MODELING THE EFFECT OF IMMUNOSUPPRESSANTS ON THE TRANSMISSION DYNAMICS OF HEPATITIS C VIRUS AFTER LIVER TRANSPLANTATION

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ABSTRACT.

Hepatitis C virus (HCV) infection is a principal source of chronic HCV infection and cirrhotic hepatitis worldwide, which needs liver transplantation (LT). But LT, being a therapeutic option for cirrhosis, has not guaranteed complete extermination of the disease. In this paper, we formulated deterministic mathematical model to study the effect of immunosuppressants on the transmission dynamics of recurrent HCV after LT. We established the existence of disease free equilibrium, P_0 and so derived the basic reproductive number, R_{01}. We also computed sensitivity indices of R_{01} pertaining to some model parameters and found that the natural death rate of graft hepatocytes, μ is the most sensitive parameter; followed by the parameters ω, β and Λ for the infection rate , virus production rate and recruitment rate of new susceptible hepatocytes respectively, while the disease-induced death rate, δ is the least negatively sensitive parameter. Besides, we performed numerical simulations and found that the results are consistent with the analytical results. Thus, we recommend that deliberate control measures should be directed to a HCV-infected transplant recipient who is incapable of clearing the virus spontaneously so as to reduce recurrent HCV transmission, or exterminate it, by targeting the most sensitive parameters with guaranteed non-rejection of the liver transplant by the recipient body immune response

Keywords: Recurrent HCV, Liver transplantation, Immunosuppressants, Basic reproductive number, Sensitivity indices.

1 INTRODUCTION

Hepatitis C virus (HCV) infection is a principal source of cirrhotic hepatitis and an increasingly a major indication for liver transplantation (LT) worldwide (Gane, 2003;Ghany *et al.*, 2009). In many developed countries, LT is mostly attributable to cirrhotic hepatitis (Adam *et al.*, 2003; Wiesner *et al.*, 2003). LT, being a therapeutic option for end-stage liver disease and acute liver failure, has proven to be an unsuccessful mainstay for disease disappearance as HCV infection reappears soon after reperfusion (Gane *et al.*, 1996a;Garcia-Retortillo *et al.*, 2002). Reinfection of liver allograft is universal in patients with pre-transplantation viremia, which and occurs at reperfusion (Garcia-Retortillo *et al.*, 2002) .Acute HCV reinfection usually transpires in more than 50% of cases between 1 and 6 months (McCaughan *et al.*, 2009) and is characterized by acute lobular hepatitis (McCaughan and Zekry, 2004) while chronic hepatitis establishes from 6 to 12 months. HCV reinfection causes fibrosing cholestatic hepatitis (FCH), liver biopsy and cirrhotic hepatitis. FCH develops in 10% of patients between 1 and 3 months following LT, and 20% of HCV -infection recipients normal or approximately normal aminotransferase levels with marginal inflammation on liver biopsy. Besides, approximately70 % of cases experience chronic hepatitis with faster development of fibrosis than observed in the immunocompitent patients, producing liver cirrhosis in 8% to 30% of cases in 5-year time. It is well-known that spontaneous viral clearance in immunocompetent patients seldom transpires in the acute period (Rodriguez-Luna and Douglas, 2004; Samuel *et al.*, 2006), but we consider it very significant for the model formulation. Thus, untreated recurrent HCV infection remains a dynamic problem of post-liver transplantation and is a major source of graft loss in the majority of transplant recipients.

Reinfection of the graft liver immediately after LT is universal (Everhart *et al*., 1999)and characterized by faster evolution to the end-stage, cirrhosis, which is a source of reduction of patient and graft survival (Prieto *et al.*, 1999; Berenguer, 2002) owing to graft damage (Forman *et al.*, 2002). This is attributable to immunosuppression and inefficiency of antiviral therapy, which has made management of it very difficult worldwide. Immunosuppressants are drugs normally given to a transplant patient immediately after LT to prevent graft rejection by the immune system. They override the activity of the immune system which attacks the new liver it

as a pathogen. These drugs function by targeting different sites in the immune system, but most graft recipients are normally given tacrolimus and cyclosporine drugs that inhibit activation and proliferation of T-cells. These are inhibitors of calcineurin in the immune system, which ultimately leads to inhibition of the T-cell activation (Smith *et al.*, 2003; Taylor *et al.*, 2005) and proliferation of the cells. Inactivity of the immune system by the drugs leads to less combating action on the virus and infected host hepatic cells, which makes HCV re-infection more aggressive. This state triggers faster impairment of the liver graft and ultimately death of the transplant patient.

Numerous antivirals have been used to treat HCV reinfection, but most drugs have practically proven less effective. Although standard therapy using interferon and ribavirin has produced higher sustained virologic response (SVR) rates (Firpi *et al.*, 2002; Samuel *et al.*, 2003; Giostra *et al.*, 2004; Mukherjee *et al.*, 2005) than interferon or peginterferon monotherapy (Féray *et al.*, 1995;Gane *et al.*, 1998; Mukherjee *et al.*, 2005), still management of HCV reinfection has been very difficult. Up to now, the only therapeutic strategies used to manage HCV re-infection are the preemptive approach and recurrence-based approach launched shortly after LT. Preemptive therapy with interferon monotherapy and a combination of interferon plus ribavirin, within the first 4 to 6 weeks following LT and before biochemical and histological evidence of recurrent HCV infection, have produced lower SVR rates ranging from 0% to 33% (Terrault, 2003; Chalasani *et al.*, 2005). Besides, preemptive therapy with a combination of peginterferon and ribavirin has been very difficult to manage owing to intolerability and less efficacy (Chalasani *et al.*, 2005; Shergill *et al.*, 2005). Thus, it is preferred to delay therapy until recurrent HCV-related chronic hepatitis is established; and thus the recurrence-based approach has been often used, but from the time of biochemical and histologic evidence of HCV reinfection (Berenguer, 2008), by using peginterferon-based therapies. Although recent clinical trials with peginterferon and ribavirin have shown improved SVR rates, antiviral therapy has not made the virus to disappear fully. Thus, the liver graft still impairs, leading to death of the transplant patient in the long run.

Mathematical models have provided key insights into hepatitis C virus pathogenesis in the pre- and post- transplant settings. Thus, they are often used to answer important biological questions about HCV infection. To date, several models have been formulated to investigate the effects of immune response and antivirals on the transmission dynamics of HCV in the pre-liver transplant setting. Generally, the model analytical results indicate that HCV-infected individuals who are immunocompitent or good responders to antivirals can clear the virus; but infected persons who are not immunocompitent or non-responders to antivirals develop chronic hepatitis leading to cirrhotic hepatitis. Conversely, few models have been formulated to study the dynamics of HCV subject to these effectors in the transplant setting; of which some have been used to investigate the natural course of HCV recurrence by analyzing serum HCV RNA levels in liver transplant recipients during and after transplantation (Dahari *et al.*, 2005; Powers *et al.*, 2006). But, in this paper, we have formulated a mathematical model to study the effect of immunosuppressants on the transmission dynamics of hepatitis C virus after liver transplantation.

2 MATERIALS AND METHODS

2.1 Model Formulation and Dynamics

The model incorporates three populations, which are graft hepatocytes population (the implanted liver cells), free hepatitis C virus population and $CD8^+$ T cells population. The graft hepatocytes population incorporates two sub-populations: susceptible graft hepatocytes and infected graft hepatocytes. Thus, the model incorporates four compartments, which are the susceptible graft hepatocytes sub-population (S), infected graft hepatocytes sub-population (I), free hepatitis C virus population (V) and $CD8^+$ T cells population (T). New susceptible hepatocytes S are continuously recruited at a constant rate Λ; die naturally at a constant rate μ and infected at the rate proportional to the product SV, with a constant of proportionality ω. The infected graft hepatocytes I die naturally at a constant rate μ. Free hepatitis C viruses V are produced from infected graft hepatocytes at a constant rate β and die naturally at the rate, α. In the presence of HCV and liver graft, the $CD8^+$ T cells are constantly produced at the

rate η and die naturally at a constant rate, ν. A proportion p of immunosuppressed $CD8^+$ T cells responses kill infected graft hepatocytes at the rate proportional to the product IZ, with a constant of proportionality γ. The remaining fraction $1-p$ of $CD8^+$ T cells responses attack susceptible graft hepatocytes at the rate proportional to the product SZ, with a constant of proportionality, π. Immediately after the liver transplantation, immunosuppressants are dispensed to the transplant recipient to block $CD8^+$ T cells responses by a fraction θ.

