GLOBAL DYNAMICS ANALYSIS OF A TIME-DELAYED DYNAMIC MODEL OF KAWASAKI DISEASE PATHOGENESIS

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(Communicated by Gail Wolkowicz)

Abstract. Kawasaki disease (KD) is an acute febrile vasculitis that occurs predominantly in infants and young children. With coronary artery abnormalities (CAAs) as its most serious complications, KD has become the leading cause of acquired heart disease in developed countries. Based on some new biological findings, we propose a time-delayed dynamic model of KD pathogenesis. This model exhibits forward/backward bifurcation. By analyzing the characteristic equations, we completely investigate the local stability of the inflammatory factors-free equilibrium and the inflammatory factors-existent equilibria. Our results show that the time delay does not affect the local stability of the inflammatory factors-free equilibrium. However, the time delay as the bifurcation parameter may change the local stability of the inflammatory factors-existent equilibrium, and stability switches as well as Hopf bifurcation may occur within certain parameter ranges. Further, by skillfully constructing Lyapunov functionals and combining Barbalat’s lemma and Lyapunov-LaSalle invariance principle, we establish some sufficient conditions for the global stability of the inflammatory factors-free equilibrium and the inflammatory factors-existent equilibrium. Moreover, it is shown that the model is uniformly persistent if the basic reproduction number is greater than one, and some explicit analytic expressions of eventual lower bounds of the solutions of the model are given by analyzing the properties of the solutions and the range of time delay very precisely. Finally, some numerical simulations are carried out to illustrate the theoretical results.

1. Introduction. KD, also referred to as mucocutaneous lymph node syndrome (MCLS), is an autoimmune disease. It was first described by Tomisaku Kawasaki in 1967 and is an acute febrile vasculitis that occurs predominantly in infants and young children (generally under the age of 5) [14, 25]. Common clinical symptoms of KD are fever persisting for 5 days or longer, rash, changes in the lips and oral cavity, ocular conjunctival hyperemia, cervical lymphadenopathy, etc. If not diagnosed and treated in time, CAAs (including coronary artery dilatations and coronary artery aneurysms) occur in about 25% of the patients, which are the most serious complications of KD and seriously affect patients’ lives and health [25, 33, 23].
Aspirin is the drug of choice for treating KD. It is a cyclooxygenase inhibitor that has an anti-inflammatory effect and prevents platelet aggregation and thrombosis, but it does not appear to lower the rates of CAAs [25]. The most effective way to prevent CAAs is the use of intravenous immunoglobulin (IVIG), which can greatly reduce the incidence of CAAs [23]. Timely IVIG treatment can reduce the incidence of coronary aneurysms from 25% to 4% [23]. However, some patients with KD show resistance to IVIG treatment and additional treatment is recommended [23, 8]. Currently, KD has replaced rheumatic fever as the leading cause of acquired heart disease in children in developed countries [25, 37, 33, 23].

Currently, KD has been diagnosed in at least 60 countries around the world, and its incidence is rising worldwide (see, e.g., [33, 22, 13, 2]). The prevention and timely diagnosis and treatment of KD are an important issue and challenge for every country. Since reported more than 50 years ago, KD has been extensively studied by many scholars, but its pathogenesis is still unknown [25, 33, 23, 15, 1, 8]. Faced with the rising trend of KD incidence year by year in many countries and the problems of missed diagnosis, misdiagnosis and improper treatment, which cause serious damage to the life and health of children with KD, it is of great urgency to study the mechanism of KD.

KD is usually accompanied by systemic vasculitis. In clinical studies, some scholars believe that KD is caused by cross-reactions between external infections and the body’s organs and tissues, resulting in the disorder of the body’s immune system and the production of various cytokines that aggravate inflammation (see, e.g., [37, 21, 32, 8, 12, 19, 36]). Many scholars have made important contributions for the exploration of the pathogenesis, transmission and control of diseases by building mathematical models related to the diseases (see, e.g., [26, 27, 24, 16, 6, 18, 29] and the references therein), such as HIV (human immunodeficiency virus) models, HCV (hepatitis C virus) models, tumor-immune interaction models, and ZIKV (Zika virus) models. Therefore, it is of significance to study the mathematical model of the pathogenesis of KD for timely diagnosis, treatment and prevention.

