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MATHEMATICAL MODEL ANALYSIS OF HEPATITIS C WITH CARDIAC SIDE EFFECTS BEFORE, DURING, AND AFTER RECEIVING DIRECT ACTING ANTIVIRALS TREATMENT

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Abstract. Hepatitis C virus (HCV) is a blood-borne infection that can lead to liver failure, cirrhosis, hepatocellular carcinoma, and death. Direct-acting antivirals (DAAs) are a relatively new therapeutic approach, the most efficient and safest hepatitis C treatment. However, DAAs can have divergent effects on heart health. The side effects of DAAs on the heart are called cardiotoxicity. Therefore, we built a mathematical model based on hepatitis C patients, showed the positivity and boundedness of the system solution, and determined the equilibrium point and its stability by exploiting the Routh Hurwitz criteria, which established an asymptotically stable equilibrium point. Finally, we performed numerical simulations to evaluate these results.

Keywords: hepatitis C; acute stage; chronic stage; direct acting antiviral; mathematical model; stability.

2020 AMS Subject Classification: 92C60, 34D20.

1. INTRODUCTION

Hepatitis C is an infectious disease that affects the liver caused by the hepatitis C virus (HCV). Hepatitis C was initially acknowledged as a distinct illness in 1975, as well as the causal agent HCV was discovered in 1989. HCV is a member of the Flaviviridae family of

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tiny, enveloped, single-stranded RNA viruses [1]. It mutates very rapidly resulting in a high genetic diversity [2]. There are currently 7 genotypes that are known and more than 67 subtypes of HCV. The hepatitis C virus exhibits diverse global distributions according to its genotype. Genotype 1 is the most common worldwide, with genotypes 3, 4, and 2 following closely behind. As for other cases of hepatitis C, roughly 5%, are caused by genotypes 5 and 6. Additionally, genotype 7 was remoted in Canada from a single patient coming from the Democratic Republic of the Congo [3]. According to the World Health Organization, an estimate indicates that 170 million people, around 3% of people worldwide have hepatitis C virus infection, resulting in approximately 290 000 deaths yearly. Hepatitis C is transmitted by coming into contact with an infected person's blood. This can be achieved by sharing syringes or other supplies needed to prepare and inject medications.

Hepatitis C has two separate stages: the acute stage and the chronic stage. HCV infection causes acute hepatitis C which is largely asymptomatic. When these symptoms appear, they include fever, nausea, joint pain, vomiting, pale stools, dark urine, jaundice (yellowing of the skin or eyes), and appetite decline. The first infection can spontaneously disappear around 30% (15-45%) of cases within the first six months following initial contact, thanks to a strong immune response. However, roughly 70% (55-85%) of HCV infections progress to chronic infections, which are defined by the presence of HCV RNA for at least six months following the initial infection. This stage of illness may take decades [4, 5]. Most people show little to no symptoms during the initial years of infection. After enduring the disease for several years, it often develops into cirrhosis or hepatocellular carcinoma (HCC). The natural evolution of HCV estimates that 60% of infected people will develop cirrhosis, 14.4% will develop HCC, and the remainder will die from HCV infection-related complications [6].

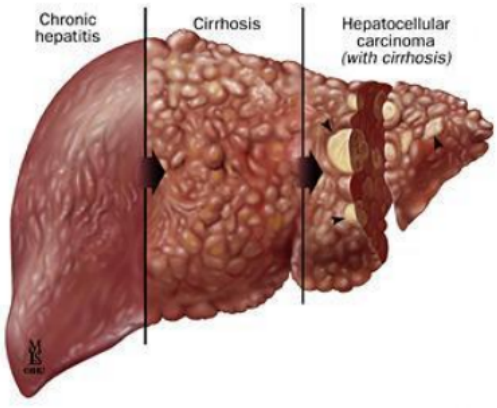

FIGURE 1. Evolution of hepatitis C infection [7]

Currently, hepatitis C has no known vaccination because of the virus's quick rate of mutation, but it can be treated with Direct-acting antiviral drugs. The FDA (Food and Drug Administration) did not approve the first oral DAA single combination medication to treat HCV genotype 1 until October 2014 [8]. Direct-acting antivirals (DAAs) are a relatively new group of drugs developed following an in-depth study of the life cycle of the hepatitis C virus (HCV). Hepatitis C is treated using direct-acting antiviral (DAA) tablets. The Tablets are the secure and most practical medication against hepatitis C [5, 9]. They are highly successful in treating the infection in over 90% of instances. Treatment period differs according to the kind of hepatitis C [10]. The DAA can not only safely and effectively eradicate HCV, but also offer unanticipated advantages over interferon-based therapy, including the recovery of immune dysfunction and metabolic impairment caused by HCV infection [11]. However, cardiotoxicity is one of the adverse consequences of DAA treatment, which can induce to paroxysmal atrial fibrillation, atrioventricular block, paroxysmal tachycardia [12].