The following assumptions were considered for the formulation of the model:

(i) The liver transplantation is attributed to cirrhotic hepatitis C.

(ii) The graft is at the risk of acute cellular rejection immediately after liver transplant.

(iii) The transplant recipient is given immunosuppressants shortly after transplantation to prevent rejection of the graft.

(iv) Graft hepatocytes are uninfected and susceptible at the time of transplantation.

(v) New susceptible hepatocytes are produced at a constant rate.

(vi) Susceptible graft hepatocytes are equally likely infected by viruses at a constant rate.

(vii) Susceptible and infected graft hepatocytes die naturally at equal constant rates.

(viii) The infected graft hepatocytes die due to recurrent HCV at a constant rate.

(ix) Free viruses are produced from infected graft hepatocytes at a constant rate.

(x) $CD8^+$ T cells are produced from the thymus gland of the transplant recipient at a constant rate.

(xi) Hepatitis C viruses and the $CD8^+$ T cells die naturally at different constant rates.

(xii) $CD8^+$ T cells reject the liver transplant and kill infected graft hepatocytes at different constant rates.

(xiii) The transplant recipient can either clear the virus spontaneously or not.

(xiv) Rejection of the liver transplant is $CD8^+$ T cells-mediated.

The variables and parameters are listed and briefly defined in Table 1 and Table 2 respectively

TABLE 1: Description of state variables

Variable	Description
$S(t)$	Susceptible graft hepatocytes
$I(t)$	Infected graft hepatocytes
$V(t)$	Free hepatitis C virions
$Z(t)$	Cytotoxic T lymphocytes($CD8^+$ T cells)

Besides, for brevity of formulations and analyses, the model state variables $S(t)$, $I(t)$, $V(t)$, and $Z(t)$ have been simply represented by the symbols S, I, V and Z respectively.

TABLE 2: Description of parameters

Parameter	Description
ω	Infection rate
β	Production rate of hepatitis C virions
γ	Rate of killing of infected graft hepatocytes by $CD8^+$ T cells
Λ	Production rate of new susceptible hepatocytes
η	Production rate of $CD8^+$ T cells in response to viral antigen derived from infected graft hepatocytes.
μ	Natural death rate of graft hepatocytes
α	Natural death rate of hepatitis C virions
ν	Natural death rate of $CD8^+$ T cells
σ	Spontaneous recovery rate of infected graft hepatocytes
δ	Disease-induced death rate of infected graft hepatocytes
θ	Fraction of $CD8^+$ T cells response suppressed by immunosuppressants
π	Rejection rate of liver transplant by $CD8^+$ T cells responses.
p	Fraction of $CD8^+$ T cells response responsible for eradicating infected graft hepatocytes subject to immunosuppression
$Z_{\max}$	Maximum level of $CD8^+$ T cells load

2.2 Model Flow Diagram

The description of transmission dynamics of hepatitis C virus can be summarized in a model flow diagram with four compartments as shown in Figure 1.

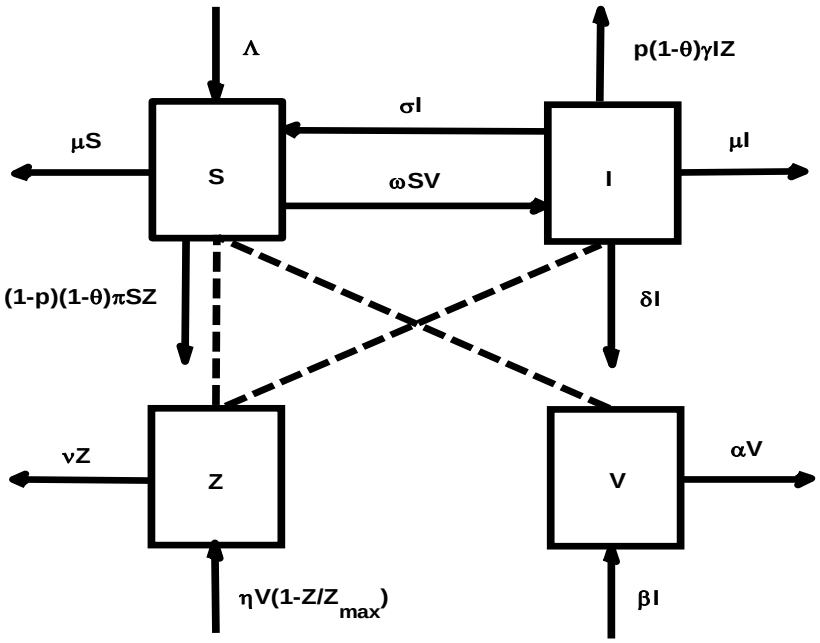

FIGURE 1: Model flow diagram illustrative of transmission dynamics of hepatitis C virus after liver transplantation.

2.3 Equations of the Model

The model flow diagram, descriptive of the transmission dynamics of recurrent HCV, produces a system of four non-linear ordinary differential equations. Equation (1) models the susceptible graft hepatocytes sub-population; (2), infected graft hepatocytes sub-population; (3), free HCV population and (4), $CD8^+$ T cells population with the following initial conditions of individual state variables: $S(0) = S_0$, $I(0) = I_0$, $V(0) = V_0$ and $Z(0) = Z_0$.

Then the system of equations is as follows:

$$\frac{dS}{dt} = \Lambda + \sigma I - \omega SV - (1-p)(1-\theta)\pi SZ - \mu S \quad (1)$$

$$\frac{dI}{dt} = \omega SV - p(1-\theta)\gamma ZI - \delta I - \sigma I - \mu I \quad (2)$$

$$\frac{dV}{dt} = \beta I - \alpha V \quad (3)$$

$$\frac{dZ}{dt} = \eta V\left(1 - \frac{Z}{Z_{\max}}\right) - \nu Z \quad (4)$$

2.4 Basic Properties of the Model

(i) Positivity of Solutions

Since the system (1)- (4)addresses the modeling of heterogeneous populations, then all the state variables and parameters of it must be non-negative for all $t \geq 0$. Here, we want to prove that the variables $S(t)$, $I(t)$, $V(t)$ and $Z(t)$ are *non-negative* $t \geq 0$, which is achieved through Theorem 1.

Theorem 1: *If the initial values of a given system are* $\{S(0), I(0), V(0), T(0) \in R_+^4\} \geq 0$ *then the solution set* $\{(S(t), I(t), V(t), T(t)\}$ *consists of non-negative entities* $\forall t \geq 0$.

Proof:

We are required to prove that each state variable in the model system is positive.

From (3) we have:

$$\frac{dV}{dt} \geq -\alpha V$$

$$\frac{dV}{V} \geq -\alpha dt \tag{5}$$

If we integrate the differential inequality (5)with respect to time t, we obtain:

$$\ln V \geq -\alpha t + K \tag{6}$$

Thus, the general solution of (6) is given by

$$V(t) \geq V_0 \exp(-\alpha t) \tag{7}$$

where V_0 represents the initial size of hepatitis C virus population.

From (7), we deduce:

$$V(t) \geq V_0 \exp(-\alpha t) \geq 0 \tag{8}$$

From (4), we have:

$$\frac{dZ}{Z} = -\left[\frac{\eta V + \nu Z_{\max}}{Z_{\max}}\right] dt \tag{9}$$

If we integrate the differential inequality (9)with respect to time t, we obtain:

$$\ln Z \geq -\int_0^t \left(\frac{\eta V(s)}{Z_{\max}} + \nu\right) ds + K \tag{10}$$

Then, the general solution of (10) is given by

$$Z(t) \geq Z_0 \exp\left[-\int_0^t \left(\frac{\eta V(s)}{Z_{\max}} + \nu\right) ds\right] \tag{11}$$

where Z_0 represents the initial size of CD8$^+$ T cells population.

