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Research article

Global dynamics of a delayed model with cytokine-enhanced viral infection and cell-to-cell transmission

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Abstract: Recent studies have demonstrated the superiority of cell-to-cell transmission over cell-free virus infection, and highlighted the role of inflammatory cytokines in enhancing viral infection. To investigate their impacts on viral infection dynamics, we have proposed an HIV infection model incorporating general incidence rates, these infection modes, and two time delays. We derived the basic reproduction number and showed that it governs the existence and local stability of steady states. Through the construction of appropriate Lyapunov functionals and application of the LaSalle invariance principle, we established the global asymptotic stability of both the infection-free and infected steady states.

Keywords: cytokine-enhanced viral infection; intercellular transmission; general incidence rate; global dynamics
Mathematics Subject Classification: 34D23, 92D30

1. Introduction

The death of CD4+ T cells following HIV infection is typically attributed to apoptosis, or programmed cell death. However, a 2010 study suggested that most infected CD4+ T cells in lymphoid tissue succumb to pyroptosis, another form of programmed cell death [1]. On one hand, when viruses lead to productive infection of CD4+ T cells, caspase-3-mediated apoptosis leads to cell death. On the other hand, when the infection is abortive, caspase-1-mediated pyroptosis results in cell death, characterized by the release of inflammatory cytokines [2]. The occurrence of inflammation attracts more CD4+ T cells to the infection site, which leads to more infecitons and pyroptosis in turn, forming a vicious cycle and eventually severely destroying the immune system [3].

In recent years, mathematical modeling has emerged as an effective and valuable tool for elucidating the mechanisms underlying CD4+ T cell death [4, 5]. Viruses require time to enter target cells and generate new viral particles, and time delays have long been utilized to investigate viral infection dynamics [6–9]. By considering the influence of inflammatory cytokines released during pyroptosis on cell death in viral infection [1], Jiang et al. introduced the following delay model:

$$\begin{cases} \dfrac{\mathrm{d}x(t)}{\mathrm{d}t} = s - f(x(t), v(t))v(t) - \beta x(t)c(t) - d_x x(t), \\ \dfrac{\mathrm{d}y(t)}{\mathrm{d}t} = e^{-\delta_1\tau_1}[f(x(t-\tau_1), v(t-\tau_1))v(t-\tau_1) + \beta x(t-\tau_1)c(t-\tau_1)] - (\alpha + d_y)y(t), \\ \dfrac{\mathrm{d}c(t)}{\mathrm{d}t} = \alpha_1 y(t) - d_c c(t), \\ \dfrac{\mathrm{d}v(t)}{\mathrm{d}t} = k e^{-\delta_2\tau_2} y(t-\tau_2) - d_v v(t). \end{cases} \tag{1.1}$$

Here, $x(t)$, $y(t)$, $c(t)$, and $v(t)$ represent the concentrations of uninfected CD4+ T cells, infected CD4+ T cells, inflammatory cytokines, and free virions at time t, respectively. The production rate of uninfected CD4+ T cells is denoted by s. The death rate of infected cells due to pyroptosis is represented by α. The parameters α_1 and k represent the rate of infected cells releasing inflammatory cytokines and the production rate of viruses, respectively. The infection function, denoted by $f(x(t), v(t))v(t)$, describes the infection of uninfected CD4+ T cells by free viruses, while $\beta x(t)c(t)$ denotes cytokine-enhanced viral infection. The survival probability of infected cells is given by $e^{-\delta_1\tau_1}$, where $1/\delta_1$ represents the average lifespan of infected cells. Similarly, the survival probability of immature viral particles is expressed as $e^{-\delta_2\tau_2}$, with $1/\delta_2$ representing the average lifespan of immature viruses. This paper investigated the global dynamics of model (1.1) using the method of Lyapunov functionals.

For quite some time, cell-free infection has been considered the primary mode of HIV transmission. However, recent literature suggests that cell-to-cell transmission may offer certain advantages over cell-free virus infection [10–12]. Inspired by this, we propose a delay model that incorporates both cell-free infection and cell-to-cell transmission, along with cytokine-enhanced viral infection and general incidence rates. The structure of this paper is as follows: Section 2 presents the model and its basic properties. In Section 3, we calculate the basic reproduction number and examine the existence of steady states. The global asymptotic stability of the steady states is given in Section 4. Finally, we provide a brief summary.

2. The model and basic properties

Motivated by the above discussion and model (1.1), we formulate the following delay model including both cell-free infection and cell-to-cell transmission, as well as cytokine-enhanced viral infection and general incidence rates:

$$
\begin{cases}
\dfrac{\mathrm{d}T(t)}{\mathrm{d}t} = s - \varphi(T(t), V(t)) - \psi(T(t), I(t)) - f(T(t), C(t)) - d_T T(t), \\
\dfrac{\mathrm{d}I(t)}{\mathrm{d}t} = e^{-\delta_1\tau_1}[\varphi(T(t-\tau_1), V(t-\tau_1)) + \psi(T(t-\tau_1), I(t-\tau_1)) + f(T(t-\tau_1), C(t-\tau_1))] \\
\qquad\quad - (\alpha + d_I)I(t), \\
\dfrac{\mathrm{d}C(t)}{\mathrm{d}t} = \alpha_1 I(t) - d_C C(t), \\
\dfrac{\mathrm{d}V(t)}{\mathrm{d}t} = k e^{-\delta_2\tau_2} I(t-\tau_2) - d_V V(t),
\end{cases}
\tag{2.1}
$$

where $T(t)$, $I(t)$, $C(t)$, and $V(t)$ are the concentrations of uninfected CD4+ T cells, infected CD4+ T cells, inflammatory cytokines, and free virions at time t, respectively. The general infection functions $\varphi(T(t), V(t))$, $\psi(T(t), I(t))$, and $f(T(t), C(t))$ represent the infection of uninfected CD4+ T cells by free viruses, infected CD4+ T cells, and enhanced infection by inflammatory cytokines, respectively. The parameters d_T, d_I, d_C, and d_V denote the natural mortality rates of uninfected CD4+ T cells, infected CD4+ T cells, inflammatory cytokines, and viruses, respectively. The parameter τ_1 represents the time between viruses entering cells and producing new viral particles, while τ_2 denotes the time it takes for a newly produced virion to mature until it becomes infectious [13]. The biological meanings of the remaining parameters remain consistent with those of model (1.1).

We let $C([-\tau, 0], \mathbb{R}_+^4)$ be the Banach space of continuous functions mapping $[-\tau, 0]$ into $\mathbb{R}_+^4$, and $\phi = (\phi_1(\theta), \phi_2(\theta), \phi_3(\theta), \phi_4(\theta)) \in C([-\tau, 0], \mathbb{R}_+^4)$ [14]. Then the initial conditions for model (2.1) are given by

$$
\begin{aligned}
&T(0) = \phi_1(0) > 0,\ I(0) = \phi_2(0) > 0,\ C(0) = \phi_3(0) > 0,\ V(0) = \phi_4(0) > 0, \\
&T(\theta) = \phi_1(\theta),\ I(\theta) = \phi_2(\theta),\ C(\theta) = \phi_3(\theta),\ V(\theta) = \phi_4(\theta),\ \ \phi_i(\theta) \geq 0 \text{ for } \theta \in [-\tau, 0),
\end{aligned}
\tag{2.2}
$$

where $i = 1, 2, 3, 4$ and $\tau = \max\{\tau_1, \tau_2\}$.

According to [15–18], we assume the following for the general incidence functions in model (2.1).

(A1) $\varphi(T, V)$, $\psi(T, I)$, and $f(T, C)$ are differentiable with $\frac{\partial\varphi(T,V)}{\partial T} > 0$, $\frac{\partial\psi(T,I)}{\partial T} > 0$, $\frac{\partial f(T,C)}{\partial T} > 0$ for $T, I, C, V > 0$, and $\frac{\partial\varphi(T,V)}{\partial V} > 0$, $\frac{\partial\psi(T,I)}{\partial I} > 0$, $\frac{\partial f(T,C)}{\partial C} > 0$ for $T > 0$, $I, C, V \geq 0$. Furthermore, $\varphi(T, 0) = \varphi(0, V) = \psi(T, 0) = \psi(0, I) = f(T, 0) = f(0, C) = 0$ for all $T, I, C, V \in \mathbb{R}_+$.