Mathematical modeling and its implications play a vital part in the study of the micro and macro levels of infectious diseases, and aid in preventing the spread of infection. Proper micro-level mathematical modeling aims to comprehend and measure the biological processes underlying the variations in the viral load and associated biomarkers, starting in the middle of the 1990s to describe the decrease in HIV with extremely aggressive antiretroviral medication treatment [13]. A few years later, it was effectively used to comprehend the dynamics of HCV RNA during treatment [14]. Martcheva and Chavez [15] have developed a model of age-structured

ODE for hepatitis C including both acute and chronic infection states. Luo et al. [16] carried out a global analysis of a four-state model "sensitive", "exposed", "acute" and "chronic" and proved certain theorems concerning the stability of the equilibrium points. An analysis of IFN-α therapy's efficacy was conducted by Neumann et al [14]. DAA therapy's impact on HCV infection is studied by Chatterjee et al. in [17]. Mondal et al. [18] identified the useful role of Sofosbuvir/Velpatasvir in controlling HCV infection. Sharma el al. [19] studied the effect of antiviral medication management on the dynamics of HCV infection transmission when hepatocyte growth is present. Thus, in light of the research that we have already discussed, none of them appear to have concentrated on a mathematical model of potential cardiac side effects in hepatitis C patients who are treated with DAA treatment or without it. Research should help identify patients in danger of developing heart disease, design efficient cardiac surveillance systems, and assess the necessity of Holter monitoring in patients treated with DAAs, given the significance of this risk and the higher mortality in patients developing the risk of cardiotoxicity after DAA therapy [11].

This work is structured as follows: In the first section, we build a mathematical model of hepatitis C stages with cardiac side effects in patients on DAA. This model includes a system of differential equations to express the five compartments, then we present its dynamic analysis. Over here we show the positivity and the boundedness of the solution, the equilibrium point, and its stability by using the Routh-Hurwitz criteria. Afterwards, we verify these results with numerical simulations. To put it succinctly, our outcomes indicate that the five populations of patients will arrive in a stable condition once arriving at the equilibrium point, which confirms the clinical results [12].

2. Model Formulation

We will formulate a five-state model in which individuals are classified as acute, chronic, treated, recovered, or who experience cardiotoxicity. Hepatitis C has a sluggardly development, making it challenging to describe the disease's natural history [20]. The following hypotheses are therefore put forward:

(1) All infected individuals experience the acute stage of hepatitis C first.

(2) Infected individuals with the acute stage of the disease either develop into a chronic stage

or heal naturally. Given that the disease's acute stage is primarily asymptomatic, there is little opportunity for a cure at this stage.

(3) Individuals infected with hepatitis C are recovered via treatment or naturally.

(4) Individuals in the recovered class may return to patients with acute or chronic hepatitis C.

Different populations of hepatitis C patients are represented by the model's five-state. Each population is indicated by variables A, C, T, R, and E with:

A represents patients with acute Hepatitis C.

C represents patients with chronic Hepatitis C.

T represents treated individuals.

R represents patients with a disease-free after DAA treatment or via recovery naturally.

E represents hepatitis C patients who experience cardiotoxicity.

The compartment diagram is shown in Figure (2).

