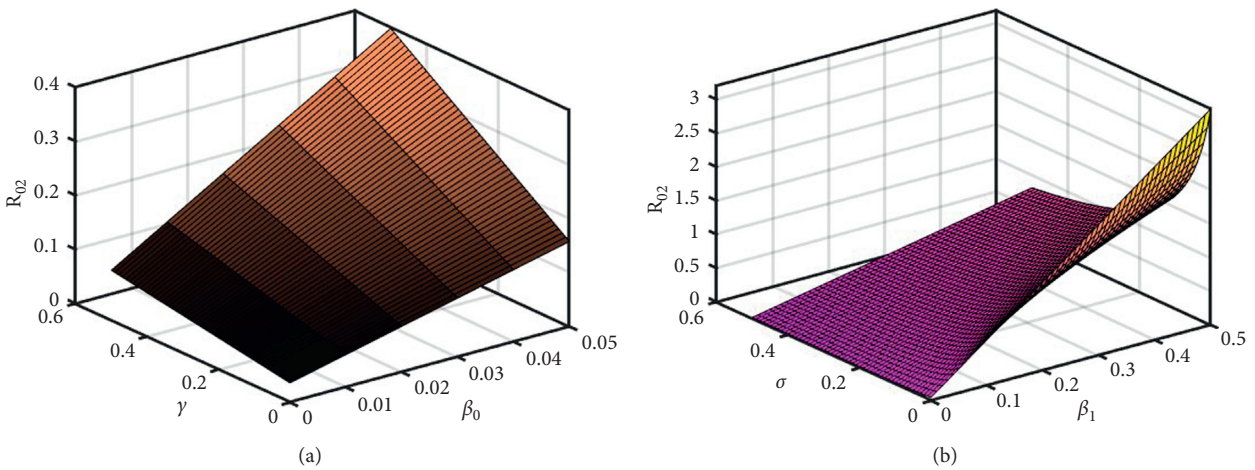

Figure 2: The phase space of (a) $\mathscr{R}_{02}$ versus γ and β_0 and (b) $\mathscr{R}_{02}$ versus σ and β_1.

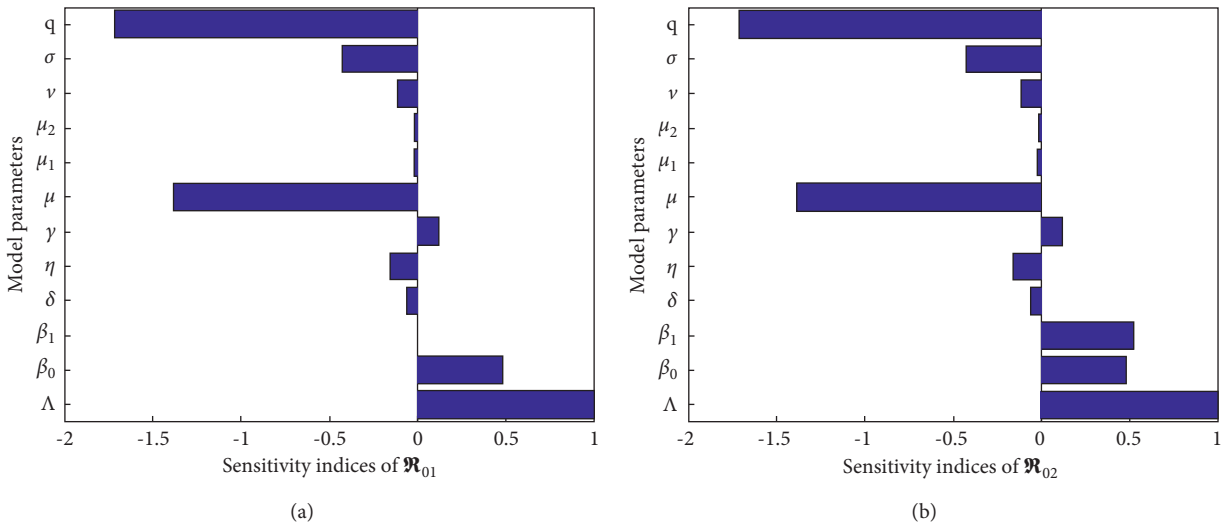

Figure 3: Sensitivity index of the model parameters in (a) $\mathscr{R}_{01}$ and (b) $\mathscr{R}_{02}$.