(A2) $\frac{\partial\varphi(T,V)}{\partial V}$, $\frac{\partial\psi(T,I)}{\partial I}$, and $\frac{\partial f(T,C)}{\partial C}$ are all continuous at point $\left(\frac{s}{d_T}, 0\right)$. Moreover, $\frac{\partial^2\varphi(T,V)}{\partial V^2} \leq 0$, $\frac{\partial^2\psi(T,I)}{\partial I^2} \leq 0$, and $\frac{\partial^2 f(T,C)}{\partial C^2} \leq 0$ for all $T, I, C, V > 0$.

From assumption (**A1**), we know $\varphi(T, V) > 0$, $\psi(T, I) > 0$, and $f(T, C) > 0$ for $T, I, C, V \in (0, \infty)$. Under assumptions (**A1**) and (**A2**), we can obtain

$$
\begin{aligned}
&\frac{\partial\varphi(T, V)}{\partial V} V \leq \varphi(T, V) \leq \frac{\partial\varphi(T, 0)}{\partial V} V \ \text{ for any } T, V \in \mathbb{R}_+, \\
&\frac{\partial\psi(T, I)}{\partial I} I \leq \psi(T, I) \leq \frac{\partial\psi(T, 0)}{\partial I} I \ \text{ for any } T, I \in \mathbb{R}_+, \\
&\frac{\partial f(T, C)}{\partial C} C \leq f(T, C) \leq \frac{\partial f(T, 0)}{\partial C} C \ \text{ for any } T, C \in \mathbb{R}_+.
\end{aligned}
\tag{2.3}
$$

(A3) If $(T_\star, I_\star, C_\star, V_\star)$ is the positive steady state of model (2.1), then for $T, I, C, V > 0$,

$$
\begin{cases}
\dfrac{V}{V_\star} \leq \dfrac{T_\star\varphi(T, V)}{T\varphi(T_\star, V_\star)} \leq 1, \ \ 0 < V \leq V_\star, \\
1 \leq \dfrac{T_\star\varphi(T, V)}{T\varphi(T_\star, V_\star)} \leq \dfrac{V}{V_\star}, \ \ 0 < V_\star \leq V,
\end{cases}
$$

$$
\begin{cases}
\dfrac{I}{I_\star} \le \dfrac{T_\star \psi(T,I)}{T\psi(T_\star, I_\star)} \le 1, & 0 < I \le I_\star, \\
1 \le \dfrac{T_\star \psi(T,I)}{T\psi(T_\star, I_\star)} \le \dfrac{I}{I_\star}, & 0 < I_\star \le I,
\end{cases}
$$

$$
\begin{cases}
\dfrac{C}{C_\star} \le \dfrac{T_\star f(T,C)}{T f(T_\star, C_\star)} \le 1, & 0 < C \le C_\star, \\
1 \le \dfrac{T_\star f(T,C)}{T f(T_\star, C_\star)} \le \dfrac{C}{C_\star}, & 0 < C_\star \le C.
\end{cases}
$$

We can verify that the general functions satisfying assumptions (**A1**)–(**A3**) generalize many common forms, such as $\frac{\beta TI}{1+aI}$ (Holling Type II functional response [19]), $\frac{\beta TV}{1+aT+bV}$ (Beddington-DeAngelis functional response [20]), and $\frac{\beta TC}{1+aT+bC+abTC}$ (Crowley-Martin functional response [21]), among others.

The following result shows that the solution $(T(t), I(t), C(t), V(t))$ of model (2.1) with the initial condition (2.2) remains non-negative and ultimately bounded.

Theorem 2.1. *Let* $(T(t), I(t), C(t), V(t))$ *be a solution of model* (2.1) *with the initial condition* (2.2). *It is positive and ultimately bounded for* $t > 0$.

Proof. We first show that $T(t) > 0$ for all $t > 0$. Assume that there exists a $t_1 > 0$ such that $T(t_1) = 0$, $T(t) > 0$, $t \in [0, t_1)$. Thus, $\frac{\mathrm{d}T(t_1)}{\mathrm{d}t} \le 0$. From the first equation of model (2.1), we have $\frac{\mathrm{d}T(t_1)}{\mathrm{d}t} = s > 0$, which is a contradiction. This implies that $T(t) > 0$ for all $t > 0$.

Next, we prove that $I(t) > 0$ for all $t > 0$. Assume that there exists a $t_2 > 0$ such that $I(t_2) = 0$, $I(t) > 0$, $t \in [0, t_2)$. Thus, $\frac{\mathrm{d}I(t_2)}{\mathrm{d}t} \le 0$. From the second equation of model (2.1), we have

$$
\frac{\mathrm{d}I(t_2)}{\mathrm{d}t} = e^{-\delta_1 \tau_1}[\varphi(T(t_2-\tau_1), V(t_2-\tau_1)) + \psi(T(t_2-\tau_1), I(t_2-\tau_1)) + f(T(t_2-\tau_1), C(t_2-\tau_1))].
$$

Since $t_2 - \tau_1 < t_2$, we get $I(t_2 - \tau_1) > 0$. Furthermore, we have $\psi(T(t_2-\tau_1), I(t_2-\tau_1)) > 0$. Hence, $\frac{\mathrm{d}I(t_2)}{\mathrm{d}t} > 0$, which is a contradiction. This implies that $I(t) > 0$ for all $t > 0$. Similarly, we can find a $t_3 > 0$ such that $V(t_3) = 0$, $V(t) > 0$, $t \in [0, t_3)$. Thus, $\frac{\mathrm{d}V(t_3)}{\mathrm{d}t} \le 0$. From the last equation of model (2.1), we have $\frac{\mathrm{d}V(t_3)}{\mathrm{d}t} = ke^{-\delta_2\tau_2} I(t_3 - \tau_2) > 0$, which is a contradiction. This implies that $V(t) > 0$ for all $t > 0$.

By the third equation of model (2.1), we have

$$
C(t) = C(0)e^{-d_C t} + \int_0^t \alpha_1 I(\xi) e^{-d_C(t-\xi)} \mathrm{d}\xi > 0.
$$

To sum up, we have shown that $T(t) > 0$, $I(t) > 0$, $C(t) > 0$, and $V(t) > 0$ for all $t > 0$.

From the positivity of the solution and the first equation of model (2.1), we obtain

$$
\frac{\mathrm{d}T(t)}{\mathrm{d}t} \le s - d_T T(t),
$$

which yields that $\limsup_{t\to\infty} T(t) \le \dfrac{s}{d_T}$.

Denote

$$
N(t) = T(t) + e^{\delta_1 \tau_1} I(t + \tau_1).
$$

It follows from the first two equations of model (2.1) that

$$\frac{\mathrm{d}N(t)}{\mathrm{d}t} = s - d_T T(t) - (\alpha + d_I)e^{\delta_1\tau_1} I(t+\tau_1) \le s - \mu N(t),$$

where $\mu = \min\{d_T, \alpha + d_I\}$. This yields $\limsup_{t\to\infty} N(t) \le \frac{s}{\mu}$. Thus, $\limsup_{t\to\infty} I(t) \le \frac{s}{\mu} e^{-\delta_1\tau_1}$.

By the third equation of $C(t)$ in model (2.1), we get

$$\frac{\mathrm{d}C(t)}{\mathrm{d}t} \le \alpha_1 \frac{s}{\mu} e^{-\delta_1\tau_1} - d_C C(t),$$

which yields $\limsup_{t\to\infty} C(t) \le \frac{\alpha_1 s e^{-\delta_1\tau_1}}{\mu d_C}$. Similarly, by the last equation of $V(t)$ in model (2.1), we get

$$\frac{\mathrm{d}V(t)}{\mathrm{d}t} \le k e^{-\delta_2\tau_2} \frac{s}{\mu} e^{-\delta_1\tau_1} - d_V V(t),$$

which implies that $\limsup_{t\to\infty} V(t) \le \frac{k s e^{-\delta_1\tau_1 - \delta_2\tau_2}}{\mu d_V}$.