Thus, we deduce:

$$Z(t) \geq Z_0 \exp\left[-\int_0^t \left(\frac{\eta V(s)}{Z_{\max}} + \nu\right) ds\right] \geq 0 \tag{12}$$

Similarly, we can prove that the other variables S and I of the model system (1)- (4) are non-negative for all $t \geq 0$, i.e.

$$S(t) \geq S_0 \exp\left[-\int_0^t \left(\omega V(s) + \mu + \pi Z(s)\right) ds\right] \geq 0 \tag{13}$$

and

$$I(t) \geq I_0 \exp\left[-\int_0^t \left(\gamma Z(s) + \mu + \sigma\right) ds\right] \geq 0 \tag{14}$$

where S_0 and I_0 represents the initial sizes of susceptible graft hepatocytes and infected graft hepatocytes respectively.

Since the set $\{S(t), I(t), V(t), T(t)\}$ consists of non-negative values, which are indicated in the results (8), (12), (13) and (14), the model (1)- (4) is epidemiologically and mathematically realistic (Hethcote, 2000).

(ii) Invariant Regions

In this case, we determine the invariant region (domain) of the model (1)-(4), which contains all feasible solutions. As the model system of equations involves modeling of the graft hepatocytes, recurrent HCV and CD8$^+$ T cells populations subject to hepatic transplantation, we assume that the model state variables and parameters are non-negative for all $t \geq 0$. This is achieved through the following theorem:

Theorem 2: *All forward solutions of the model system (1)-(4), are contained in the region* $\Psi \subset R_+^4$, $\forall t \geq 0$ *and* $\Psi = \Phi_N \times \Phi_V \times \Phi_Z$ *where*

$$\Phi_N = (S, I) \in R_+^2 : S + I \le N$$

$$\Phi_V = \{V \in R_+^1 : (4) \text{ is satisfied}\}$$

$$\Phi_Z = \{Z \in R_+^1 : (4) \text{ is satisfied}\}$$

and Ψ *is the positive invariant region for the whole system* (1)-(4).

Proof:

The proof begins with determination of bounded regions for individual populations.

Graft Hepatocytes Population

Here, we determine the bounded region containing all feasible solutions for the graft hepatocytes population $\forall t \ge 0$. Suppose Φ_N is the bounded region for the pupation; and let $\Phi_N = (S, I) \in R_+^2$ be the solution with non-negative initial conditions S_0 and I_0. Then, we have:

$$N = S + I \tag{15}$$

where N represents the graft hepatic population.

From (15), we deduce:

$$\frac{dN}{dt} = \frac{dS}{dt} + \frac{dI}{dt} \tag{16}$$

Substitution of (1) and (2) into (16) yields:

$$\frac{dN}{dt} = \Lambda - N\mu - (\pi S + \gamma I)Z - \delta I$$

This implies that

$$\frac{dN}{dt} + N\mu \le \Lambda \tag{17}$$

Then the general solution of the differential inequality (17) is:

$$N(t) \le \frac{\Lambda}{\mu} + (N_0 - \frac{\Lambda}{\mu}) \exp(-\mu t) \tag{18}$$

where N_0 represents the initial size of the graft hepatic cells population evaluated at the initial conditions $S_0 = S(0) \ge 0$ and $I_0 = I(0) \ge 0$.

From (18), we deduce two cases for all $t \ge 0$.

Case 1: When $N_0 > \frac{\Lambda}{\mu}$, the largest value of right hand side (RHS) of inequality (18) is obtained at $t = 0$; and the value is N_0. Hence $N(t) \le N_0$

Case 2: When $N_0 < \frac{\Lambda}{\mu}$, the value $\left(N_0 - \frac{\Lambda}{\mu}\right)\exp(-\mu t)$ is negative and approaches zero as $t \to \infty$.So, the largest value in the RHS of inequality(18) is $\frac{\Lambda}{\mu}$. Hence $N(t) \le \frac{\Lambda}{\mu}$

In respect of this, we deduce:

$$N(t) \le \max\left\{N_0, N^*\right\} \forall t \ge 0 \text{ and whatever value of } N_0,$$

where $N^* = \Lambda/\mu$.

Thus, $N(t)$ is bounded above.

Hence all feasible solutions for the graft hepatic cells population are contained in the following bounded region:

$$\Phi_N = \left\{N(t) : N(t) \le N^*\right\}. \tag{19}$$

Hepatitis C Viral Population

Here, we determine the bounded region that contains all feasible solutions for the hepatitis C virus population $\forall t \ge 0$. Let Φ_V be the bounded region for the population; and let $\Phi_V = V \in R_+^1$ be the solution with non-negative initial condition V_0. Then we have:

From (3), we have:

$$\frac{dV}{dt} = \beta I - \upsilon V$$

This implies that

$$\frac{dV}{dt} \le \beta N^* - \upsilon V, \tag{20}$$

The general solution of the differential inequality (20) is:

$$V(t) \le \frac{\beta N^*}{\nu} + \left(V_0 - \frac{\beta N^*}{\nu}\right)\exp(-\nu t) \tag{21}$$

where V_0 represents the initial size of hepatitis C viral population.

From (21), we deduce two cases for all $t \ge 0$.

Case 1: When $V_0 > \frac{\beta N^*}{\nu}$, the largest value of the RHS of inequality (21) is obtained at $t = 0$. This is V_0. Hence $V(t) \le V_0$.

Case 2: When $V_0 < \frac{\beta N^*}{\nu}$, the value $\left(V_0 - \frac{\beta N^*}{\nu}\right)\exp(-\alpha t)$ is negative and approaches zero as $t \to \infty$. So, the largest value in the RHS of inequality (21) is $\frac{\beta N^*}{\nu}$. Hence $V(t) \le \frac{\beta N^*}{\nu}$

In respect of this, we deduce:

$$V(t) \le \max\left\{V_0, V^*\right\} \forall t \ge 0 \text{ and whatever value of } V_0.$$

where $V^* = \frac{\beta N^*}{\nu}$

Thus, $V(t)$ is bounded above.

Hence all feasible solutions for the graft hepatic cells population are contained in the following bounded region:

$$\Phi_V = \left\{V(t) : V(t) \le V^*\right\}. \tag{22}$$

CD8$^+$ T cells Population

Here, we determine the bounded region that contains all feasible solutions for the CD8$^+$ T cells population $\forall t \ge 0$. Let Φ_Z be the bounded region for the population; and let $\Phi_Z = Z \in R_+^1$ be the solution with non-negative initial condition Z_0. Then, we have:

From (4), we have:

$$\frac{dZ}{dt} = \eta V(1 - \frac{Z}{Z_{\max}}) - \nu Z$$

This implies that

$$\frac{dZ}{dt} \le \eta V^*\left(1 - \frac{Z}{Z_{\max}}\right) - \nu Z \tag{23}$$

The general solution of the differential inequality (23) is:

$$Z(t) \le \frac{\eta Z_{\max} V^*}{\eta V^* + \nu Z_{\max}} + \left(Z_0 - \frac{\eta Z_{\max} V^*}{\eta V^* + \nu Z_{\max}}\right)\exp\left[-\left(\frac{\eta V^*}{Z_{\max}} + \nu\right)t\right] \tag{24}$$

where Z_0 represents the initial size of CD8$^+$ T cells population.

From (24), we deduce two cases for all $t \geq 0$.

Case 1: When $Z_0 > \frac{\eta Z_{\max} V^*}{\eta V^* + \nu Z_{\max}}$, the largest value of the RHS of inequality (24) is obtained at $t = 0$, which is Z_0. Hence $Z(t) \leq Z_0$.

Case2: When $Z_0 < \frac{\eta Z_{\max} V^*}{\eta V^* + \nu Z_{\max}}$ the value $\left(Z_0 - \frac{\eta Z_{mac} V^*}{\eta V^* + \nu Z_{\max}} \right) \exp\left[-\left(\frac{\eta V^*}{Z_{\max}} + \nu \right) t \right]$ is negative and approaches zero as $t \to \infty$. So the largest value in the RHS of inequality (24) is $\frac{\eta Z_{\max} V^*}{\eta V^* + \nu Z_{\max}}$.

Hence $Z(t) \leq \frac{\eta Z_{\max} V^*}{\eta V^* + \nu Z_{maz}}$

In respect of this, we deduce:

$$Z(t) \leq \max\left\{Z_0, Z^*\right\} \forall t \geq 0 \text{ and whatever value of } Z_0.$$

where $Z^* = \frac{\eta Z_{\max} V^*}{\eta V^* + \nu Z_{maz}}$

Thus, $Z(t)$ is bounded above.