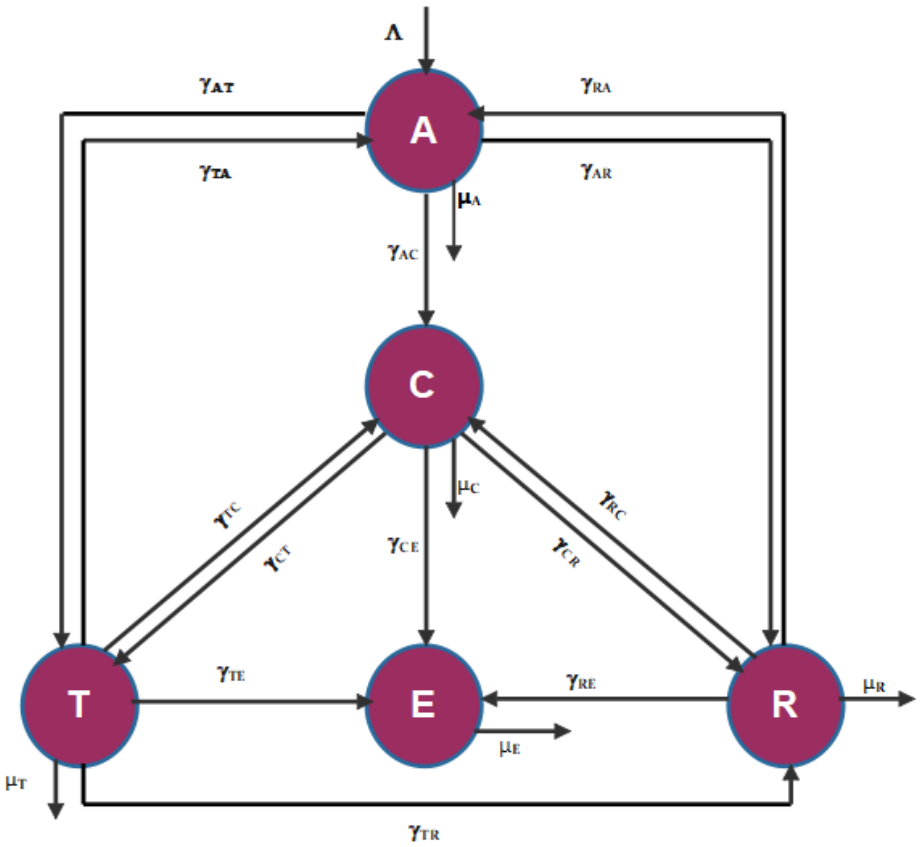

FIGURE 2. Compartment Diagram

New acute hepatitis C individuals enter into the A class at a fixed rate Λ and die at rate μ_A. An individual at the acute stage who can naturally eliminate the virus recovers at rate γ_{AR} or can receive DAA treatment at rate γ_{AT}. Individuals with the acute form of the infection develop the chronic form of hepatitis C disease at a rate γ_{AC}.

Individuals in C receive DAA treatment at the rate γ_{CT} or can spontaneously recover at a rate γ_{CR}, or die at the rate μ_C. Furthermore, the individuals in state C experiencing cardiotoxicity without undergoing treatment at the rate γ_{CE}.

After the treatment, some patients successfully clear the hepatitis C virus and move to the state R at a rate γ_{TR}, while the others, who have not reacted to the treatment, return to states A or C with the rates γ_{TA} and γ_{TC} respectively, this population may also be reduced with a death rate of μ_T. On the other hand, this population may also experience cardiotoxicity due to the DAA treatment with a rate γ_{TE}.

Individuals in class R can return to classes A or C with the rates γ_{RA} and γ_{RC}. Individuals in R may also experience cardiotoxicity due to the DAA treatment with a rate γ_{RE} or die at a disease-induced death rate μ_R.

Finally, the patients in state E come from C, T, or R and experience cardiac death at a rate μ_E.

See Table 1 for a clear description of the parameters used.

Parameter	Description
Λ	Recruitment rate
γ_{AR}	Natural recuperation rate of acutely infected individuals
γ_{RA}	Incidence rate of acute hepatitis C after natural recovery
γ_{AC}	Rate of progression to chronic stage from the acute stage
γ_{AT}	Treatment rate of acutely infected individuals
γ_{TA}	Treatment failure rate of the acutely infected individuals
γ_{TR}	Treatment heal rate
γ_{RE}	Rate of cardiotoxicity after recovery
γ_{CE}	Rate of cardiotoxicity of the chronically infected individuals without DAA treatment
γ_{TE}	Rate of cardiotoxicity during DAA treatment
γ_{CR}	Natural recuperation rate of chronically infected individuals
γ_{RC}	Incidence rate of chronic hepatitis C after natural recovery
γ_{CT}	Treatment rate of the chronically infected population
γ_{TC}	Treatment failure rate of the chronically infected population
μ_A	Disease-related mortality rate among the acutely infected individuals
μ_C	Disease-related mortality rate among the chronically infected individuals
μ_T	Disease-related mortality rate among treated individuals
μ_R	Disease-related mortality rate among recovered individuals
μ_E	Disease-related mortality rate among the individuals who experience cardiotoxicity