Recently, based on the interactions among normal endothelial cells, vascular endothelial growth factors, adhesion factors/chemokines and inflammatory factors in the lesion area of patients with KD, Qiang et al. [28] proposed a novel mathematical model that describes the pathogenesis of KD, which is governed by a set of ordinary differential equations (ODEs),

\[
\begin{align*}
\dot{E}(t) &= r + \frac{k_6 V(t) E(t)}{1 + V(t)} - k_3 E(t) P(t) - d_1 E(t), \\
\dot{V}(t) &= k_2 E(t) P(t) - d_2 V(t), \\
\dot{C}(t) &= k_3 E(t) P(t) + k_4 V(t) - d_3 C(t), \\
\dot{P}(t) &= k_5 C(t) - d_4 P(t).
\end{align*}
\]

Here, \(E(t), V(t), C(t)\) and \(P(t)\) represent concentrations of normal endothelial cells, vascular endothelial growth factors, activated adhesion factors/chemokines, inflammatory factors in the lesion area at time \(t\) in acute stage of KD, respectively. All the parameters in model (1) are assumed to be positive constants and their biological meanings are given in Table 1. It is assumed that the vascular endothelial growth factors promote the proliferation of endothelial cells following saturating functional response (the term \(k_6 V(t) E(t)/(1 + V(t))\)) [16].
Table 1. Biological meanings of the parameters in model (1) [28].

| Parameters | Biological meanings |
|------------|---------------------|
| \( r \)   | Proliferation rate of normal endothelial cells (pg\(^{-1}\)ml\(^{-1}\)day\(^{-1}\)) |
| \( d_1 \) | Apoptosis rate of normal endothelial cells (day\(^{-1}\)) |
| \( d_2 \) | Hydrolytic rate of endothelial growth factors (day\(^{-1}\)) |
| \( d_3 \) | Hydrolytic rate of activated adhesion factors/chemokines (day\(^{-1}\)) |
| \( d_4 \) | Hydrolytic rate of inflammatory factors (day\(^{-1}\)) |
| \( k_1 \) | The rate of injury of endothelial cells caused by inflammatory factors (pg\(^{-1}\)ml\(^{-1}\)day\(^{-1}\)) |
| \( k_2 \) | Production rate of endothelial growth factors caused by inflammatory factors (pg\(^{-1}\)ml\(^{-1}\)day\(^{-1}\)) |
| \( k_3 \) | Production rate of activated adhesion factors/chemokines caused by inflammatory factors (pg\(^{-1}\)ml\(^{-1}\)day\(^{-1}\)) |
| \( k_4 \) | Production rate of activated adhesion factors/chemokines caused by endothelial growth factors (day\(^{-1}\)) |
| \( k_5 \) | Production rate of inflammatory factors by increasing of abnormally activated immune cells (day\(^{-1}\)) |
| \( k_6 \) | Proliferation rate of endothelial cells promoted by endothelial growth factors (day\(^{-1}\)) |

In the modeling of many biological processes, time delays are usually introduced for more accurate description of biological phenomena (see, e.g., [3, 31, 4, 34, 20, 5]). In the lesion area of patients with KD, inflammatory factors can damage endothelial cells and induce the expression of endothelial cell growth factor and adhesion factors/chemokines. However, the expression of various factors is generated by transduction of multiple signaling pathways, which is not instantaneous, but exhibits some time delays. Therefore, we introduce the time delay \( \tau \geq 0 \) in model (1), which is more biologically significant. In this paper, we consider the following delay differential equations (DDEs),

\[
\begin{align*}
\dot{E}(t) &= r + \frac{k_6 V(t)E(t)}{1 + V(t)} - k_1 E(t)P(t) - d_1 E(t), \\
\dot{V}(t) &= k_2 E(t - \tau)P(t - \tau) - d_2 V(t), \\
\dot{C}(t) &= k_3 E(t - \tau)P(t - \tau) + k_4 V(t) - d_3 C(t), \\
\dot{P}(t) &= k_5 C(t) - d_4 P(t)
\end{align*}
\]

The biological significance of all parameters of model (2) are the same as model (1) except that the time delay \( \tau \). \( \tau \) represents the time between inflammatory factors stimulating the body to produce an immune response until the production of vascular endothelial growth factors and activated adhesion factors/chemokines. As a matter fact, the second and third equations in model (2) are described with different time delays, which is of greater biological significance. For the sake of analysis, in model (2), we assume that inflammatory factors stimulate an immune response until it takes the same time for the body to produce vascular endothelial growth factors and activated adhesion factors/chemokines.