Therefore, $T(t)$, $I(t)$, $C(t)$, and $V(t)$ are ultimately uniformly bounded. □

3. Existence and local stability of steady states

3.1. Existence of steady states

Model (2.1) always has an infection-free steady state $E_0 = (T_0, 0, 0, 0)$, where $T_0 = \frac{s}{d_T}$. Inspired by the method of [22], we define the new infection and transfer matrices $\mathbb{F}$ and $\mathbb{V}$ by

$$\mathbb{F} = \begin{pmatrix} e^{-\delta_1\tau_1}\frac{\partial\psi(T_0,0)}{\partial I} & e^{-\delta_1\tau_1}\frac{\partial f(T_0,0)}{\partial C} & e^{-\delta_1\tau_1}\frac{\partial\varphi(T_0,0)}{\partial V} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}$$

and

$$\mathbb{V} = \begin{pmatrix} \alpha + d_I & 0 & 0 \\ -\alpha_1 & d_C & 0 \\ -k e^{-\delta_2\tau_2} & 0 & d_V \end{pmatrix}.$$

The basic reproduction number R_0 is defined as the spectral radius of the next generation operator $\mathbb{F}\mathbb{V}^{-1}$, that is,

$$R_0 = \rho(\mathbb{F}\mathbb{V}^{-1}) = R_1 + R_2 + R_3, \tag{3.1}$$

where

$$R_1 = \frac{e^{-\delta_1\tau_1}}{\alpha + d_I}\frac{\partial\psi(T_0,0)}{\partial I}, \quad R_2 = \frac{\alpha_1 e^{-\delta_1\tau_1}}{d_C(\alpha + d_I)}\frac{\partial f(T_0,0)}{\partial C}, \quad R_3 = \frac{k e^{-(\delta_1\tau_1+\delta_2\tau_2)}}{d_V(\alpha + d_I)}\frac{\partial\varphi(T_0,0)}{\partial V}. \tag{3.2}$$

Let $E_\star = (T_\star, I_\star, C_\star, V_\star)$ be an infected steady state of model (2.1), which satisfies

$$\begin{cases} s - \varphi(T_\star, V_\star) - \psi(T_\star, I_\star) - f(T_\star, C_\star) - d_T T_\star = 0, \\ e^{-\delta_1\tau_1}(\varphi(T_\star, V_\star) + \psi(T_\star, I_\star) + f(T_\star, C_\star)) - (\alpha + d_I)I_\star = 0, \\ \alpha_1 I_\star - d_C C_\star = 0, \\ k e^{-\delta_2\tau_2} I_\star - d_V V_\star = 0. \end{cases} \tag{3.3}$$

Solving (3.3) gives

$$T_\star = \frac{s - e^{\delta_1\tau_1}(\alpha + d_I)I_\star}{d_T}, \;\; C_\star = \frac{\alpha_1 I_\star}{d_C}, \;\; V_\star = \frac{ke^{-\delta_2\tau_2}I_\star}{d_V}. \tag{3.4}$$

It can be seen from the second equation of (3.3) that $I_\star$ is a positive root of $F(x) = 0$, where

$$\begin{aligned} F(x) =&\varphi\left(\frac{s - e^{\delta_1\tau_1}(\alpha + d_I)x}{d_T}, \frac{ke^{-\delta_2\tau_2}x}{d_V}\right) + \psi\left(\frac{s - e^{\delta_1\tau_1}(\alpha + d_I)x}{d_T}, x\right) + f\left(\frac{s - e^{\delta_1\tau_1}(\alpha + d_I)x}{d_T}, \frac{\alpha_1 x}{d_C}\right) \\ &- e^{\delta_1\tau_1}(\alpha + d_I)x. \end{aligned} \tag{3.5}$$

First, we assume $R_0 \le 1$. By (2.3) and (3.5), for any $x > 0$, we have

$$\begin{aligned} F(x) \le&\left(\frac{\partial\varphi(T_0, 0)}{\partial V}\frac{ke^{-\delta_2\tau_2}}{d_V} + \frac{\partial\psi(T_0, 0)}{\partial I} + \frac{\partial f(T_0, 0)}{\partial C}\frac{\alpha_1}{d_C} - e^{\delta_1\tau_1}(\alpha + d_I)\right)x \\ =&e^{\delta_1\tau_1}(\alpha + d_I)(R_0 - 1)x \\ \le&0. \end{aligned}$$

Clearly, $F(x) = 0$ has no positive roots and hence there are no infected steady states when $R_0 \le 1$.

Second, we assume $R_0 > 1$. It is clear that $F(0) = 0$ and

$$\begin{aligned} F'(0) =&\frac{\partial\varphi(T_0, 0)}{\partial V}\frac{ke^{-\delta_2\tau_2}}{d_V} + \frac{\partial\psi(T_0, 0)}{\partial I} + \frac{\partial f(T_0, 0)}{\partial C}\frac{\alpha_1}{d_C} - e^{\delta_1\tau_1}(\alpha + d_I) \\ =&e^{\delta_1\tau_1}(\alpha + d_I)\left(\frac{\partial\varphi(T_0, 0)}{\partial V}\frac{ke^{(-\delta_1\tau_1-\delta_2\tau_2)}}{d_V(\alpha + d_I)} + \frac{\partial\psi(T_0, 0)}{\partial I}\frac{e^{-\delta_1\tau_1}}{\alpha + d_I} + \frac{\partial f(T_0, 0)}{\partial C}\frac{\alpha_1 e^{-\delta_1\tau_1}}{d_C(\alpha + d_I)} - 1\right) \\ =&e^{\delta_1\tau_1}(\alpha + d_I)(R_0 - 1) \\ >&0. \end{aligned}$$

This, combined with the intermediate value theorem and $F\left(\frac{s}{e^{\delta_1\tau_1}(\alpha+d_I)}\right) = -s < 0$, implies that there exists $I_\star \in \left(0, \frac{s}{e^{\delta_1\tau_1}(\alpha+d_I)}\right)$ such that $F(I_\star) = 0$. That is, model (2.1) has at least one infected steady state.

Next, we will show that infected steady states are unique. Otherwise, suppose that there exist two infected steady states, say $E_{1\star} = (T_{1\star}, I_{1\star}, C_{1\star}, V_{1\star})$ and $E_{2\star} = (T_{2\star}, I_{2\star}, C_{2\star}, V_{2\star})$. Without loss of generality, we assume that $I_{2\star} > I_{1\star}$. It follows from (3.4) that

$$T_{1\star} = \frac{s - e^{\delta_1\tau_1}(\alpha + d_I)I_{1\star}}{d_T} > \frac{s - e^{\delta_1\tau_1}(\alpha + d_I)I_{2\star}}{d_T} = T_{2\star}. \tag{3.6}$$

Setting $m = \frac{I_{2\star}}{I_{1\star}}(> 1)$ and by (3.4), we have

$$V_{1\star} = \frac{ke^{-\delta_2\tau_2}I_{1\star}}{d_V} = \frac{ke^{-\delta_2\tau_2}\frac{1}{m}I_{2\star}}{d_V} = \frac{1}{m}V_{2\star}, \;\; C_{1\star} = \frac{\alpha_1 I_{1\star}}{d_C} = \frac{\alpha_1\frac{1}{m}I_{2\star}}{d_C} = \frac{1}{m}C_{2\star}. \tag{3.7}$$

It follows from (**A1**), (**A2**), (3.6), and (3.7) that we get

$$\begin{aligned} &\varphi(T_{1\star}, V_{1\star}) > \varphi(T_{2\star}, V_{1\star}) = \varphi\left(T_{2\star}, \frac{1}{m}V_{2\star}\right) > \varphi\left(\frac{1}{m}T_{2\star}, \frac{1}{m}V_{2\star}\right) \ge \frac{1}{m}\varphi(T_{2\star}, V_{2\star}), \\ &\psi(T_{1\star}, I_{1\star}) > \psi(T_{2\star}, I_{1\star}) = \psi\left(T_{2\star}, \frac{1}{m}I_{2\star}\right) > \psi\left(\frac{1}{m}T_{2\star}, \frac{1}{m}I_{2\star}\right) \ge \frac{1}{m}\psi(T_{2\star}, I_{2\star}), \\ &f(T_{1\star}, C_{1\star}) > f(T_{2\star}, C_{1\star}) = f\left(T_{2\star}, \frac{1}{m}C_{2\star}\right) > f\left(\frac{1}{m}T_{2\star}, \frac{1}{m}C_{2\star}\right) \ge \frac{1}{m}f(T_{2\star}, C_{2\star}). \end{aligned} \tag{3.8}$$

It follows from the second equation of (3.3) and (3.8) that

$$\begin{aligned} I_{1\star} &= \frac{\varphi(T_{1\star}, V_{1\star}) + \psi(T_{1\star}, I_{1\star}) + f(T_{1\star}, C_{1\star})}{\alpha + d_I} e^{-\delta_1\tau_1} \\ &> \frac{\frac{1}{m}(\varphi(T_{2\star}, V_{2\star}) + \psi(T_{2\star}, I_{2\star}) + f(T_{2\star}, C_{2\star}))}{\alpha + d_I} e^{-\delta_1\tau_1} \\ &= \frac{1}{m} I_{2\star}, \end{aligned}$$

which is a contradiction to $I_{1\star} = \frac{1}{m} I_{2\star}$. This proves the uniqueness of the infected steady states.