TABLE 1. Description of parameters used in the DAA treatment model

Based on Figure 2, and the description of the model, we have the following system of ordinary differential equations:

$$
(1)\qquad \begin{cases} \frac{dA}{dt} &= \Lambda + \gamma_{RA}R + \gamma_{TA}T - \gamma_{AR}A - \gamma_{AT}A - \gamma_{AC}A - \mu_A A \\ \frac{dC}{dt} &= \gamma_{AC}A + \gamma_{RC}R + \gamma_{TC}T - \gamma_{CE}C - \gamma_{CR}C - \gamma_{CT}C - \mu_C C \\ \frac{dT}{dt} &= \gamma_{AT}A + \gamma_{CT}C - \gamma_{TA}T - \gamma_{TR}T - \gamma_{TE}T - \gamma_{TC}T - \mu_T T \\ \frac{dR}{dt} &= \gamma_{AR}A + \gamma_{CR}C + \gamma_{TR}T - \gamma_{RA}R - \gamma_{RC}R - \gamma_{RE}R - \mu_R R \\ \frac{dE}{dt} &= \gamma_{CE}C + \gamma_{TE}T + \gamma_{RE}R - \mu_E E \end{cases}
$$

with appropriate initial conditions for vector

$$A(0) > 0, C(0) > 0, T(0) > 0, R(0) > 0, E(0) > 0.$$

3. Dynamical Analysis

In this section, we show the positivity and boundedness of the solution, and we study the existence and stability of the equilibrium point.

3.1. Positivity and boundedness of the system solution.

We introduce $N(t) = A(t) + C(t) + T(t) + R(t) + E(t)$: Total population, and $\mu = min(\mu_A, \mu_C, \mu_T, \mu_R, \mu_E)$.
We have the following results:

Theorem 3.1. *The solutions of the system $(A(t), C(t), T(t), R(t), E(t))$ for all $t \geq 0$ are bounded in the set D, which is given by*

$$D = \left\{ (A,C,T,R,E) \in \mathbb{R}^5_+ : A + C + T + R + E \leq \frac{\Lambda}{\mu} \right\}$$

Moreover, D is positively invariant.

Proof 1. *Adding all the equations of the model* (1) *gives*

$$\frac{dN}{dt} = \frac{dA}{dt} + \frac{dC}{dt} + \frac{dT}{dt} + \frac{dR}{dt} + \frac{dE}{dt} \leq \Lambda - \mu N$$

Using the method of variation of parameters from [21]*, we obtain*

$$\text{for all} \quad t \geqslant 0 \qquad 0 < N \leq \frac{\Lambda}{\mu} + (N(0) - \frac{\Lambda}{\mu})e^{-\mu t}$$

where $N(0)$ *represents the initial value. As* $t \to \infty$*, we have*

$$0 < N \leq \frac{\Lambda}{\mu}$$

We deduce that $\frac{\Lambda}{\mu}$ *is the upper bound for* N*, hence the set D is positively invariant.*

3.2. Equilibrium Point. To obtain the equilibrium point of the system (1), we fix all fractional derivatives of (1) to zero. The equilibrium point is given by

$$Q^* = (A^*, C^*, T^*, R^*, E^*) = (\frac{\beta}{\alpha l_1}, \frac{\delta}{\alpha l_1 l_2}, 0, \frac{\eta}{\alpha}, \frac{\sigma}{\alpha l_1 l_2 l_5})$$

Where

$\sigma = \Lambda\ (\ \gamma_{CE}\ \gamma_{AC}\ \alpha\ +\ \gamma_{CE}\ \gamma_{AC}\ \gamma_{RA}\ \gamma_{AR}\ l_2\ +\ \gamma_{CE}\ \gamma_{AC}\ \gamma_{RA}\ \gamma_{CR}\ \gamma_{AC} + \gamma_{CE}\ \gamma_{RC}\ \gamma_{AR}\ l_1\ l_2\ +$
$\gamma_{CE}\ \gamma_{RC}\ \gamma_{CR}\ \gamma_{AC}\ l_1\ +\ \gamma_{AR}\ \gamma_{RE}\ l_1\ (l_2)^2 + \gamma_{CR}\ \gamma_{AC}\ \gamma_{RE}\ l_1\ l_2.$

$\delta = \alpha\ \gamma_{AC}\ +\ \gamma_{AC}\ \gamma_{RA}\ \gamma_{AR}\ l_2 + (\gamma_{AC})^2\ \gamma_{RA}\ \gamma_{CR} + \gamma_{RC}\ \gamma_{AR}\ l_1\ l_2\ +\ \gamma_{RC}\ \gamma_{CR}\ \gamma_{AC}\ l_1.$

$\alpha = l_1\ l_2\ l_4 - l_2\ \gamma_{AR}\ \gamma_{RA} - \gamma_{CR}\ \gamma_{AC}\ \gamma_{RA} - \gamma_{CR}\ \gamma_{RC}\ l_1.$

$\beta = \Lambda\ (\alpha\ +\ \gamma_{AR}\ l_2 +\ \gamma_{CR}\ \gamma_{AC}).$ $\qquad$ $\eta = \Lambda\ (\gamma_{AR}\ l_2 +\ \gamma_{CR}\ \gamma_{AC}).$

$l_1 = \gamma_{AR} + \gamma_{AT} + \gamma_{AC} + \mu_A,$ $\qquad$ $l_2 = \gamma_{CE} + \gamma_{CT} + \gamma_{CR} + \mu_C,$

$l_3 = \gamma_{TA} + \gamma_{TR} + \gamma_{TE} + \gamma_{TC} + \mu_T$ $\qquad$ $l_4 = \gamma_{RA} + \gamma_{RC} + \gamma_{RE} + \mu_R$

$$l_5 = \mu_E$$

These equilibrium points are important for the analysis of the hepatitis C model with DAA treatment, and predict the conditions required for the expansion of infection.