Since model (1) has higher dimensions and undergoes a forward bifurcation or a backward bifurcation under some conditions, which imply that model (1) may have
complicated dynamic properties. In [28], Qiang et al. discussed the local stability of the equilibria of model (1). Then, in [9], by constructing suitable Lyapunov functions and using Lyapunov-LaSalle invariance principle, Guo et al. further established some sufficient conditions for the global stability of the equilibria of model (1). In model (2), we find that the time delay $\tau$ can lead to stability switches as well as the existence of Hopf bifurcation. The main purpose of this paper is to study the global stability of the inflammatory factors-free equilibrium and the inflammatory factors-existent equilibrium, by skillfully constructing suitable Lyapunov functionals and combining Barbalat’s lemma and Lyapunov-LaSalle invariance principle. In addition, we give some explicit analytic expressions of eventual lower bounds of the solutions of model (2) by analyzing the properties of the solutions and the range of time delay very precisely (see, e.g., [34, 7, 35, 10]), which can be used to the study of the global stability of the inflammatory factors-existent equilibrium.

The rest of this paper is organized as follows. In Section 2, we provide some preliminary results, including the well-posedness, dissipativeness, classification of the equilibria of model (2), and several important lemmas. In Section 3, we study the local and global stability of the inflammatory factors-free equilibrium of model (2). In Section 4, we discuss the uniform persistence of model (2), and obtain some explicit analytic expressions of eventual lower bounds of the solutions of model (2). In Subsection 5.1, we first consider the local stability of the inflammatory factors-existent equilibria and the existence of Hopf bifurcations using the time delay as a bifurcation parameter, and then establish some sufficient conditions for the global stability of the inflammatory factors-existent equilibrium. Finally, in Section 6, we summarize the conclusions of this paper and give some numerical simulations.

2. Preliminary results. We define $\mathbb{C}$ as a Banach space of continuous functions $\phi : [-\tau, 0] \to \mathbb{R}^4$ equipped with the sup-norm. Further, let

$$\mathbb{C}^+ = \left\{ \phi = (\phi_1, \phi_2, \phi_3, \phi_4)^T \in \mathbb{C} : \phi_i(\theta) \geq 0, \ \theta \in [-\tau, 0], \ i = 1, 2, 3, 4 \right\}.$$ 

The initial condition of model (2) is given as follows,

$$E(\theta) = \phi_1(\theta), \ V(\theta) = \phi_2(\theta), \ C(\theta) = \phi_3(\theta), \ P(\theta) = \phi_4(\theta), \ \theta \in [-\tau, 0],$$

(3)

where $\phi = (\phi_1, \phi_2, \phi_3, \phi_4)^T \in \mathbb{C}^+$. 

From a biological point of view, the concentrations of normal endothelial cells, vascular endothelial growth factors, activated adhesion factors/chemokines, inflammatory factors in the lesion area should vary within some finite ranges at any time rather than blow up in finite time or tend to infinity with the increase of time. Based on this, we assume the following restrictive condition (H) (i.e., the production rate of endothelial cells promoted by endothelial growth factors is less than their normal apoptosis rate) to ensure that the solutions of model (2) are ultimately bounded,

$$(H): k_6 < d_1.$$ 

2.1. The well-posedness and dissipativeness. The following result establishes the well-posedness and dissipativeness of model (2).
Lemma 2.1. The solution \((E(t), V(t), C(t), P(t))^T\) of model (2) with the initial condition (3) is existent, unique and nonnegative on \([0, \infty)\), which satisfies

\[
\limsup_{t \to \infty} E(t) \leq \frac{r}{d_1 - k_6} \equiv E_{\text{max}},
\]

\[
\limsup_{t \to \infty} V(t) \leq \frac{r(2k_2k_4 + d_2k_3)}{2\nu k_1k_4} \equiv V_{\text{max}},
\]

\[
\limsup_{t \to \infty} C(t) \leq \frac{r(2k_2k_4 + d_2k_3)}{\nu k_1d_2} \equiv C_{\text{max}},
\]

\[
\limsup_{t \to \infty} P(t) \leq \frac{r_k(2k_2k_4 + d_2k_3)}{\nu k_1d_2d_4} \equiv P_{\text{max}},
\]

where \(\nu = \min\{d_1 - k_6, \frac{d_2}{2}, d_3\}\).