Table 2: Model parameter's value and source.

Parameter	Value (per year)	Source
μ	0.0300	[5]
β_0	0.0050	[5]
μ_1	0.0020	[5]
σ	0.2500	[2]
μ_2	0.0020	Assumed
γ	0.1600	[5]
q	0.2500	[2]
δ	0.0600	[5]
r	0.0650	Assumed
η	0.0500	[5]
β_1	0.0250	Assumed
ν	0.0200	[5]
Λ	0.0400	[5]
A_0	20 kg	[3, 27]
$A_{\max}$	75 kg	[11]

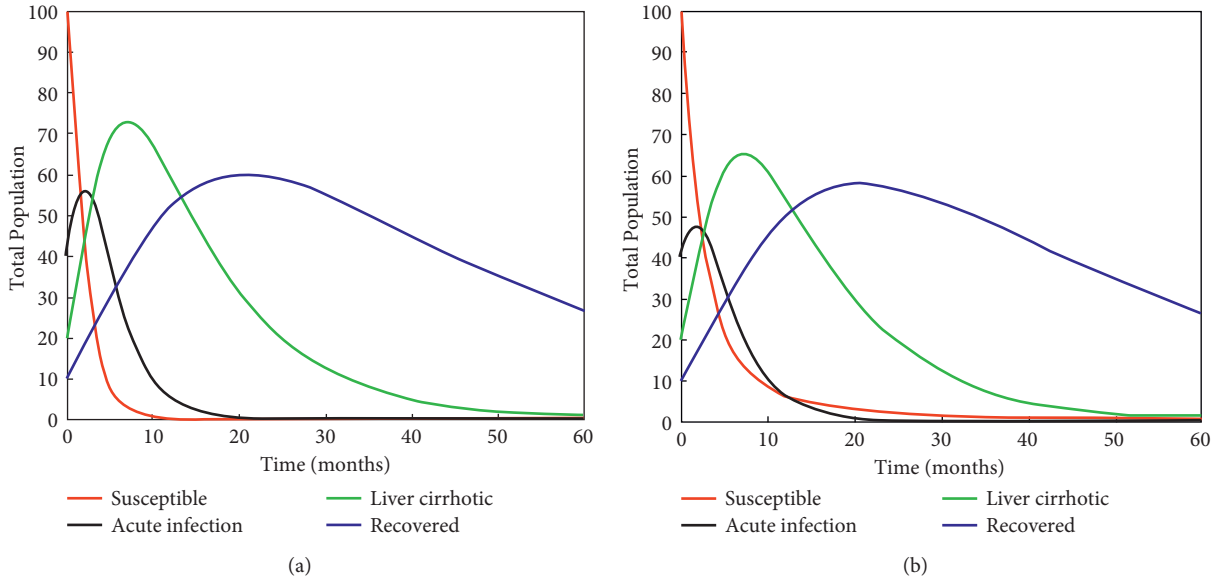

Figure 4: The plots demonstrate the simulation results of all trajectories $S(t), I(t), C(t), R(t)$ converging to disease free-equilibrium (a) when the amount of alcohol consumed is $A(t) = A_{\max}$ and (b) when the amount of alcohol consumed is $A(t) = A_0$.