3.3. Stability. Next, we check the stability of the equilibrium point. To determine the stability of this point, we will use the Routh-Hurwitz criterion [22]. The system (1) is first transformed into the form of a matrix

$$\begin{pmatrix} A'(t) \\ C'(t) \\ T'(t) \\ R'(t) \\ E'(t) \end{pmatrix} = \begin{pmatrix} -l_1 & 0 & \gamma_{TA} & \gamma_{RA} & 0 \\ \gamma_{AC} & -l_2 & \gamma_{TC} & \gamma_{RC} & 0 \\ \gamma_{AT} & \gamma_{CT} & -l_3 & 0 & 0 \\ \gamma_{AR} & \gamma_{CR} & \gamma_{TR} & -l_4 & 0 \\ 0 & \gamma_{CE} & \gamma_{TE} & \gamma_{RE} & -l_5 \end{pmatrix} \begin{pmatrix} A(t) \\ C(t) \\ T(t) \\ R(t) \\ E(t) \end{pmatrix} + \begin{pmatrix} \Lambda \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}$$

which we will note by $M' = LM + \Delta$

To calculate the eigenvalues of the matrix L, we introduce the characteristic polynomial

$$P(\lambda) = |L - \lambda I| = \begin{vmatrix} -l_1 - \lambda & 0 & \gamma_{TA} & \gamma_{RA} & 0 \\ \gamma_{AC} & -l_2 - \lambda & \gamma_{TC} & \gamma_{RC} & 0 \\ \gamma_{AT} & \gamma_{CT} & -l_3 - \lambda & 0 & 0 \\ \gamma_{AR} & \gamma_{CR} & \gamma_{TR} & -l_4 - \lambda & 0 \\ 0 & \gamma_{CE} & \gamma_{TE} & \gamma_{RE} & -l_5 - \lambda \end{vmatrix}$$

We get

$$P(\lambda) = -(l_5 + \lambda)(\lambda^4 + Q_3\,\lambda^3 + Q_2\,\lambda^2 + Q_1\,\lambda + Q_0) \tag{2}$$

Where the coefficients are:

$Q_0 = l_1\ l_2\ l_3\ l_4 + \gamma_{TA}\ \gamma_{RC}\ \gamma_{AT}\ \gamma_{CR} + \gamma_{RA}\ \gamma_{TC}\ \gamma_{AR}\ \gamma_{CT} - l_1\ (\ l_3\ \gamma_{RC}\ \gamma_{CR} + \gamma_{RC}\ \gamma_{CT}\ \gamma_{TR} + l_4\ \gamma_{CT}\ \gamma_{TC}) - l_2\ (\ l_3\ \gamma_{RA}\ \gamma_{AR} + \gamma_{RA}\ \gamma_{AT}\ \gamma_{TR} + l_4\ \gamma_{AT}\ \gamma_{TA}\ ) - \gamma_{RA}\ \gamma_{AC}\ \gamma_{CR}\ l_3 - \gamma_{TA}\ \gamma_{AC}\ \gamma_{CT}\ l_4 - \gamma_{TA}\ \gamma_{RC}\ \gamma_{AR}\ \gamma_{CT} - \gamma_{RA}\ \gamma_{AC}\ \gamma_{CT}\ \gamma_{TR} - \gamma_{RA}\ \gamma_{TC}\ \gamma_{AT}\ \gamma_{CR}.$

$Q_1 = l_1\ l_2\ l_4 + l_1\ l_3\ l_4 + l_1\ l_2\ l_3 + l_2\ l_3\ l_4 - \gamma_{RC}\ \gamma_{CR}\ (\ l_1 + l_3) - \gamma_{TC}\ \gamma_{CT}\ (l_1 + l_4) - \gamma_{TA}\ \gamma_{AT}\ (\ l_2 + l_4) - \gamma_{AR}\ \gamma_{RA}\ (l_2 + l_3) - \gamma_{CT}\ (\ \gamma_{TR}\ \gamma_{RC} + \gamma_{TA}\ \gamma_{AC}) - \gamma_{RA}\ (\gamma_{AT}\ \gamma_{TR} + \gamma_{AC}\ \gamma_{CR}\ ).$