Proof. By using the standard theory of DDEs (see [11, 17]), we can easily show that the solution \((E(t), V(t), C(t), P(t))^T\) of model (2) with the initial condition (3) is existent, unique and nonnegative on \([0, \infty)\). Next, let us consider ultimate boundedness of model (2). According to the first equation of model (2), we have that for \(t \geq 0\), \(E(t) \leq r - (d_1 - k_6)E(t)\). Hence, it follows from the condition (H) that \(\limsup_{t \to \infty} E(t) \leq E_{\text{max}}\). Let

\[
N(t) = E(t) + \frac{2k_1k_4}{2k_2k_4 + d_2k_3}V(t + \tau) + \frac{k_1d_2}{2k_2k_4 + d_2k_3}C(t + \tau),
\]

then it follows from model (2) that, for \(t \geq 0\),

\[
\dot{N}(t) \leq r - (d_1 - k_6)E(t) - \frac{d_2k_1k_4}{2k_2k_4 + d_2k_3}V(t + \tau) - \frac{k_1d_2d_3}{2k_2k_4 + d_2k_3}C(t + \tau)
\]

\[
\leq r - \nu N(t).
\]

Thus, \(\limsup_{t \to \infty} N(t) \leq r/\nu\), which implies that \(\limsup_{t \to \infty} V(t) \leq V_{\text{max}}\) and \(\limsup_{t \to \infty} C(t) \leq C_{\text{max}}\). Finally, from the last equation of model (2), we can easily obtain \(\limsup_{t \to \infty} P(t) \leq P_{\text{max}}\).

The proof is completed. \(\square\)

2.2. The classification of equilibria. From [28], we can easily obtain the basic reproduction number and classification of equilibria of model (2). The basic reproduction number \(R_0\) can be written as the following from,

\[
R_0 = \frac{rk_5(2k_2k_4 + d_2k_3)}{d_1d_2d_3d_4} = R_1 + R_2,
\]

\[
R_1 = \frac{rk_2k_4k_5}{d_1d_2d_3d_4}, \quad R_2 = \frac{rk_3k_5}{d_1d_3d_4}.
\]

In biology, \(R_1\) represents the amount of endothelial cells damage that a damaged endothelial cell eventually causes in the average survival period when the endothelial growth factor causes the growth of adhesion and chemokines in the acute phase of KD and \(R_2\) represents the amount of endothelial cells damage that a damaged endothelial cell eventually causes in the average survival period when the inflammatory factors increases the adhesion factors and chemokines in the acute phase of KD. \(R_0\) is expressed as the number of endothelial cells damaged by a damaged endothelial cell during its average survival period in the acute phase of KD. Therefore, there are two pathways leading to the presence of inflammation in KD, and this fact suggests that effective control of inflammation in KD should be integrated for both \(R_1\) and \(R_2\) components.

Model (2) always has an inflammatory factors-free equilibrium (boundary equilibrium) \(Q_0(E_0, 0, 0, 0)\), where \(E_0 = r/d_1\).
In addition, in the following two cases, there exist the inflammatory factors-existent equilibria (positive equilibria).

(a) If \( r k_6 k_6 \leq d_1 d_2 k_1 \) (i.e. \( d_2 k_1 \geq k_3 k_6 E_0 \)) and \( R_0 > 1 \) (i.e., model (2) undergoes a forward bifurcation) then there exists a unique inflammatory factors-existent equilibrium \( E^* (E^*, V^*, C^*, P^*) \), where

\[
E^* = \frac{d_2 d_3 d_4}{k_5 (k_2 k_4 + d_2 k_3)}, \quad C^* = \frac{k_2 k_4 + d_2 k_3}{d_3 k_2} V^*,
\]

\[
P^* = \frac{k_5}{d_4} C^* = \frac{(k_2 k_4 + d_2 k_3) k_5}{d_3 d_4 k_2} V^*,
\]

\[
V^* = \frac{r k_2 k_6 - d_1 d_2 k_1 R_0 + r d_1 k_2 (R_0 - 1) + \sqrt{\Delta_1}}{2 d_1 d_2 k_1 R_0},
\]

\[
\Delta_1 = [r k_2 k_6 - d_1 d_2 k_1 R_0 + r d_1 k_2 (R_0 - 1)]^2 + 4 r d_1^2 d_2 k_1 k_2 R_0 (R_0 - 1).
\]

(b) If \( r k_2 k_6 > d_1 d_2 k_1 \) (i.e. \( k_2 k_6 E_0 > d_2 k_1 \)), there are the following three sub-cases (i.e., model (2) undergoes a backward bifurcation).

(b) If \( R_0 \geq 1 \), then there exists a unique inflammatory factors-existent equilibrium \( Q^*(E^*, V^*, C^*, P^*) \).