Hence all feasible solutions for the $CD8^+$ T cells population are contained in the following bounded region:

$$\Phi_Z = \left\{Z(t) : Z(t) \leq Z^*\right\}. \tag{25}$$

Hence $\Psi = \Phi_L \times \Phi_V \times \Phi_T$, where

$$\Phi_N = \left\{N(t) : N(t) \leq N^*\right\}$$

$$\Phi_V = \left\{V(t) : V(t) \leq V^*\right\}$$

and

$$\Phi_Z = \left\{Z(t) : Z(t) \leq Z^*\right\}$$

As the region Ψ is positively invariant, it is sufficient to consider all solutions of the model in it. Hence the model system (1)-(4) is epidemiologically and mathematically realistic. So, we have proved Theorem 2.

3. RESULTS AND DISCUSSIONS

The model system (1)-(4) is analyzed qualitatively to acquire more insights into its dynamic features for better understanding of the effect of immunosuppressants on the transmission dynamics of HCV following hepatic transplantation.

3.1 Disease Free Equilibrium (DFE), P_0

We usually establish existence of model equilibria by setting the time derivatives equal to zero. Then solving the resulting system in the absence of infection yields the disease free equilibrium. Thus, we obtain the disease free equilibrium, P_0 of the model system (1)-(4) by setting the right hand side of the model equations equal to zero, i.e.

$$\frac{dS}{dt}=\frac{dI}{dt}=\frac{dV}{dt}=\frac{dZ}{dt}=0$$

This implies that

$$\begin{cases}\Lambda+\sigma I-\omega SV-(1-p)(1-\theta)\pi SV-\mu S=0\\ \omega SV-p(1-\theta)\gamma ZI-\delta I-\mu I=0\\ \beta I-\alpha V=0\\ \eta V(1-Z/Z_{\max})-\nu Z=0\end{cases} \qquad (26)$$

Then at the disease free equilibrium P_0, $V=I=0$

Substitution of $V=I=0$ in new system (26)produces $S=\Lambda/\mu$, $I=0$, $V=0$ and $Z=0$.

Hence the disease free equilibrium P_0 of the model system (1)-(4)exists and is given by

$$P_0(S^*,I^*,V^*,Z^*)=\left(\frac{\Lambda}{\mu},0,0,0\right)$$

3.1.1 The Basic Reproductive Number, R_{01}

The basic reproductive number R_{01} is one of the key concepts that are useful in epidemiology, where many different problems of infectious diseases are studied. It denotes the expected number of secondary cases triggered by a single infectious individual hosted in a completely susceptible population during the entire infectious period (Heesterbeek and Dietz, 1996) . Its

value describes the ability of a microbe to invade a susceptible population; and its quantity shows the threshold behavior of disease transmission. More accurately, if $R_{10}<1$ then the infection cannot establish itself in the population. This implies that the disease outbreak is triggered by only few infectious individuals. If $R_{01}>1$, the disease can invade the population, which may trigger a large outbreak of the disease transmission. Moreover, it is a device that measures the amount of efforts required for a control measure to remove an infection that has already established itself in the population.

Generally, the basic reproductive number R_{01}, is computed by using the next generation method (Dieckman *et al*., 1990; Van den Driessche and Watmough, 2002) .This is the spectral radius of the next generation matrix K, donated by $R_{01}=\rho(K)$. But the matrix K is given by $K=FV^{-1}$, where the matrices F and Y are obtained by evaluating the Jacobian matrices F_i and Y_i at P_o respectively. That is,

$$F=\left[\frac{\partial F_i(P_0)}{\partial X_j}\right] \text{ and } Y=\left[\frac{\partial Y_i(P_0)}{\partial X_j}\right]$$

where F_i is the rate of occurrence of new infections in compartment i, Y_i is the transfer of individuals out of the compartment i by all other means and P_0 is the disease free equilibrium.

It implies that

$$F=\begin{bmatrix}0 & \omega S^*\\ \beta & 0\end{bmatrix}$$

and

$$Y=\begin{bmatrix}p(1-\theta)\gamma Z^*+\delta+\sigma+\mu & 0\\ 0 & \alpha\end{bmatrix}$$

Then at the disease free equilibrium P_0, we obtain

$$F=\begin{bmatrix}0 & \frac{\omega\Lambda}{\mu}\\ \beta & 0\end{bmatrix}$$

and

$$Y=\begin{bmatrix}\delta+\sigma+\mu & 0\\ 0 & \alpha\end{bmatrix}$$

Computing the inverse of Y we obtain

$$Y^{-1} = \begin{bmatrix} \frac{1}{\delta+\sigma+\mu} & 0 \\ 0 & \frac{1}{\alpha} \end{bmatrix}$$

Hence we have:

$$K = FY^{-1} = \begin{bmatrix} 0 & \frac{\omega\Lambda}{\alpha\mu} \\ \frac{\beta}{\delta+\sigma+\mu} & 0 \end{bmatrix}$$

Computing the eigenvalues $\lambda_i (i=1,2)$ of K we obtain

$$\lambda_1 = -\sqrt{\frac{\beta\omega\Lambda}{\alpha\mu(\delta+\sigma+\mu)}} \text{ and } \lambda_2 = \sqrt{\frac{\beta\omega\Lambda}{\alpha\mu(\delta+\sigma+\mu)}}$$

Here, we find that the spectral radius of K .is the dominant eigenvalue λ_2.

Hence the basic reproductive number, R_{01} is given by

$$R_{01} = \sqrt{\frac{\beta\omega\Lambda}{\alpha\mu(\delta+\sigma+\mu)}} \tag{27}$$

From our assumptions, we find that the immune system does not determine secondary infection in the graft hepatic cells population as all parameters of R_{01} in (27) are derived from the hepatic cells and hepatitis C virus populations. On the other hand, the immune response, subjected to immunosuppressants, does not determine the course of HCV infection in the graft hepatic cells population because all parameters founding the equation for CD8+ T cells in the model system (1)-(4) are not integrated in the expression for R_{01}.

In the absence of spontaneous clearance of the virus, i.e. σ , the basic reproductive number R_{01} reduces to R_{02}, which is given by

$$R_{02} = \sqrt{\frac{\beta\omega\Lambda}{\alpha\mu(\delta+\mu)}}$$

Analytically, R_{01} and R_{02} are connected as follows:

$$\sqrt{\alpha\mu(\delta+\mu)} < \sqrt{\alpha\mu(\delta+\sigma+\mu)} \Rightarrow \sqrt{\frac{\beta\omega\Lambda}{\alpha\mu(\delta+\mu)}} > \sqrt{\frac{\beta\omega\Lambda}{\alpha\mu(\delta+\sigma+\mu)}}$$

Hence we obtain $R_{02} > R_{01}$. This implies that the infection is more epidemic in the hepatic cells population for a patient who cannot clear the virus spontaneously.

3.1.2 Sensitivity Analysis

Sensitivity analysis is very important in mathematical modeling. It helps to study how variations on input parameters influence projected model outputs (Gariboni *et al*., 2017). In epidemiology, sensitivity analysis helps to analyze the behaviour of a model formulated for the dynamics of an infectious microorganism. Basically, this is achieved by considering the impact of variations of different parameters on the model. In this case, very influential parameters that require special numerical attention are highlighted and targeted for developing management strategies (Lutambi *et al*., 2013).It is usually performed by computing sensitivity indices of the basic reproductive number pertaining to some model parameters. They allow us to measure the relative change in a state variale when a particular parameter changes (Chitnis *et al.,* 2008). Specifically, sensitivity analysis helps to highlight parameters that have high influence on the basic reproductive number, which are then targeted for control measures.

In this study, we present calculated normalized sensitivity indices $X_{Q_i}^{R_0}$ of the basic reproductive number R_{01} using the approaches of Chitnis *et al.* (2008).and Gariboni *et al*. (2017), where partial derivatives of $R_{01}$with respect to each parameter $Q_i (1 \le i \le 7)$ were obtained by the formula.

$$X_{Q_i}^{R_{01}} = \frac{\partial R_{01}}{\partial Q_i} \times \frac{Q_i}{R_{01}} \tag{28}$$

Sensitivity indices of R_{01} relating to all parameters were computed by substituting each of the parameter values presented in Table 3 in the formula (28).The results are listed in Table 4.