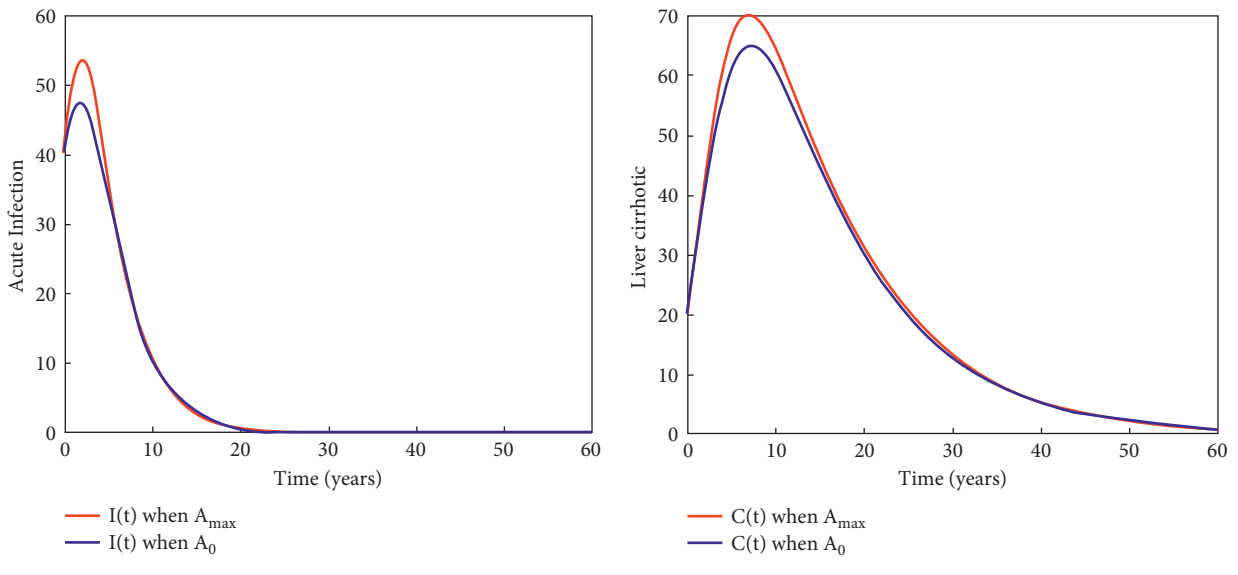

Figure 5: The plots demonstrate the simulation results of $I(t)$ and $C(t)$.