$Q_2 = l_1\ l_4 + l_1\ l_2 + l_1\ l_3 + l_2\ l_4 + l_3\ l_4 + l_2\ l_3 - \gamma_{RC}\gamma_{CR} - \gamma_{TC}\ \gamma_{CT} - \gamma_{TA}\ \gamma_{AT} - \gamma_{RA}\ \gamma_{AR}.$

$Q_3 = l_1 + l_2 + l_3 + l_4.$

We can see that this equation (2) has five eigenvalues, one of which is $-l_5$ and the other eigenvalues are the roots of the following equation :

$$\lambda^4 + Q_3\,\lambda^3 + Q_2\,\lambda^2 + Q_1\,\lambda + Q_0 = 0 \tag{3}$$

To study the nature of eigenvalues, we create a Routh table for this equation, and we get :

λ^4	1	Q_2	Q_0
λ^3	Q_3	Q_1	0
λ^2	b_1	b_2	
λ^1	c_1		
λ^0	Q_0		

Where

$$b_1 = \frac{Q_2\,Q_3 - Q_1}{Q_3}, \qquad b_2 = Q_0, \qquad c_1 = \frac{b_1\,Q_1 - Q_3\,b_2}{b_1}.$$

We found that all elements of the Routh Array are positive, which means that all eigenvalues are negative. So it can be concluded that the equilibrium point in this system is asymptotically stable.

4. Numerical Simulation

Numerical simulations for the DAA treatment model given by system (1) are carried out using Matlab, to describe the behavior of the system's solutions over time, and assert the results obtained. The simulation is performed using the initial values:
$(A(0), C(0), T(0), R(0), E(0)) = (130730, 87589, 87589, 83209, 1398)$ and using parameter values: $\Lambda = 4000$, $\gamma_{RA} = 0.01$, $\gamma_{TA} = 0.045$, $\gamma_{AR} = 0.27$, $\gamma_{AC} = 0.67$, $\gamma_{AT} = 0.1545$, $\gamma_{RE} = 0.269$, $\gamma_{TR} = 0.95$, $\gamma_{CR} = 0.015$, $\gamma_{RC} = 0.0476$, $\gamma_{CT} = 0.9$, $\gamma_{TC} = 0.5$, $\gamma_{CE} = 0.245$, $\gamma_{TE} = 0.375$, $\mu_A = 0.067$, $\mu_C = 0.0733$, $\mu_T = 0.0195$, $\mu_R = 0.003$, $\mu_E = 0.18$.
We have the following numerical results:

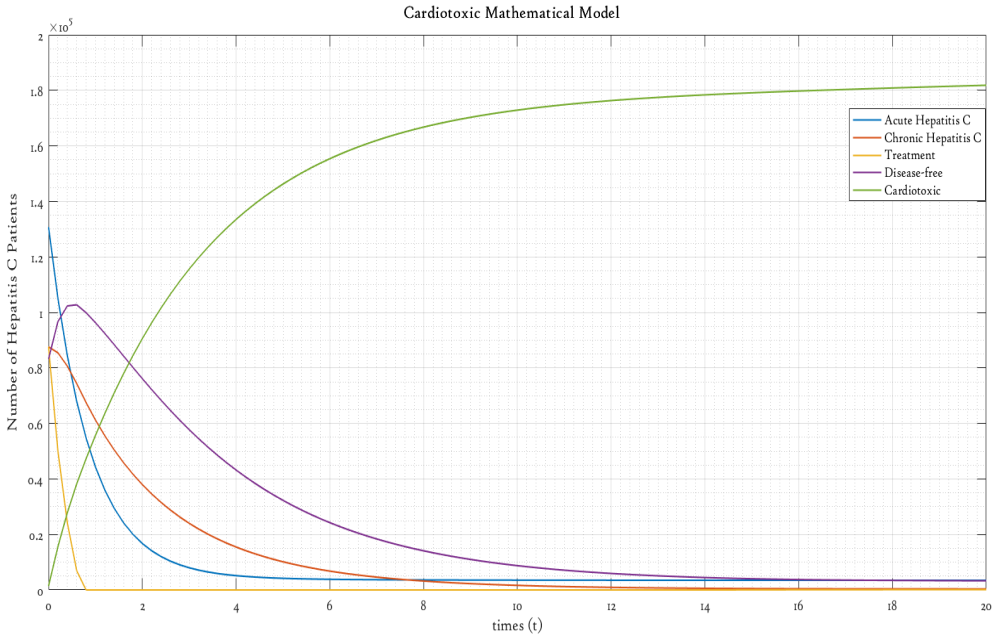

FIGURE 3. The simulation result of the ACTRE model with initial condition $A(0) = 130730$, $C(0) = 87589$, $T(0) = 87589$, $R(0) = 83209$, $E(0) = 1398$.