We summarize our results on the existence of the steady states in the following theorem.

Theorem 3.1. (i) *If* $R_0 \le 1$, *then model* (2.1) *has only the infection-free steady state* $E_0 = \left(\frac{s}{d_T}, 0, 0, 0\right)$. (ii) *If* $R_0 > 1$, *then besides the infection-free steady state* E_0, *model* (2.1) *has an infected steady state* $E_\star = (T_\star, I_\star, C_\star, V_\star) = \left(\frac{s - e^{\delta_1\tau_1}(\alpha + d_I)I_\star}{d_T}, I_\star, \frac{\alpha_1 I_\star}{d_C}, \frac{ke^{-\delta_2\tau_2} I_\star}{d_V}\right)$, *where* $I_\star$ *is the unique positive root of* $F(x) = 0$ *defined by* (3.5) *in the interval* $\left(0, \frac{s}{e^{\delta_1\tau_1}(\alpha + d_I)}\right)$.

3.2. Local stability of steady states

Let $\overline{E} = (\overline{T}, \overline{I}, \overline{C}, \overline{V})$ be a steady state of model (2.1). Linearizing model (2.1) at $\overline{E}$ leads to

$$\begin{cases} \dfrac{\mathrm{d}T(t)}{\mathrm{d}t} = -\left(d_T + \dfrac{\partial\varphi(\overline{T}, \overline{V})}{\partial T} + \dfrac{\partial\psi(\overline{T}, \overline{I})}{\partial T} + \dfrac{\partial f(\overline{T}, \overline{C})}{\partial T}\right) T(t) - \dfrac{\partial\varphi(\overline{T}, \overline{V})}{\partial V} V(t) \\ \qquad - \dfrac{\partial\psi(\overline{T}, \overline{I})}{\partial I} I(t) - \dfrac{\partial f(\overline{T}, \overline{C})}{\partial C} C(t), \\ \dfrac{\mathrm{d}I(t)}{\mathrm{d}t} = -(\alpha + d_I) I(t) + \left(\dfrac{\partial\varphi(\overline{T}, \overline{V})}{\partial T} + \dfrac{\partial\psi(\overline{T}, \overline{I})}{\partial T} + \dfrac{\partial f(\overline{T}, \overline{C})}{\partial T}\right) T(t - \tau_1) e^{-\delta_1\tau_1} \\ \qquad + \dfrac{\partial\varphi(\overline{T}, \overline{V})}{\partial V} V(t - \tau_1) e^{-\delta_1\tau_1} + \dfrac{\partial\psi(\overline{T}, \overline{I})}{\partial I} I(t - \tau_1) e^{-\delta_1\tau_1} + \dfrac{\partial f(\overline{T}, \overline{C})}{\partial C} C(t - \tau_1) e^{-\delta_1\tau_1}, \\ \dfrac{\mathrm{d}C(t)}{\mathrm{d}t} = \alpha_1 I(t) - d_C C(t), \\ \dfrac{\mathrm{d}V(t)}{\mathrm{d}t} = k e^{-\delta_2\tau_2} I(t - \tau_2) - d_V V(t). \end{cases} \tag{3.9}$$

The characteristic equation of (3.9) at $\overline{E}$ is

$$\Delta_{\overline{E}}(\lambda) = \begin{vmatrix} \lambda + d_T + \Lambda & \dfrac{\partial\psi(\overline{T}, \overline{I})}{\partial I} & \dfrac{\partial f(\overline{T}, \overline{C})}{\partial C} & \dfrac{\partial\varphi(\overline{T}, \overline{V})}{\partial V} \\ -\Lambda e^{-(\lambda+\delta_1)\tau_1} & \lambda + \alpha + d_I - \dfrac{\partial\psi(\overline{T}, \overline{I})}{\partial I} e^{-(\lambda+\delta_1)\tau_1} & -\dfrac{\partial f(\overline{T}, \overline{C})}{\partial C} e^{-(\lambda+\delta_1)\tau_1} & -\dfrac{\partial\varphi(\overline{T}, \overline{V})}{\partial V} e^{-(\lambda+\delta_1)\tau_1} \\ 0 & -\alpha_1 & \lambda + d_C & 0 \\ 0 & -k e^{-(\lambda+\delta_2)\tau_2} & 0 & \lambda + d_V \end{vmatrix} = 0,$$

where

$$\Lambda = \frac{\partial\varphi(\overline{T}, \overline{V})}{\partial T} + \frac{\partial\psi(\overline{T}, \overline{I})}{\partial T} + \frac{\partial f(\overline{T}, \overline{C})}{\partial T}.$$

Theorem 3.2. (i) *If* $R_0 < 1$*, the infection-free steady state* E_0 *of model* (2.1) *is locally asymptotically stable. Otherwise, it is unstable if* $R_0 > 1$.
(ii) *If* $R_0 > 1$*, the infected steady state* $E_\star$ *of model* (2.1) *is locally asymptotically stable.*

Proof. (i) Note that

$$\frac{\partial\varphi(T_0,0)}{\partial T} = \frac{\partial\psi(T_0,0)}{\partial T} = \frac{\partial f(T_0,0)}{\partial T} = 0.$$

The characteristic equation at the infection-free steady state E_0 is

$$\Delta_{E_0}(\lambda) = (\lambda + d_T)h(\lambda) = 0,$$

where

$$\begin{aligned} h(\lambda) =&(\lambda + d_V)(\lambda + \alpha + d_I)(\lambda + d_C) - (\lambda + d_V)(\lambda + d_C)\frac{\partial\psi(T_0,0)}{\partial I}e^{-(\lambda+\delta_1)\tau_1} \\ &- \alpha_1(\lambda + d_V)\frac{\partial f(T_0,0)}{\partial C}e^{-(\lambda+\delta_1)\tau_1} - k(\lambda + d_C)\frac{\partial\varphi(T_0,0)}{\partial V}e^{-\lambda(\tau_1+\tau_2)-\delta_1\tau_1-\delta_2\tau_2}. \end{aligned}$$

It is clear that the stability of E_0 is determined by the roots of $h(\lambda) = 0$.

If $R_0 > 1$, then $h(0) = d_V d_C(\alpha + d_I)(1 - R_0) < 0$. Note that $\lim\limits_{\lambda\to+\infty} h(\lambda) = +\infty$. By the intermediate value theorem, we know that $h(\lambda) = 0$ admits one positive root, and hence E_0 is unstable.

If $R_0 < 1$, we claim that all roots of $h(\lambda) = 0$ have negative real parts [23]. We will prove by contradiction. If λ_0 is a root with $\mathrm{Re}(\lambda_0) \geq 0$, then from the expression of $h(\lambda)$ we have

$$\begin{aligned} 1 =&\left|\frac{\partial\psi(T_0,0)}{\partial I}\frac{e^{-(\lambda_0+\delta_1)\tau_1}}{\lambda_0 + \alpha + d_I} + \frac{\partial f(T_0,0)}{\partial C}\frac{\alpha_1 e^{-(\lambda_0+\delta_1)\tau_1}}{(\lambda_0 + \alpha + d_I)(\lambda_0 + d_C)}\right. \\ &\left.+\frac{\partial\varphi(T_0,0)}{\partial V}\frac{ke^{-\lambda_0(\tau_1+\tau_2)-\delta_1\tau_1-\delta_2\tau_2}}{(\lambda_0 + d_V)(\lambda_0 + \alpha + d_I)}\right| \\ \leq&\left|\frac{\partial\psi(T_0,0)}{\partial I}\frac{e^{-(\lambda_0+\delta_1)\tau_1}}{\lambda_0 + \alpha + d_I}\right| + \left|\frac{\partial f(T_0,0)}{\partial C}\frac{\alpha_1 e^{-(\lambda_0+\delta_1)\tau_1}}{(\lambda_0 + \alpha + d_I)(\lambda_0 + d_C)}\right| \\ &+\left|\frac{\partial\varphi(T_0,0)}{\partial V}\frac{ke^{-\lambda_0(\tau_1+\tau_2)-\delta_1\tau_1-\delta_2\tau_2}}{(\lambda_0 + d_V)(\lambda_0 + \alpha + d_I)}\right| \\ \leq&\left|\frac{\partial\psi(T_0,0)}{\partial I}\frac{e^{-(\lambda_0+\delta_1)\tau_1}}{\alpha + d_I}\right| + \left|\frac{\partial f(T_0,0)}{\partial C}\frac{\alpha_1 e^{-(\lambda_0+\delta_1)\tau_1}}{(\alpha + d_I)d_C}\right| + \left|\frac{\partial\varphi(T_0,0)}{\partial V}\frac{ke^{-\lambda_0(\tau_1+\tau_2)-\delta_1\tau_1-\delta_2\tau_2}}{d_V(\alpha + d_I)}\right| \\ \leq&\frac{\partial\psi(T_0,0)}{\partial I}\frac{e^{-\delta_1\tau_1}}{\alpha + d_I} + \frac{\partial f(T_0,0)}{\partial C}\frac{\alpha_1 e^{-\delta_1\tau_1}}{(\alpha + d_I)d_C} + \frac{\partial\varphi(T_0,0)}{\partial V}\frac{ke^{-\delta_1\tau_1-\delta_2\tau_2}}{d_V(\alpha + d_I)} \\ =&R_0, \end{aligned}$$

which leads to a contradiction. This proves the claim and hence E_0 is locally asymptotically stable if $R_0 < 1$.