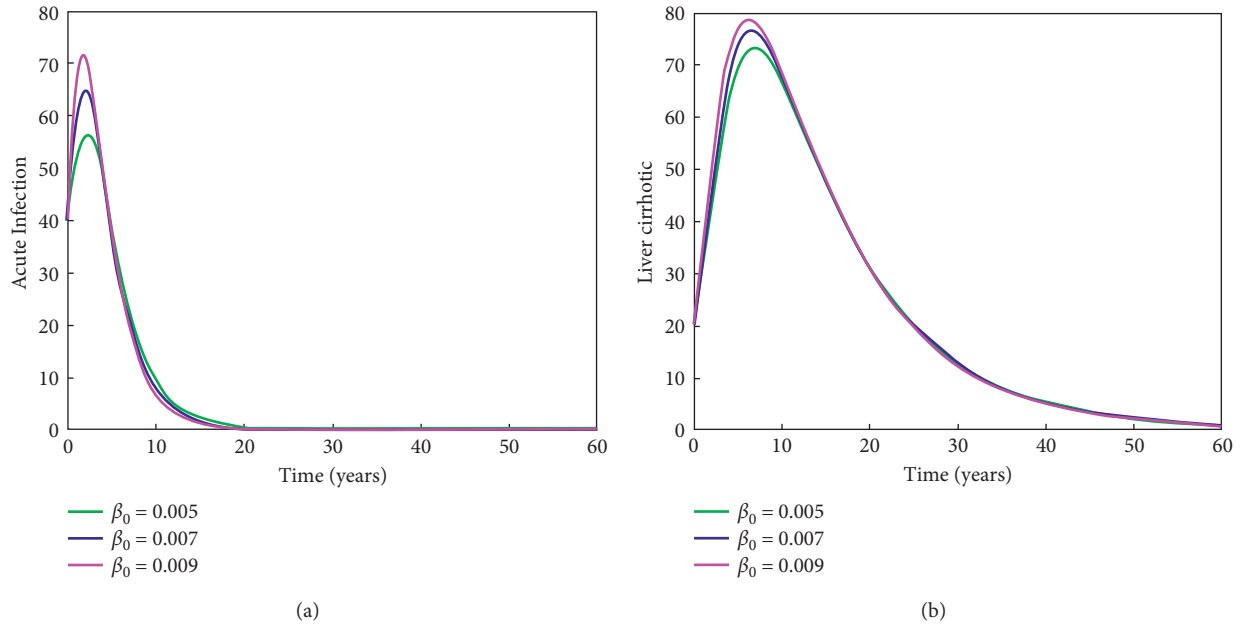

FIGURE 6: The simulation results of $I(t)$ and $C(t)$ with respect to various mean transmission coefficient β_0 when all other parameters are kept fixed.

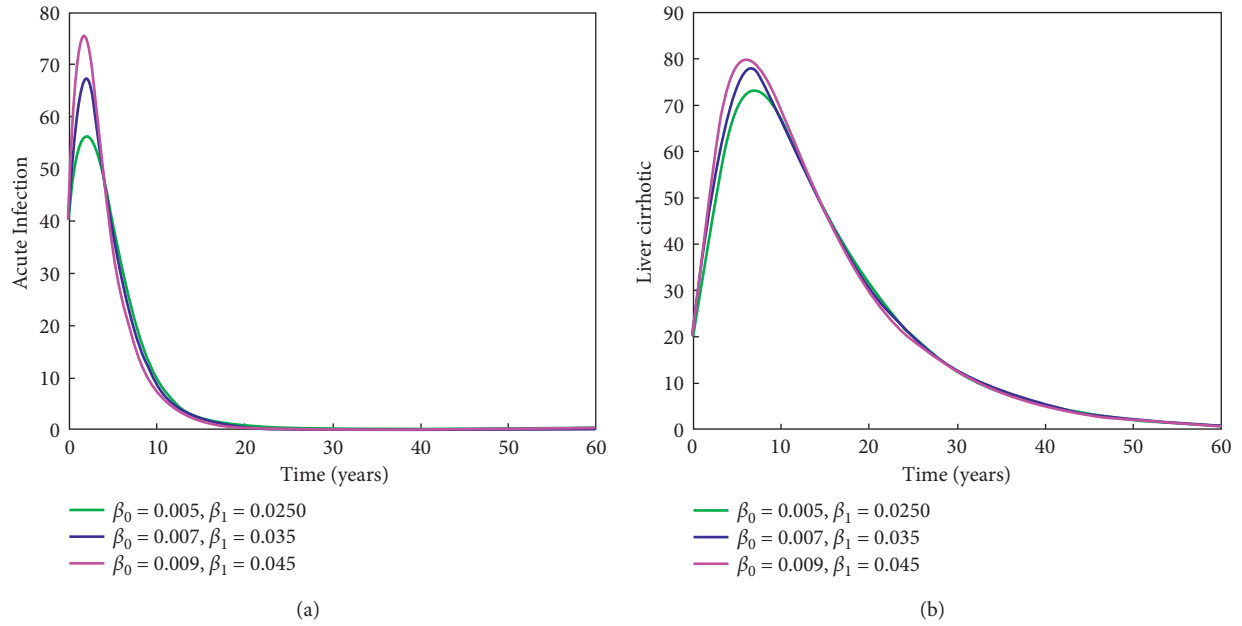

FIGURE 7: The simulation results of $I(t),$ and $C(t)$ with various mean transmission coefficients β_0 and the incremental rate β_1 by keeping the remaining parameters fixed.