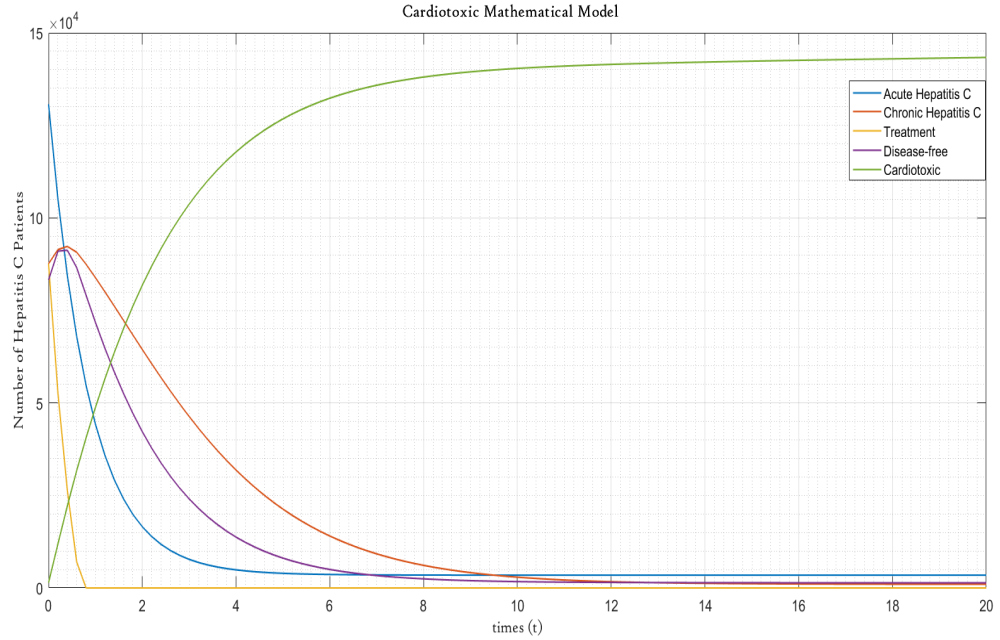

FIGURE 4. The simulation result with $\gamma_{TE} = 0.1$, and $\gamma_{RC} = 0.4$

Figure 3 shows that the acute hepatitis C patient population, which started at 130 730, fell to 3 307 patients under equilibrium conditions. Similar results were observed for the chronic hepatitis C patient population, which fell from 87 589 patients to 194 at equilibrium. The same applies to the treatment population, which started from 8 759 patients to 87 at equilibrium. Also, the disease-free population experienced a notable rise from 78 830 patients initially to 2918 patients at equilibrium. Conversely, the cardiotoxic population increased significantly, from 1 398 patients initially to 181 520 patients at equilibrium.

Figure 4 illustrate the results of the numerical simulation obtained by setting the rates γ_{TE} to 0.1 and γ_{RC} to 0.4. Under these circumstances, we observed a significant decrease in the cardiotoxic population to 150 000 patients and a decrease in the acute hepatitis C population to 3 064 patients at equilibrium, which confirmed the medical results [12].