(ii) If $R_0 > 1$, the characteristic equation at the infected steady state $E_\star$ is

$$
\begin{aligned}
&(\lambda + d_T + \Lambda_\star)(\lambda + d_V)(\lambda + \alpha + d_I)(\lambda + d_C)\\
=&(\lambda + d_T)(\lambda + d_V)(\lambda + d_C)\frac{\partial\psi(T_\star, I_\star)}{\partial I}e^{-(\lambda+\delta_1)\tau_1}\\
&+ \alpha_1(\lambda + d_T)(\lambda + d_V)\frac{\partial f(T_\star, C_\star)}{\partial C}e^{-(\lambda+\delta_1)\tau_1}\\
&+ k(\lambda + d_T)(\lambda + d_C)\frac{\partial\varphi(T_\star, V_\star)}{\partial V}e^{-\lambda(\tau_1+\tau_2)-\delta_1\tau_1-\delta_2\tau_2},
\end{aligned}
\tag{3.10}
$$

where $\Lambda_\star = \dfrac{\partial\varphi(T_\star, V_\star)}{\partial T} + \dfrac{\partial f(T_\star, C_\star)}{\partial T} + \dfrac{\partial\psi(T_\star, I_\star)}{\partial T} > 0$. We now prove that all roots of (3.10) have negative real parts. If λ_1 is an eigenvalue with a nonnegative real part, we have

$$
\begin{aligned}
1 =&\left|\frac{(\lambda_1 + d_T)\frac{\partial\psi(T_\star, I_\star)}{\partial I}e^{-(\lambda_1+\delta_1)\tau_1}}{(\lambda_1 + d_T + \Lambda_\star)(\lambda_1 + \alpha + d_I)} + \frac{\alpha_1(\lambda_1 + d_T)\frac{\partial f(T_\star, C_\star)}{\partial C}e^{-(\lambda_1+\delta_1)\tau_1}}{(\lambda_1 + d_T + \Lambda_\star)(\lambda_1 + \alpha + d_I)(\lambda_1 + d_C)}\right.\\
&\left.+\frac{k(\lambda_1 + d_T)\frac{\partial\varphi(T_\star, V_\star)}{\partial V}e^{-\lambda_1(\tau_1+\tau_2)-\delta_1\tau_1-\delta_2\tau_2}}{(\lambda_1 + d_V)(\lambda_1 + d_T + \Lambda_\star)(\lambda_1 + \alpha + d_I)}\right|\\
\le&\left|\frac{(\lambda_1 + d_T)\frac{\partial\psi(T_\star, I_\star)}{\partial I}e^{-(\lambda_1+\delta_1)\tau_1}}{(\lambda_1 + d_T + \Lambda_\star)(\lambda_1 + \alpha + d_I)}\right| + \left|\frac{\alpha_1(\lambda_1 + d_T)\frac{\partial f(T_\star, C_\star)}{\partial C}e^{-(\lambda_1+\delta_1)\tau_1}}{(\lambda_1 + d_T + \Lambda_\star)(\lambda_1 + \alpha + d_I)(\lambda_1 + d_C)}\right|\\
&+\left|\frac{k(\lambda_1 + d_T)\frac{\partial\varphi(T_\star, V_\star)}{\partial V}e^{-\lambda_1(\tau_1+\tau_2)-\delta_1\tau_1-\delta_2\tau_2}}{(\lambda_1 + d_V)(\lambda_1 + d_T + \Lambda_\star)(\lambda_1 + \alpha + d_I)}\right|\\
<&\left|\frac{\frac{\partial\psi(T_\star, I_\star)}{\partial I}e^{-(\lambda_1+\delta_1)\tau_1}}{\lambda_1 + \alpha + d_I}\right| + \left|\frac{\alpha_1\frac{\partial f(T_\star, C_\star)}{\partial C}e^{-(\lambda_1+\delta_1)\tau_1}}{(\lambda_1 + \alpha + d_I)(\lambda_1 + d_C)}\right| + \left|\frac{k\frac{\partial\varphi(T_\star, V_\star)}{\partial V}e^{-\lambda_1(\tau_1+\tau_2)-\delta_1\tau_1-\delta_2\tau_2}}{(\lambda_1 + d_V)(\lambda_1 + \alpha + d_I)}\right|\\
\le&\frac{\partial\psi(T_\star, I_\star)}{\partial I}\frac{e^{-\delta_1\tau_1}}{\alpha + d_I} + \frac{\partial f(T_\star, C_\star)}{\partial C}\frac{\alpha_1 e^{-\delta_1\tau_1}}{d_C(\alpha + d_I)} + \frac{\partial\varphi(T_\star, V_\star)}{\partial V}\frac{ke^{-\delta_1\tau_1-\delta_2\tau_2}}{d_V(\alpha + d_I)}.
\end{aligned}
\tag{3.11}
$$

From (2.3) and (3.4), we have

$$
\begin{aligned}
&\frac{\partial\psi(T_\star, I_\star)}{\partial I}\frac{e^{-\delta_1\tau_1}}{\alpha + d_I} + \frac{\partial f(T_\star, C_\star)}{\partial C}\frac{\alpha_1 e^{-\delta_1\tau_1}}{d_C(\alpha + d_I)} + \frac{\partial\varphi(T_\star, V_\star)}{\partial V}\frac{ke^{-\delta_1\tau_1-\delta_2\tau_2}}{d_V(\alpha + d_I)}\\
\le&\frac{\psi(T_\star, I_\star)e^{-\delta_1\tau_1}}{(\alpha + d_I)I_\star} + \frac{\alpha_1 f(T_\star, C_\star)e^{-\delta_1\tau_1}}{d_C(\alpha + d_I)C_\star} + \frac{k\varphi(T_\star, V_\star)e^{-\delta_1\tau_1-\delta_2\tau_2}}{d_V(\alpha + d_I)V_\star}\\
=&\frac{\psi(T_\star, I_\star)e^{-\delta_1\tau_1}}{(\alpha + d_I)I_\star} + \frac{f(T_\star, C_\star)e^{-\delta_1\tau_1}}{(\alpha + d_I)I_\star} + \frac{\varphi(T_\star, V_\star)e^{-\delta_1\tau_1}}{(\alpha + d_I)I_\star}\\
=&1,
\end{aligned}
$$

which contradicts with (3.11). This completes the proof. □

4. Global stability of steady states

Theorem 4.1. *When $R_0 < 1$, the infection-free steady state E_0 of model* (2.1) *is globally asymptotically stable.*

Proof. We define a Lyapunov function as follows:

$$\begin{aligned}L_1(t) =& I(t) + \frac{(\alpha+d_I)R_2}{\alpha_1 R_0}C(t) + \frac{(\alpha+d_I)R_3}{ke^{-\delta_2\tau_2}R_0}V(t) + e^{-\delta_1\tau_1}\int_{t-\tau_1}^{t}\psi(T(s),I(s))\mathrm{d}s \\ &+ e^{-\delta_1\tau_1}\int_{t-\tau_1}^{t}\varphi(T(s),V(s))\mathrm{d}s + e^{-\delta_1\tau_1}\int_{t-\tau_1}^{t}f(T(s),C(s))\mathrm{d}s + \frac{(\alpha+d_I)R_3}{R_0}\int_{t-\tau_2}^{t}I(s)\mathrm{d}s.\end{aligned}$$