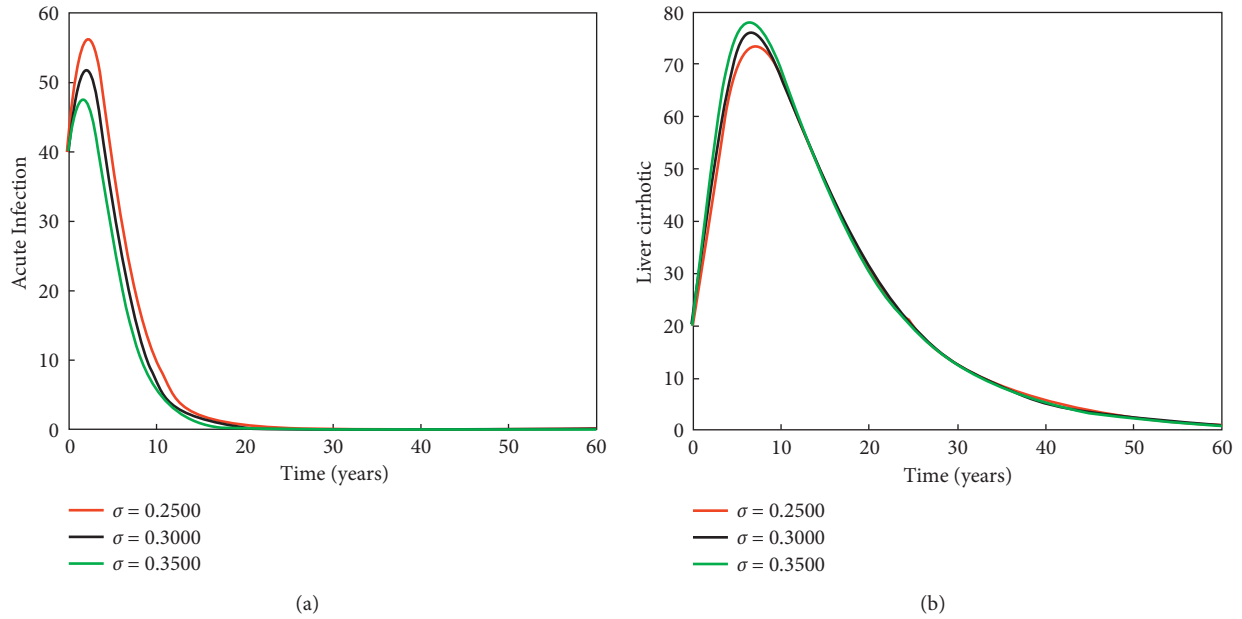

Figure 8: The plot demonstrates the simulation results of acute infection and chronic liver cirrhosis with various progression rate σ.