TABLE 3: Parameter values used to compute sensitivity indices of R_{01}

Parameter	Value	Unit	Source
ν	0.02	day^{-1}	Avendano *et al.*(2002)
η	0.0003	day^{-1}	Avendano *et al.*(2002)
ω	0.0001	virus^{-1}ml^{-1}day^{-1}	Estimated
σ	2	day^{-1}	Estimated
β	60	virus cell^{-1}day^{-1}	Estimated
μ	0.192	day^{-1}	Estimated
α	4.53	day^{-1}	Estimated
δ	0.139	day^{-1}	Estimated
Λ	1000	cells ml^{-1}day^{-1}	Estimated
γ	0.0001	virus cell^{-1}day^{-1}	Estimated
θ	0.79		Estimated
π	0.001	cells ml^{-1} day^{-1}	Estimated
p	0.5		Estimated
$Z_{\max}$	1000	cells	Estimated

TABLE 4: The sensitivity indices R_{01} relating to each parameter

Parameter	Sensitivity index
μ	-0.5412
α	-0.5000
ω	$+0.5000$
β	$+0.5000$
Λ	$+0.5000$
σ	-0.4290
δ	-0.0298

In Table 4, we observe that the natural death rate of graft hepatic cells, μ is the most negatively sensitive parameter $(X_{\mu}^{R_{01}} = -0.5412)$, followed by the natural death rate, α of hepatitis C virus $(X_{\alpha}^{R_{01}} = -0.5000)$ which means that the parameters have the greatest negative impact on R_{01}. For instance, an increase of 10% on μ will cause a decrease on R_{01} by 10% and vice versa.

Moreover, we find that the infection rate, ω; virus production rate, β and recruitment rate of new susceptible hepatocytes, Λ are the next highest parameters that have positive sensitivity indices $(X_{\omega}^{R_{01}} = +0.5000,\ X_{\beta}^{R_{01}} = +0.5000,\ X_{\Lambda}^{R_{01}} = +0.5000)$. This means that the parameters have positive impact on R_{01}. For instance, an increase of 10% on β will increase R_{01} by 10% and vice versa. Also, we found that the rate of spontaneous clearance of the virus, σ and the disease-induced death rate, δ are the least negatively sensitive parameters $(X_{\sigma}^{R_{01}} = -0.4290,\ X_{\delta}^{R_{01}} = -0.0298)$, which implies that they have the least negative impact on R_{01}

3.2 Numerical Simulations

The main objective of this study was to investigate the effect of immunosuppressive therapy on the transmission dynamics of recurrent HCV infection after liver transplantation. In this case, we present graphical representations showing variations in parameters with respect to different state variables numerical simulations to support the analytical results. Since most parameter values were not obtained from literatures, we had to estimate them just for illustration purposes so as to examine how the model would behave in different scenarios. All parameters values used for simulations are listed in Table 3.

Using these parameter values with the help of Maple 12 software, we calculated R_{01} and R_{02} and obtained 1.7203 and 4.5652 respectively, which implies that $R_{02} > R_{01}$. Besides, all simulations pertaining to variations of the state variables were performed using ode 45 Matlab solver for first order differential equations.

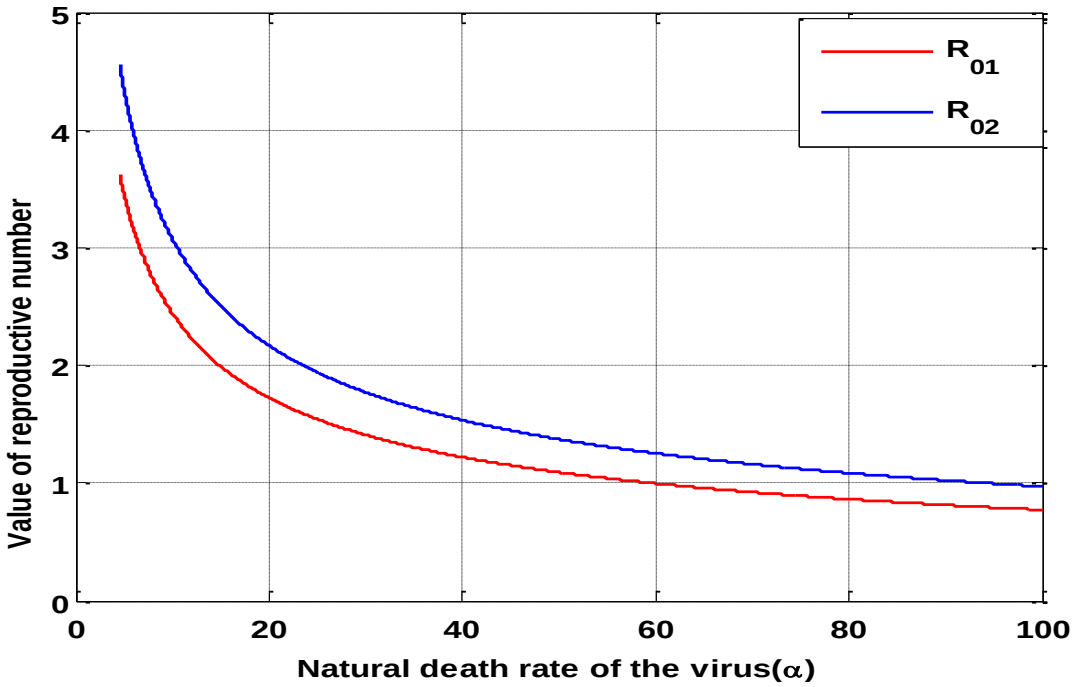

FIGURE 2: Variation of reproductive numbers R_{01} and R_{02} with virus natural death rate .

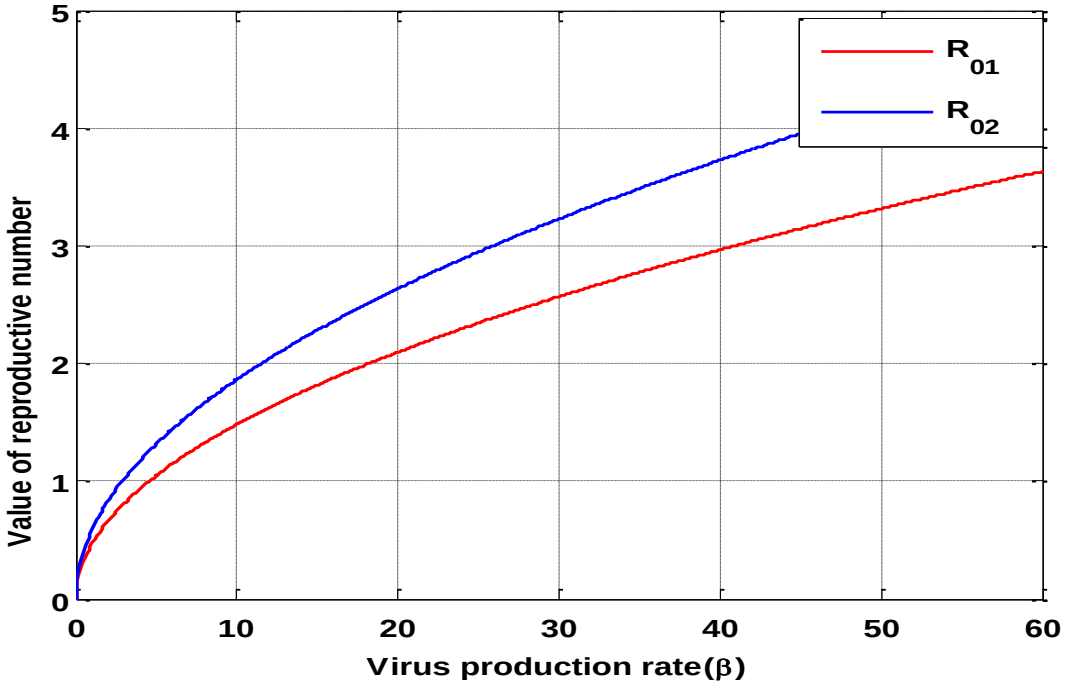

FIGURE 3: Variation of reproductive numbers R_{01} and R_{02} with virus production rate