Calculating the derivative of $L_1(t)$ with respect to t along the solution of model (2.1) obtains

$$\begin{aligned}\frac{\mathrm{d}L_1(t)}{\mathrm{d}t} =& e^{-\delta_1\tau_1}[\varphi(T(t-\tau_1),V(t-\tau_1)) + \psi(T(t-\tau_1),I(t-\tau_1)) + f(T(t-\tau_1),C(t-\tau_1))] \\ &- (\alpha+d_I)I(t) + \frac{(\alpha+d_I)R_2}{\alpha_1 R_0}(\alpha_1 I(t) - d_C C(t)) + \frac{(\alpha+d_I)R_3}{ke^{-\delta_2\tau_2}R_0}(ke^{-\delta_2\tau_2}I(t-\tau_2) \\ &- d_V V(t)) + e^{-\delta_1\tau_1}\psi(T(t),I(t)) + e^{-\delta_1\tau_1}\varphi(T(t),V(t)) + e^{-\delta_1\tau_1}f(T(t),C(t)) \\ &- e^{-\delta_1\tau_1}\psi(T(t-\tau_1),I(t-\tau_1)) - e^{-\delta_1\tau_1}\varphi(T(t-\tau_1),V(t-\tau_1)) \\ &- e^{-\delta_1\tau_1}f(T(t-\tau_1),C(t-\tau_1)) + \frac{(\alpha+d_I)R_3}{R_0}(I(t) - I(t-\tau_2)) \\ =& e^{-\delta_1\tau_1}\varphi(T(t),V(t)) + e^{-\delta_1\tau_1}\psi(T(t),I(t)) + e^{-\delta_1\tau_1}f(T(t),C(t)) - \frac{(\alpha+d_I)d_C R_2}{\alpha_1 R_0}C(t) \\ &- \frac{(\alpha+d_I)d_V R_3}{ke^{-\delta_2\tau_2}R_0}V(t) - (\alpha+d_I)I(t) + \frac{(\alpha+d_I)R_2}{R_0}I(t) + \frac{(\alpha+d_I)R_3}{R_0}I(t) \\ =& e^{-\delta_1\tau_1}\varphi(T(t),V(t))\left(1 - \frac{(\alpha+d_I)d_V e^{\delta_1\tau_1+\delta_2\tau_2}R_3}{kR_0}\frac{V(t)}{\varphi(T(t),V(t))}\right) \\ &+ e^{-\delta_1\tau_1}\psi(T(t),I(t))\left(1 - \frac{(\alpha+d_I)e^{\delta_1\tau_1}R_1}{R_0}\frac{I(t)}{\psi(T(t),I(t))}\right) \\ &+ e^{-\delta_1\tau_1}f(T(t),C(t))\left(1 - \frac{(\alpha+d_I)d_C e^{\delta_1\tau_1}R_2}{\alpha_1 R_0}\frac{C(t)}{f(T(t),C(t))}\right).\end{aligned}$$

It follows from (**A1**), (**A2**), (3.1), and (3.2) that

$$\begin{aligned}\frac{\mathrm{d}L_1(t)}{\mathrm{d}t} \le& e^{-\delta_1\tau_1}\varphi(T(t),V(t))\left(1 - \frac{(\alpha+d_I)d_V e^{\delta_1\tau_1+\delta_2\tau_2}R_3}{kR_0\dfrac{\partial\varphi(T_0,0)}{\partial V}}\right) + e^{-\delta_1\tau_1}\psi(T(t),I(t))\left(1 - \frac{(\alpha+d_I)e^{\delta_1\tau_1}R_1}{R_0\dfrac{\partial\psi(T_0,0)}{\partial I}}\right) \\ &+ e^{-\delta_1\tau_1}f(T(t),C(t))\left(1 - \frac{(\alpha+d_I)d_C e^{\delta_1\tau_1}R_2}{\alpha_1 R_0\dfrac{\partial f(T_0,0)}{\partial C}}\right) \\ =& e^{-\delta_1\tau_1}\left(1 - \frac{1}{R_0}\right)[\varphi(T(t),V(t)) + \psi(T(t),I(t)) + f(T(t),C(t))].\end{aligned}$$

Thus, $\frac{\mathrm{d}L_1(t)}{\mathrm{d}t} \leq 0$ if $R_0 < 1$ and $\frac{\mathrm{d}L_1(t)}{\mathrm{d}t} = 0$ if and only if $I(t) = C(t) = V(t) = 0$, which implies that $T(t) = T_0$. By the LaSalle invariance principle, we see that $\{E_0\}$ is the largest invariant set in $\left\{\frac{\mathrm{d}L_1(t)}{\mathrm{d}t} = 0\right\}$. Hence, the infection-free steady state E_0 is globally asymptotically stable. □

Theorem 4.2. *When* $R_0 > 1$ *and* **(A1)–(A3)** *are satisfied, the infected steady state* $E_\star$ *of model* (2.1) *is globally asymptotically stable.*

Proof. Let $G(x) = x - 1 - \ln x$ for $x \in (0, \infty)$. Clearly, $G(x) \geq 0$ and $G(x) = 0$ if and only if $x = 1$. We consider a Lyapunov function $L_2(t) = L_{21}(t) + L_{22}(t) + L_{23}(t) + L_{24}(t)$, where

$$\begin{aligned}
L_{21}(t) =& T_\star G\left(\frac{T(t)}{T_\star}\right), \ \ L_{22}(t) = e^{\delta_1\tau_1} I_\star G\left(\frac{I(t)}{I_\star}\right), \ \ L_{23}(t) = \frac{f(T_\star, C_\star)}{d_C} G\left(\frac{C(t)}{C_\star}\right) + \frac{\varphi(T_\star, V_\star)}{d_V} G\left(\frac{V(t)}{V_\star}\right), \\
L_{24}(t) =& \varphi(T_\star, V_\star) \int_{t-\tau_1}^{t} G\left(\frac{\varphi(T(s), V(s))}{\varphi(T_\star, V_\star)}\right) \mathrm{d}s + \psi(T_\star, I_\star) \int_{t-\tau_1}^{t} G\left(\frac{\psi(T(s), I(s))}{\psi(T_\star, I_\star)}\right) \mathrm{d}s \\
&+ f(T_\star, C_\star) \int_{t-\tau_1}^{t} G\left(\frac{f(T(s), C(s))}{f(T_\star, C_\star)}\right) \mathrm{d}s + \varphi(T_\star, V_\star) \int_{t-\tau_2}^{t} G\left(\frac{I(s)}{I_\star}\right) \mathrm{d}s.
\end{aligned}$$

In the following, we respectively compute the derivatives of $L_{2n}(t)$ $(n = 1, 2, 3, 4)$ with respect to t along the solution of model (2.1).

First, from

$$s = \varphi(T_\star, V_\star) + \psi(T_\star, I_\star) + f(T_\star, C_\star) + d_T T_\star,$$

we can get

$$\begin{aligned}
\frac{\mathrm{d}L_{21}(t)}{\mathrm{d}t} =& \left(1 - \frac{T_\star}{T(t)}\right)(s - \varphi(T(t), V(t)) - \psi(T(t), I(t)) - f(T(t), C(t)) - d_T T(t)) \\
=& \left(1 - \frac{T_\star}{T(t)}\right)(-d_T(T(t) - T_\star)) - [(\varphi(T(t), V(t)) - \varphi(T_\star, V_\star)) \\
&+ (\psi(T(t), I(t)) - \psi(T_\star, I_\star)) + (f(T(t), C(t)) - f(T_\star, C_\star))] \\
&- (\varphi(T_\star, V_\star) + \psi(T_\star, I_\star) + f(T_\star, C_\star))\frac{T_\star}{T(t)} \\
&+ [\varphi(T(t), V(t)) + \psi(T(t), I(t)) + f(T(t), C(t))]\frac{T_\star}{T(t)} \\
=& -\frac{d_T}{T(t)}(T(t) - T_\star)^2 - \varphi(T_\star, V_\star)\left(\frac{\varphi(T(t), V(t))}{\varphi(T_\star, V_\star)} - 1 - \ln\frac{\varphi(T(t), V(t))}{\varphi(T_\star, V_\star)}\right) \\
&- \psi(T_\star, I_\star)\left(\frac{\psi(T(t), I(t))}{\psi(T_\star, I_\star)} - 1 - \ln\frac{\psi(T(t), I(t))}{\psi(T_\star, I_\star)}\right) \\
&- f(T_\star, C_\star)\left(\frac{f(T(t), C(t))}{f(T_\star, C_\star)} - 1 - \ln\frac{f(T(t), C(t))}{f(T_\star, C_\star)}\right) \\
&- \varphi(T_\star, V_\star)\left(\frac{T_\star}{T(t)} - 1 - \ln\frac{T_\star}{T(t)}\right) - \psi(T_\star, I_\star)\left(\frac{T_\star}{T(t)} - 1 - \ln\frac{T_\star}{T(t)}\right) \\
&- f(T_\star, C_\star)\left(\frac{T_\star}{T(t)} - 1 - \ln\frac{T_\star}{T(t)}\right)
\end{aligned}$$

$$+\varphi(T_\star,V_\star)\left(\frac{T_\star\varphi(T(t),V(t))}{T(t)\varphi(T_\star,V_\star)}-1-\ln\frac{T_\star\varphi(T(t),V(t))}{T(t)\varphi(T_\star,V_\star)}\right)$$
$$+\psi(T_\star,I_\star)\left(\frac{T_\star\psi(T(t),I(t))}{T(t)\psi(T_\star,I_\star)}-1-\ln\frac{T_\star\psi(T(t),I(t))}{T(t)\psi(T_\star,I_\star)}\right)$$
$$+f(T_\star,C_\star)\left(\frac{T_\star f(T(t),C(t))}{T(t)f(T_\star,C_\star)}-1-\ln\frac{T_\star f(T(t),C(t))}{T(t)f(T_\star,C_\star)}\right).$$