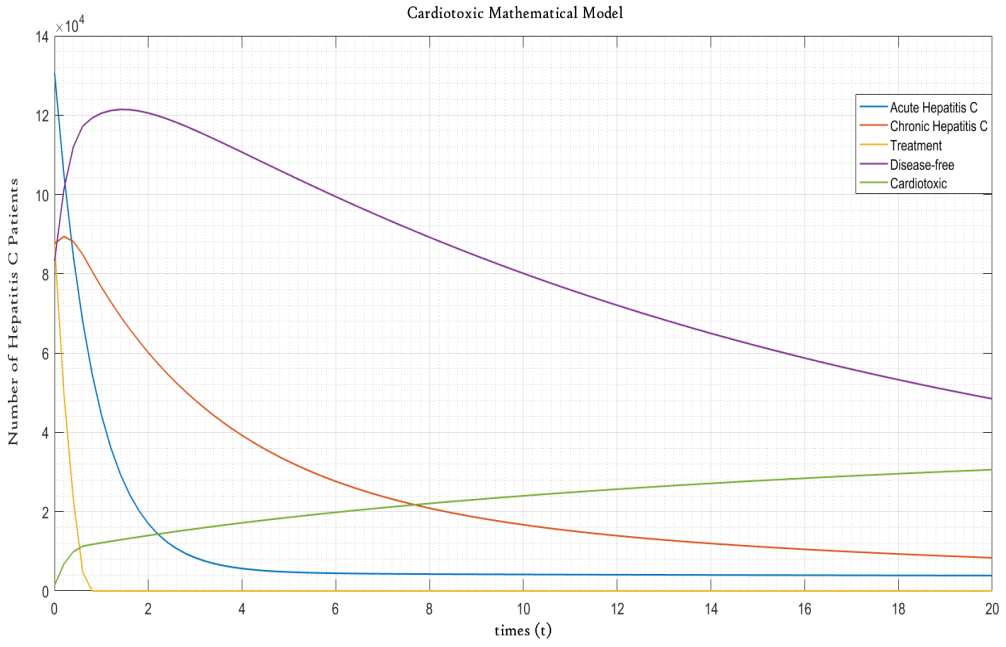

FIGURE 5. The simulation result with $\gamma_{RE} = 0.01$, and $\gamma_{CE} = 0.01$

Figure 5 shows the results of the numerical simulation obtained by setting the rates γ_{RE}, and γ_{CE} to 0.01. The results of this simulation are not comparable to those of the initial simulation (figure 2), except of the population of treated individuals, we observed a notable increase in the population of cured individuals to 48 346 patients, as well as in the chronic hepatitis C

population at 8 035 patients, similarly in the cardiotoxicity population at 30 370 patients, and in the acute hepatitis C population to 3 677 at equilibrium.

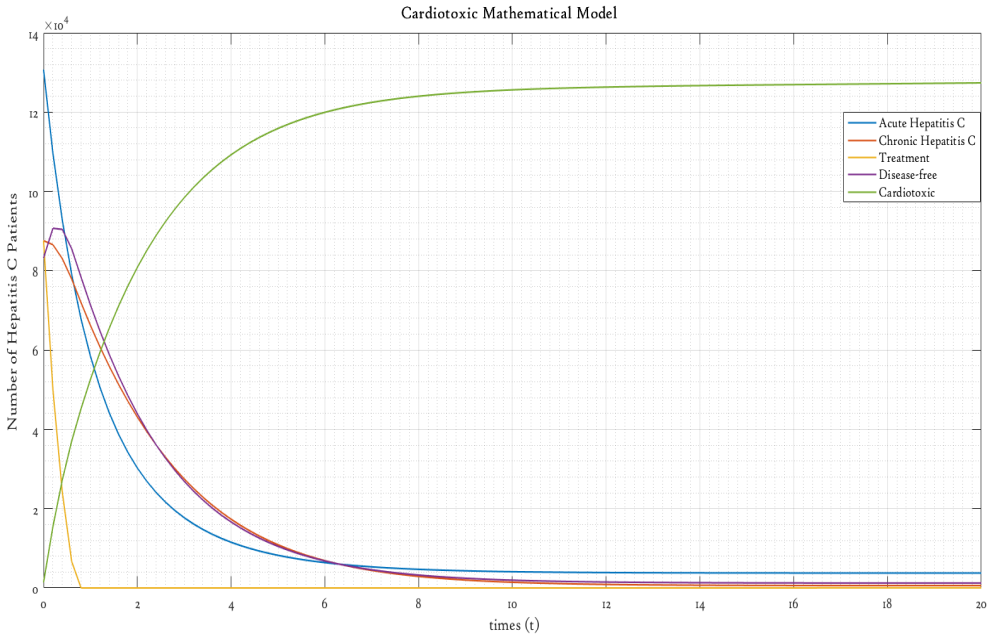

FIGURE 6. The simulation result with $\gamma_{RA} = 0.3$, and $\gamma_{CR} = 0.3$

Figure 6 represents the simulation outcomes acquired by setting the γ_{RA} and γ_{CR} rates at 0.3. Under these circumstances, we noted a significant decrease in the disease-free population to 1036 patients and a decrease in the cardiotoxic population to 127 060 patients at equilibrium.

5. CONCLUSION

In this paper, we built a compartmental mathematical model for hepatitis C stages with the cardiotoxicity of DAA treatment. The model consists of five states and nineteen parameters. A dynamic analysis is performed to identify the dynamics of the number of individuals in each population at any time. The stable equilibrium point is the result of the dynamic analysis. Numerical simulations are carried out to confirm the behavior of solutions around the equilibrium point. Based on the findings of simulations, we can conclude that the population's state will be stable at any time if all parameters are taken to be constant. This demonstrates that the system's equilibrium point turned out to be stable. Improved results are achieved by reducing the cardiac rates γ_{RE} and γ_{CE}, where we observed a significant decrease in the cardiotoxic population.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests.

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