β β α

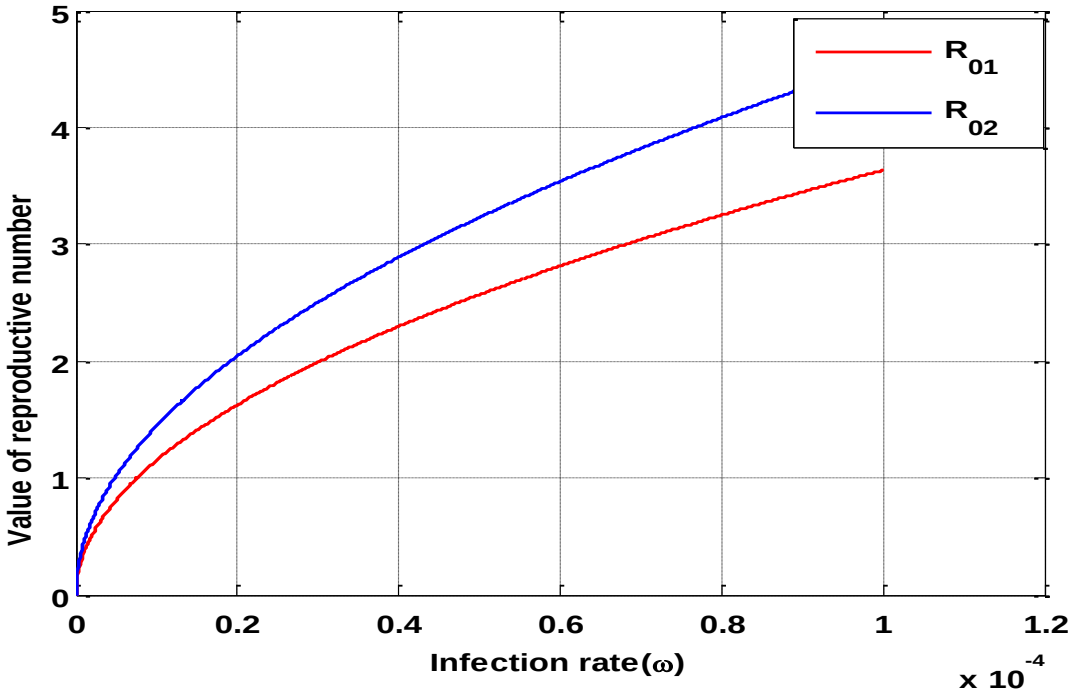

FIGURE4: Variation of reproductive numbers R_{01} and R_{02} with infection rate

Figures 2-4 show that the basic reproductive numbers R_{01} and R_{02} differ when plotted against the natural death rate of the virus, α; the virus production rate, β and the infection rate, ω in a way that $R_{02} > R_{01}$. This verifies that the absence of spontaneous clearance of the virus $(\sigma = 0)$ increases the value of the basic reproductive number, which implies that more graft hepatocytes are infected as more HCV virions are produced from the infected graft hepatocytes to interact with susceptible graft hepatocytes. Figure 3 shows that the values of R_{01} and R_{02} decrease with increases of α while they increase with increase of β and ω (Fig.3 and Fig.4 respectively). This implies that as the natural death rate of the virus increases fewer graft hepatocytes are infected as fewer hepatitis C virions interact with susceptible graft hepatocytes. Conversely, as the infection rate and virus production rate increase more graft hepatocytes are infected and so more hepatitis C virions are produced to interact with susceptible graft hepatocytes. This implies that deliberate intervention can be directed to at least one of the parameters leading to reduction of the HCV virus transmission in the graft hepatic cells population (the liver transplant).

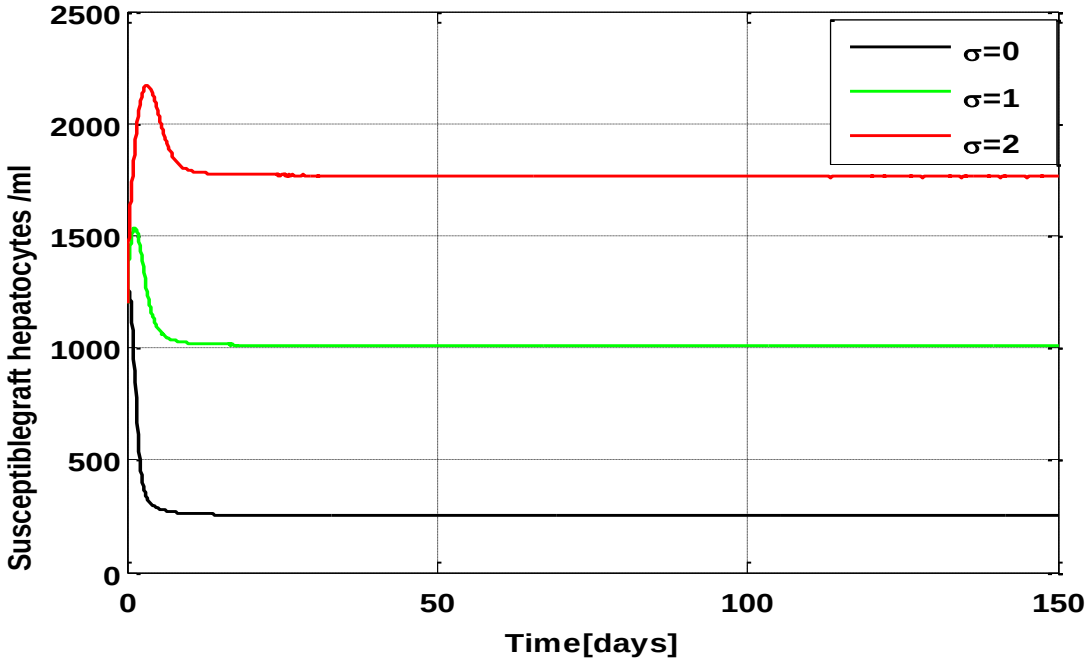

FIGURE 5: Variation of susceptible graft hepatocytes with time spontaneous viral clearance

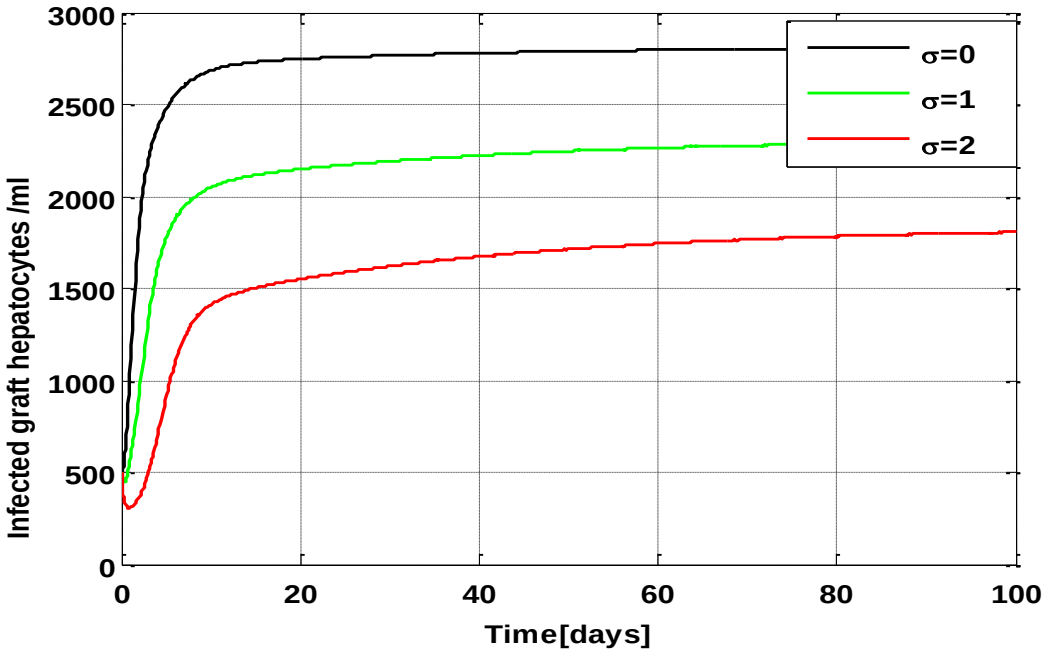

FIGURE 6: Variation of infected graft hepatocytes with spontaneous viral clearance