Second, from

$$\frac{1}{I_\star}(\varphi(T_\star,V_\star)+\psi(T_\star,I_\star)+f(T_\star,C_\star))=e^{\delta_1\tau_1}(\alpha+d_I),$$

we have

$$\begin{aligned}\frac{\mathrm{d}L_{22}(t)}{\mathrm{d}t}=&\left(1-\frac{I_\star}{I(t)}\right)\bigg(\varphi(T(t-\tau_1),V(t-\tau_1))+\psi(T(t-\tau_1),I(t-\tau_1))\\&+f(T(t-\tau_1),C(t-\tau_1))-\left((\varphi(T_\star,V_\star)+\psi(T_\star,I_\star)+f(T_\star,C_\star))\frac{I(t)}{I_\star}\right)\bigg)\\=&\varphi(T(t-\tau_1),V(t-\tau_1))+\psi(T(t-\tau_1),I(t-\tau_1))+f(T(t-\tau_1),C(t-\tau_1))\\&-(\varphi(T_\star,V_\star)+\psi(T_\star,I_\star)+f(T_\star,C_\star))\frac{I(t)}{I_\star}\\&-\varphi(T_\star,V_\star)\left(\frac{I_\star\varphi(T(t-\tau_1),V(t-\tau_1))}{I(t)\varphi(T_\star,V_\star)}-1-\ln\frac{I_\star\varphi(T(t-\tau_1),V(t-\tau_1))}{I(t)\varphi(T_\star,V_\star)}\right)\\&-\psi(T_\star,I_\star)\left(\frac{I_\star\psi(T(t-\tau_1),I(t-\tau_1))}{I(t)\psi(T_\star,I_\star)}-1-\ln\frac{I_\star\psi(T(t-\tau_1),I(t-\tau_1))}{I(t)\psi(T_\star,I_\star)}\right)\\&-f(T_\star,C_\star)\left(\frac{I_\star f(T(t-\tau_1),C(t-\tau_1))}{I(t)f(T_\star,C_\star)}-1-\ln\frac{I_\star f(T(t-\tau_1),C(t-\tau_1))}{I(t)f(T_\star,C_\star)}\right)\\&-\varphi(T_\star,V_\star)\ln\frac{I_\star\varphi(T(t-\tau_1),V(t-\tau_1))}{I(t)\varphi(T_\star,V_\star)}-\psi(T_\star,I_\star)\ln\frac{I_\star\psi(T(t-\tau_1),I(t-\tau_1))}{I(t)\psi(T_\star,I_\star)}\\&-f(T_\star,C_\star)\ln\frac{I_\star f(T(t-\tau_1),C(t-\tau_1))}{I(t)f(T_\star,C_\star)}.\end{aligned}$$

By $\alpha_1 I_\star=d_C C_\star$ and $ke^{-\delta_2\tau_2}I_\star=d_V V_\star$, the derivative of $L_{23}(t)$ satisfies

$$\begin{aligned}\frac{\mathrm{d}L_{23}(t)}{\mathrm{d}t}=&\frac{f(T_\star,C_\star)}{d_C}\left(\frac{1}{C_\star}-\frac{1}{C(t)}\right)(\alpha_1 I(t)-d_C C(t))\\&+\frac{\varphi(T_\star,V_\star)}{d_V}\left(\frac{1}{V_\star}-\frac{1}{V(t)}\right)(ke^{-\delta_2\tau_2}I(t-\tau_2)-d_V V(t))\\=&f(T_\star,C_\star)\left(1-\frac{C_\star}{C(t)}\right)\left(\frac{I(t)}{I_\star}-\frac{C(t)}{C_\star}\right)+\varphi(T_\star,V_\star)\left(1-\frac{V_\star}{V(t)}\right)\left(\frac{I(t-\tau_2)}{I_\star}-\frac{V(t)}{V_\star}\right)\\=&f(T_\star,C_\star)\left(\frac{I(t)}{I_\star}-\frac{C(t)}{C_\star}-\frac{C_\star I(t)}{C(t)I_\star}+1\right)\\&+\varphi(T_\star,V_\star)\left(\frac{I(t-\tau_2)}{I_\star}-\frac{V(t)}{V_\star}-\frac{V_\star I(t-\tau_2)}{V(t)I_\star}+1\right)\end{aligned}$$

$$
\begin{aligned}
&= - f(T_\star, C_\star)\left(\frac{C_\star I(t)}{C(t)I_\star} - 1 - \ln \frac{C_\star I(t)}{C(t)I_\star}\right) - f(T_\star, C_\star)\left(\frac{C(t)}{C_\star} - 1 - \ln \frac{C(t)}{C_\star}\right) \\
&\quad + f(T_\star, C_\star)\left(\frac{I(t)}{I_\star} - 1 - \ln \frac{I(t)}{I_\star}\right) - \varphi(T_\star, V_\star)\left(\frac{V_\star I(t-\tau_2)}{V(t)I_\star} - 1 - \ln \frac{V_\star I(t-\tau_2)}{V(t)I_\star}\right) \\
&\quad - \varphi(T_\star, V_\star)\left(\frac{V(t)}{V_\star} - 1 - \ln \frac{V(t)}{V_\star}\right) + \varphi(T_\star, V_\star)\left(\frac{I(t-\tau_2)}{I_\star} - 1 - \ln \frac{I(t-\tau_2)}{I_\star}\right).
\end{aligned}
$$

Last, we have

$$
\begin{aligned}
\frac{\mathrm{d}L_{24}(t)}{\mathrm{d}t} =& \varphi(T_\star, V_\star)\left(G\left(\frac{\varphi(T(t), V(t))}{\varphi(T_\star, V_\star)}\right) - G\left(\frac{\varphi(T(t-\tau_1), V(t-\tau_1))}{\varphi(T_\star, V_\star)}\right)\right) \\
&+ \psi(T_\star, I_\star)\left(G\left(\frac{\psi(T(t), I(t))}{\psi(T_\star, I_\star)}\right) - G\left(\frac{\psi(T(t-\tau_1), I(t-\tau_1))}{\psi(T_\star, I_\star)}\right)\right) \\
&+ f(T_\star, C_\star)\left(G\left(\frac{f(T(t), C(t))}{f(T_\star, C_\star)}\right) - G\left(\frac{f(T(t-\tau_1), C(t-\tau_1))}{f(T_\star, C_\star)}\right)\right) \\
&+ \varphi(T_\star, V_\star)\left(G\left(\frac{I(t)}{I_\star}\right) - G\left(\frac{I(t-\tau_2)}{I_\star}\right)\right).
\end{aligned}
$$