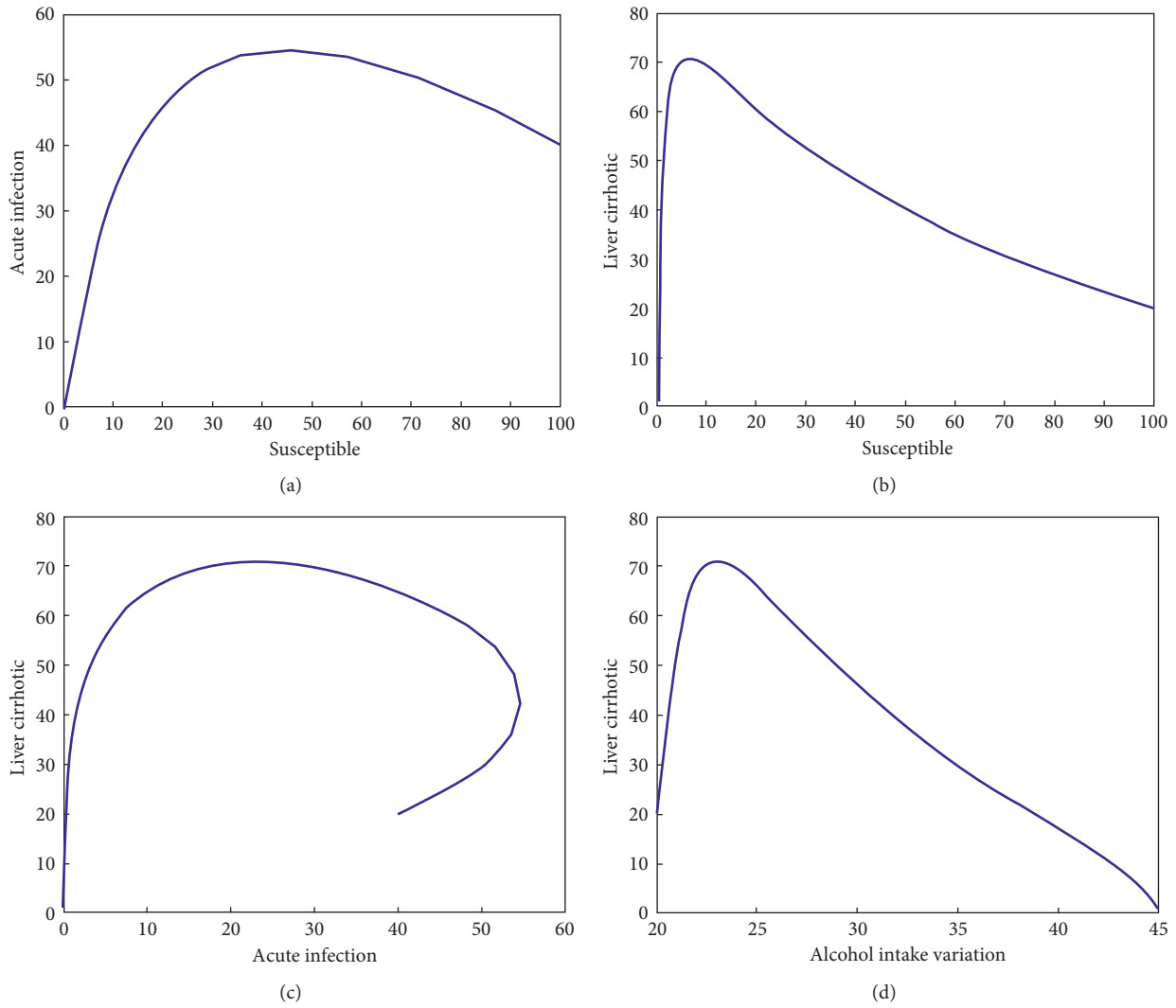

Figure 9: The phase portrait for (a) $S(t)$versus $I(t)$, (b) $S(t)$versus $C(t)$, (c) $I(t)$ versus $C(t)$, and (d) $A(t)$versus $C(t)$.

8. Conclusion

We proposed a deterministic epidemic model to study the combined effect of HBV infection and heavy alcohol consumption on the dynamics of liver cirrhosis progression along with a logistic model to describe the alcohol consumption variation over a period of time. The basic mathematical properties are presented to elaborate the biological feasibility of the proposed model. We analyzed the basic reproduction number, local and global stabilities of disease free-equilibrium, and endemic equilibrium. The local sensitivity indices are employed in order to investigate the impact of various parameters in the proposed model of liver cirrhosis transmission dynamics. We proved the local stability using the Jacobian matrix approach and the global stability of the two equilibria using the Lyapunov function approach. We established and proved the existence of forward and backward bifurcations with the help of central manifold theory. Finally, large scale of numerical simulations was performed for the proposed model and verified the analytical work. The numerical simulation reveals the impacts of the combination of HBV infection and heavy alcohol consumption and it accelerates the progression of liver cirrhosis unless alcohol intake reduction policy is not implemented. The authors recommend that any interested researcher can apply optimal control strategy in order to minimize the risk of alcohol consumption in chronic HBV carriers to eliminate liver cirrhosis in the population.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest on the manuscript.

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