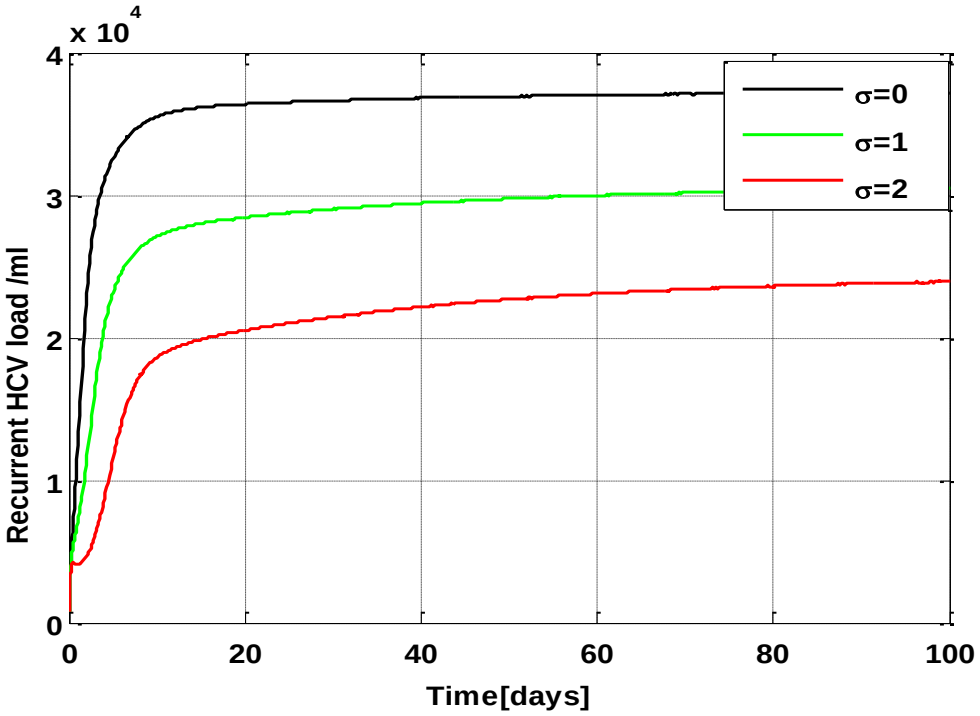

FIGURE 7: Variation of recurrent HCV load with spontaneous viral clearance

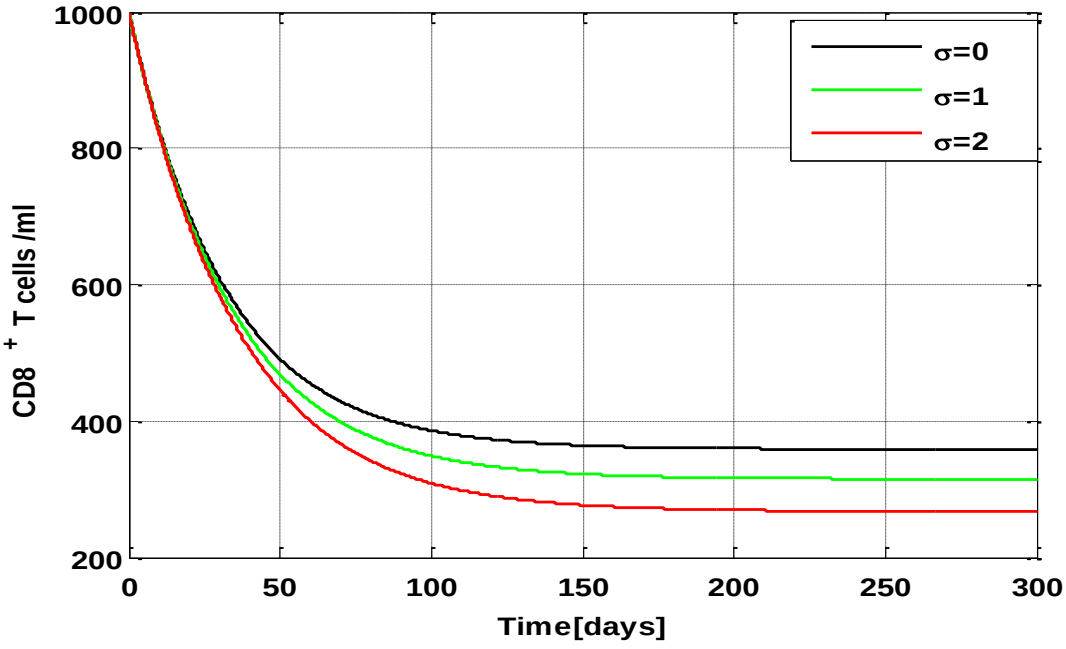

FIGURE 8: Variation of $CD8^+$ T cells with spontaneous viral clearance

Figures 5-8 show plots of susceptible graft hepatocytes, infected graft hepatocytes, recurrent HCV load and $CD8^+$ T cells against time respectively at various rates of spontaneous clearance of the virus (recovery of infected graft hepatocytes), σ. Figure 5 shows variation of susceptible

graft hepatocytes with σ, whereby we see that at a higher value of σ the number of susceptible graft hepatocytes is also higher and vice versa. This implies that more infected graft hepatocytes recover naturally adding to the susceptible graft hepatocytes at a higher value of σ while fewer infected graft hepatocytes recover to the susceptible graft hepatocytes at a smaller value of σ. Figure 6 shows variation of infected graft hepatocytes with σ, whereby we observe a decrease of the number of infected graft hepatocytes as σ increases and vice versa. This implies that more infected graft hepatocytes recover naturally at a higher value of σ, which absolutely reduces the number of them. Conversely, fewer infected graft hepatocytes recover at a smaller value of σ. Figure 7 shows variation of HCV load with σ, where we see that the HCV load is lower at a higher value of σ and vice versa. This means fewer infected graft hepatocytes produce fewer hepatitis C virions and vice versa. In Figure 8, we shows the variation of $CD8^+$ T cells with σ, whereby observe that as the recovery rate of infected graft hepatocytes increases the number of $CD8^+$ T cells decreases and vice versa, implying that fewer $CD8^+$ T cells are produced to kill infected graft hepatocytes at a higher value of σ while more $CD8^+$ T cells are produced to kill them at a smaller value of σ due to a greater number of infected graft hepatocytes at this value.

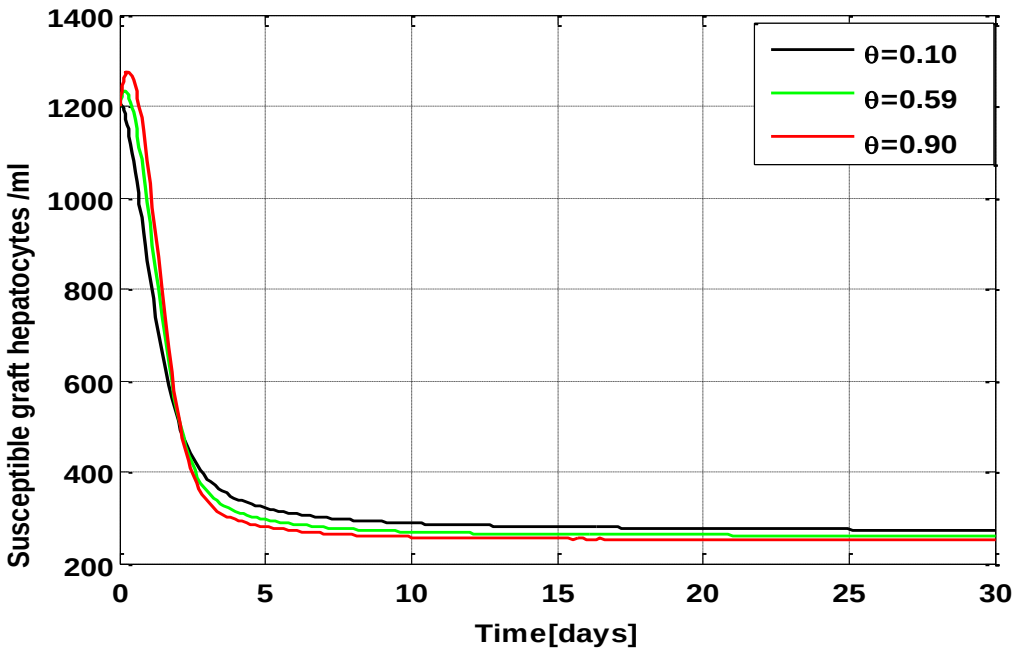

FIGURE 9: Variation of susceptible graft hepatocytes with efficacy of immunosuppressants θ