To sum up, we have obtained

$$
\begin{aligned}
\frac{\mathrm{d}L_2(t)}{\mathrm{d}t} =& \frac{\mathrm{d}L_{21}(t)}{\mathrm{d}t} + \frac{\mathrm{d}L_{22}(t)}{\mathrm{d}t} + \frac{\mathrm{d}L_{23}(t)}{\mathrm{d}t} + \frac{\mathrm{d}L_{24}(t)}{\mathrm{d}t} \\
=& - \frac{d_T}{T(t)}(T(t) - T_\star)^2 - (\varphi(T_\star, V_\star) + \psi(T_\star, I_\star) + f(T_\star, C_\star))\, G\left(\frac{T_\star}{T(t)}\right) \\
&+ \varphi(T_\star, V_\star)G\left(\frac{T_\star \varphi(T(t), V(t))}{T(t)\varphi(T_\star, V_\star)}\right) + \psi(T_\star, I_\star)G\left(\frac{T_\star \psi(T(t), I(t))}{T(t)\psi(T_\star, I_\star)}\right) \\
&+ f(T_\star, C_\star)G\left(\frac{T_\star f(T(t), C(t))}{T(t) f(T_\star, C_\star)}\right) + \varphi(T(t-\tau_1), V(t-\tau_1)) \\
&+ \psi(T(t-\tau_1), I(t-\tau_1)) + f(T(t-\tau_1), C(t-\tau_1)) \\
&- (\varphi(T_\star, V_\star) + \psi(T_\star, I_\star) + f(T_\star, C_\star))\frac{I(t)}{I_\star} \\
&- \varphi(T_\star, V_\star)G\left(\frac{I_\star \varphi(T(t-\tau_1), V(t-\tau_1))}{I(t)\varphi(T_\star, V_\star)}\right) - f(T_\star, C_\star)G\left(\frac{C_\star I(t)}{C(t)I_\star}\right) \\
&- \psi(T_\star, I_\star)G\left(\frac{I_\star \psi(T(t-\tau_1), I(t-\tau_1))}{I(t)\psi(T_\star, I_\star)}\right) - f(T_\star, C_\star)G\left(\frac{C(t)}{C_\star}\right) \\
&- f(T_\star, C_\star)G\left(\frac{I_\star f(T(t-\tau_1), C(t-\tau_1))}{I(t) f(T_\star, C_\star)}\right) + f(T_\star, C_\star)G\left(\frac{I(t)}{I_\star}\right) \\
&- \varphi(T_\star, V_\star) \ln \frac{I_\star \varphi(T(t-\tau_1), V(t-\tau_1))}{I(t)\varphi(T_\star, V_\star)} - \varphi(T_\star, V_\star)G\left(\frac{V_\star I(t-\tau_2)}{V(t)I_\star}\right) \\
&- \psi(T_\star, I_\star) \ln \frac{I_\star \psi(T(t-\tau_1), I(t-\tau_1))}{I(t)\psi(T_\star, I_\star)} - \varphi(T_\star, V_\star)G\left(\frac{V(t)}{V_\star}\right) \\
&- f(T_\star, C_\star) \ln \frac{I_\star f(T(t-\tau_1), C(t-\tau_1))}{I(t) f(T_\star, C_\star)} + \varphi(T_\star, V_\star)G\left(\frac{I(t)}{I_\star}\right)
\end{aligned}
$$

$$
\begin{aligned}
&-\varphi(T_\star,V_\star)G\left(\frac{\varphi(T(t-\tau_1),V(t-\tau_1))}{\varphi(T_\star,V_\star)}\right)\\
&-\psi(T_\star,I_\star)G\left(\frac{\psi(T(t-\tau_1),I(t-\tau_1))}{\psi(T_\star,I_\star)}\right)\\
&-f(T_\star,C_\star)G\left(\frac{f(T(t-\tau_1),C(t-\tau_1))}{f(T_\star,C_\star)}\right)\\
=&-\frac{d_T}{T(t)}(T(t)-T_\star)^2-(\varphi(T_\star,V_\star)+\psi(T_\star,I_\star)+f(T_\star,C_\star))\,G\left(\frac{T_\star}{T(t)}\right)\\
&+f(T_\star,C_\star)G\left(\frac{T_\star f(T(t),C(t))}{T(t)f(T_\star,C_\star)}\right)+\varphi(T_\star,V_\star)G\left(\frac{T_\star\varphi(T(t),V(t))}{T(t)\varphi(T_\star,V_\star)}\right)\\
&+\psi(T_\star,I_\star)G\left(\frac{T_\star\psi(T(t),I(t))}{T(t)\psi(T_\star,I_\star)}\right)-\psi(T_\star,I_\star)G\left(\frac{I(t)}{I_\star}\right)\\
&-\varphi(T_\star,V_\star)G\left(\frac{I_\star\varphi(T(t-\tau_1),V(t-\tau_1))}{I(t)\varphi(T_\star,V_\star)}\right)\\
&-\psi(T_\star,I_\star)G\left(\frac{I_\star\psi(T(t-\tau_1),I(t-\tau_1))}{I(t)\psi(T_\star,I_\star)}\right)-f(T_\star,C_\star)G\left(\frac{C(t)}{C_\star}\right)\\
&-f(T_\star,C_\star)G\left(\frac{I_\star f(T(t-\tau_1),C(t-\tau_1))}{I(t)f(T_\star,C_\star)}\right)-f(T_\star,C_\star)G\left(\frac{C_\star I(t)}{C(t)I_\star}\right)\\
&-\varphi(T_\star,V_\star)G\left(\frac{V_\star I(t-\tau_2)}{V(t)I_\star}\right)-\varphi(T_\star,V_\star)G\left(\frac{V(t)}{V_\star}\right).
\end{aligned}
$$

It follows from the monotonicity of $G(x)$ and (**A3**) that

$$
\begin{aligned}
\varphi(T_\star,V_\star)G\left(\frac{T_\star\varphi(T(t),V(t))}{T(t)\varphi(T_\star,V_\star)}\right)&\le\varphi(T_\star,V_\star)G\left(\frac{V(t)}{V_\star}\right),\\
\psi(T_\star,I_\star)G\left(\frac{T_\star\psi(T(t),I(t))}{T(t)\psi(T_\star,I_\star)}\right)&\le\psi(T_\star,I_\star)G\left(\frac{I(t)}{I_\star}\right),\\
f(T_\star,C_\star)G\left(\frac{T_\star f(T(t),C(t))}{T(t)f(T_\star,C_\star)}\right)&\le f(T_\star,C_\star)G\left(\frac{C(t)}{C_\star}\right).
\end{aligned}
$$

Thus, we have

$$
\begin{aligned}
\frac{\mathrm{d}L_2(t)}{\mathrm{d}t}\le&-\frac{d_T}{T(t)}(T(t)-T_\star)^2-(\varphi(T_\star,V_\star)+\psi(T_\star,I_\star)+f(T_\star,C_\star))\,G\left(\frac{T_\star}{T(t)}\right)\\
&-\varphi(T_\star,V_\star)G\left(\frac{I_\star\varphi(T(t-\tau_1),V(t-\tau_1))}{I(t)\varphi(T_\star,V_\star)}\right)\\
&-\psi(T_\star,I_\star)G\left(\frac{I_\star\psi(T(t-\tau_1),I(t-\tau_1))}{I(t)\psi(T_\star,I_\star)}\right)\\
&-f(T_\star,C_\star)G\left(\frac{I_\star f(T(t-\tau_1),C(t-\tau_1))}{I(t)f(T_\star,C_\star)}\right)\\
&-f(T_\star,C_\star)G\left(\frac{C_\star I(t)}{C(t)I_\star}\right)-\varphi(T_\star,V_\star)G\left(\frac{V_\star I(t-\tau_2)}{V(t)I_\star}\right).
\end{aligned}
$$

Clearly, $\frac{dL_2(t)}{dt} \leq 0$ and $\frac{dL_2(t)}{dt} = 0$ if and only if $T(t) = T_\star$, $I(t) = I_\star$, $C(t) = C_\star$, and $V(t) = V_\star$. It is easy to see that $\{E_\star\}$ is the largest invariant set in $\left\{\frac{dL_2(t)}{dt} = 0\right\}$. Therefore, by the LaSalle invariance principle, the infected steady state $E_\star$ is globally asymptotically stable. □

5. Conclusions

This paper proposed a delay model incorporating general incidence rates and two modes of viral transmission. Pyroptosis-enhanced viral infection was also included in the model. We derived the basic reproduction number and established the existence and local stability of steady states. By applying the LaSalle invariance principle and Lyapunov functional methods, we demonstrated the global asymptotic stability of both the infection-free and infected steady states. This model enhances our understanding of the impact of cell-to-cell transmission and inflammatory cytokines on viral infection dynamics. Additionally, considering that the death rate of infected cells is dependent on the time of infection, future work may focus on establishing an age-structured model to further explore the influence of infection age on viral dynamics.

Author contributions

L. Hong: Methodology, Writing-original draft; J. Li: Validation, Writing-original draft; L. Rong: Writing-Reviewing and Editing; X. Wang: Supervision, Writing-Reviewing and Editing. All authors have read and approved the final version of the manuscript for publication.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

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Conflict of interest

All authors declare that there is no conflict of interest in this paper.

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