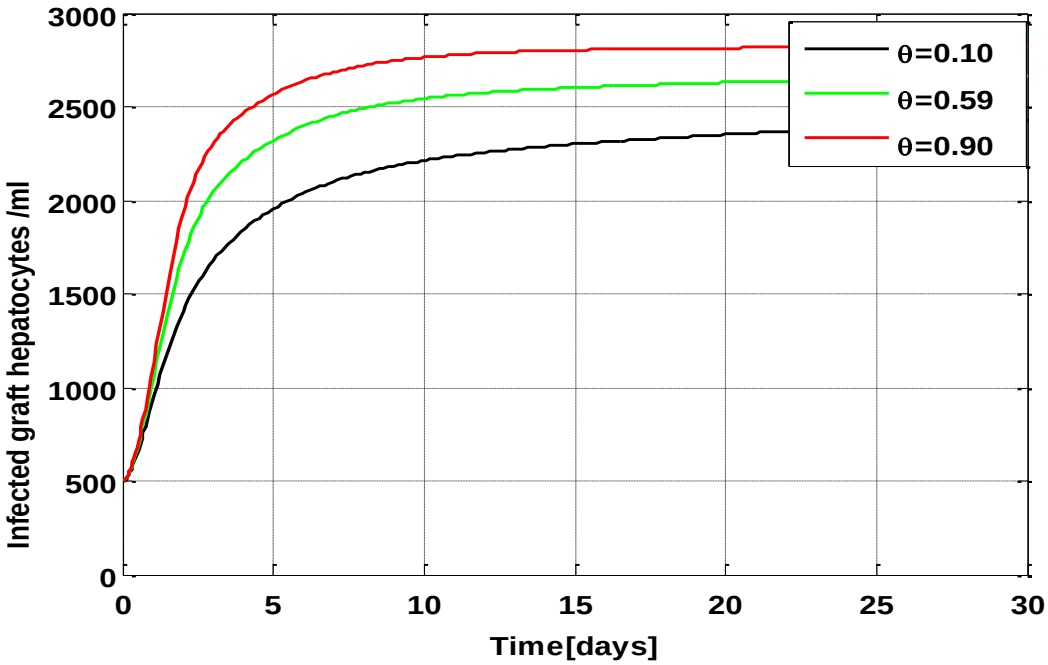

FIGURE10: Variation of infected graft hepatocytes with efficacy of immunosuppressants θ

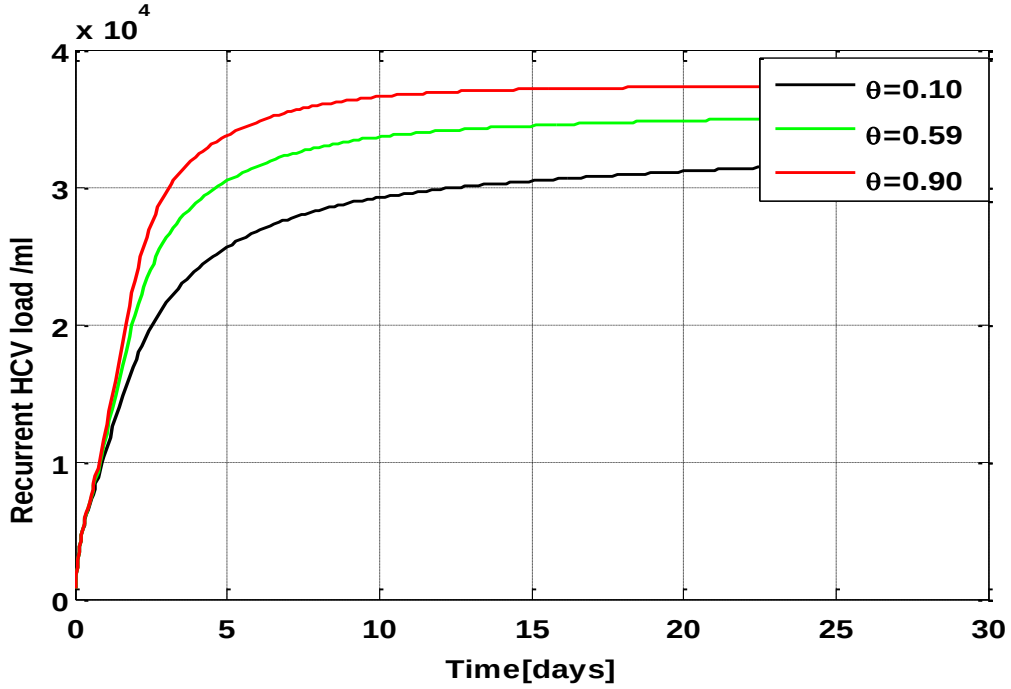

FIGURE 11: Variation of recurrent HCV load with efficacy of immunosuppressants θ

Figures 9-11 show plots of the susceptible graft hepatocytes, infected graft hepatocytes and HCV load against time with various efficacies of immunosuppressants, θ respectively. Figure 9 shows the variation of the number of susceptible graft hepatocytes with θ, whereby observe that as θ increases the number of susceptible graft hepatocytes generally decreases and vice versa . This implies fewer susceptible graft hepatocytes are eradicated as more $CD8^+$ T cells are suppressed by immunosuppressants to reduce the killing ability and vice versa. In Figure 10, we observe that the number of infected graft hepatocytes decreases as θ increases and vice versa. This implies that fewer infected graft hepatocytes are killed as more produced $CD8^+$ T cells are suppressed by immunosuppressants and vice versa. Figure 11 shows that fhe HCV load decreases as θ increases and vice versa, implying that fewer infected graft hepatocytes produce fewer hepatitis C virions. Here, we observe that immunosuppressants significantly reduce rejection of the liver transplant but does not guarantee full extinction of transmission of HCV infection because of the endemic equilibrium attained in the long run (Fig. 9, Fig. 10 and Fig, 11).

4. CONCLUSION

In this paper, we have presented a deterministic mathematical model formulated to investigate the impact of immunosuppressants on the transmission dynamics of hepatitis C virus following liver transplantation with the possibility of the liver transplant recipient capability of clearing the virus spontaneously. The model was formulated based on the assumption that the HCV-infected person had been subjected to the liver transplantation due to the liver failure caused by cirrhosis. We established that the model state variables are non-negative for time $t \geq 0$, which verifies that the model is mathematically and epidemiologically realistic.

Analytically, we established that the disease free equilibrium, P_0 exists and so derived the basic reproductive number, R_{01} when the transplant recipient can clear the virus spontaneously, which reduces to R_{02} when there is no spontaneous viral clearance. Also, we established that $R_{02} > R_{01}$, implying that HCV infection is more epidemic for a patient who cannot clear the virus naturally. The sensitivity indices of R_{01} were calculated; and we noticed that the natural death

rate of the graft hepatocytes is the most negatively sensitive parameter μ, followed by the infection rate, ω; the virus production rate β and the recruitment rate of new susceptible hepatocytes, Λ; which are positively sensitive parameters, while the parameter, δ for the disease-induced death rate is the least negatively sensitive. This implies that deliberate actions can be taken to control the disease transmission by targeting the most sensitive parameters. Numerical simulations were performed that generally confirm certain analytical results; and we noticed that variation of the efficacy of immunosuppressants θ and rate of spontaneous viral clearance σ have significant effects on the transmission dynamics of HCV, whereby the increase of θ triggers reduction of damage of the liver transplant by the immune response but accelerate HCV infection, θ leading to faster damage of the transplant in the long run. Besides, at a greater rate of spontaneous viral clearance the chance of disease extermination is higher as well while the disease transmission is more epidemic for a transplant recipient who cannot clear the virus spontaneously. Thus, this study recommends that deliberate control measures should be directed to a HCV-infected person who cannot clear the virus naturally so as to reduce recurrent HCV transmission, or eradicate it, by targeting the most sensitive parameters with assured non-rejection of the liver transplant by the transplant recipient body immune response.

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Conflicts of Interest

The authors declare that there are no conflicts of interest concerning the publication of this paper

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