(b) If \( R_0 < 1 \), then there exist two inflammatory factors-existent equilibrium \( Q^* (E^*, V^*, C^*, P^*) \) and \( Q^{**} (E^{**}, V^{**}, C^{**}, P^{**}) \), where

\[
0 < \omega = \frac{r k_2 (d_1 - k_6) (r d_1 d_2 k_1 + d_1 d_2 k_1) + 2 d_1 d_2 k_1 r d_1 k_2 + 2 \sqrt{\Delta_2}}{(r d_1 k_2 + d_1 d_2 k_1)^2} < 1,
\]

\[
\Delta_2 = (d_1 d_2 k_1 r d_1 k_2)^2 + r k_2 (d_1 - k_6) (r k_2 k_6 - d_1 d_2 k_1) d_1 d_2 k_1 r d_1 k_2,
\]

\[
E^{**} = \frac{d_2 d_3 d_4}{k_5 (k_2 k_4 + d_2 k_3)}, \quad C^{**} = \frac{k_2 k_4 + d_2 k_3}{d_3 k_2} V^{**},
\]

\[
P^{**} = \frac{k_5}{d_4} C^{**} = \frac{(k_2 k_4 + d_2 k_3) k_5}{d_3 d_4 k_2} V^{**},
\]

\[
V^{**} = \frac{r k_2 k_6 - d_1 d_2 k_1 R_0 + r d_1 k_2 (R_0 - 1) - \sqrt{\Delta_1}}{2 d_1 d_2 k_1 R_0}.
\]

(b) If \( R_0 = \omega \), then there exists a unique inflammatory factors-existent equilibrium \( Q_0^* (E^*, V^*, C^*, P^*) \).

From above the cases (a) and (b), we see that the proliferation rate \( k_6 \) plays an important role in the occurrence of backward bifurcation. For larger value of \( k_6 \) such that the inequality \( r k_2 k_6 > d_1 d_2 k_1 \) holds, the existence of backward bifurcation means that the control of inflammation in KD becomes more difficult and that the basic reproduction number \( R_0 < 1 \) is not sufficient and further condition \( R_0 < \omega \) is required.

2.3. Some lemmas. In this subsection, some important lemmas will be given and used in subsequent sections.

**Lemma 2.2.** (Barbalat’s lemma [30]) If the differentiable function \( f(t) \) \((t \geq 0)\) has a finite limit as \( t \to \infty \), and if \( f(t) \) is uniformly continuous (a sufficient condition that a differentiable function is uniformly continuous is that its derivative is bounded), then \( f(t) \to 0 \) as \( t \to \infty \).

**Lemma 2.3.** Let \( \mathbb{C}^+ = \{ \phi \in \mathbb{C}^+ : \phi_2(0) + \phi_3(0) + \phi_4(0) > 0 \} \). The solution \( (E(t), V(t), C(t), P(t))^T \) of model (2) with the initial function \( \phi \in \mathbb{C}^+ \) is positive for \( t \geq \tau + 1 \).
Proof. Let \((E(t), V(t), C(t), P(t))\) be any solution of model (2) with the initial function \(\phi \in \mathbb{C}^+\). We can easily obtain \(E(t) > 0\) for \(t > 0\). Without loss of generality, we assume that \(\phi_3(0) > 0\). According to the last equation of model (2), we can obtain \(P(t) \geq P(0)e^{-d_d t} > 0\) for \(t > 0\). Claim that there is a \(\bar{t} \in [0, \tau + 1]\) such that \(V(\bar{t}) > 0\). Suppose, by contradiction, then according to Lemma 2.1, we know that \(V(t) = 0\) for \(t \in [0, \tau + 1]\). Note that \(V(t)\) is continuously differentiable on \([\tau, \infty)\) (see [17], p.20, Theorem 2.8) and \(V(\tau + 1) = k_2E(1)P(1) > 0\), which means \(\dot{V}(t) < 0\) for \(t \in (\tau + 1 - \varepsilon, \tau + 1]\), where \(\varepsilon\) is an arbitrarily small positive constant. This leads to a contradiction with Lemma 2.1. Hence, \(V(t) \geq V(\bar{t})e^{-d_d t} > 0\), for \(t \geq \tau + 1(\geq \bar{t})\). With a similar proof, we can also obtain \(C(t) > 0\) for \(t \geq \tau + 1\). The proof is completed.

Lemma 2.4. Let \((E(t), V(t), C(t), P(t))\) be any solution of model (2) that satisfies the initial condition (3), then \(V(t)\) satisfies \(V(t + \tau) \geq V(t)e^{-d_d \tau}\) for \(t \geq 0\).

Proof. From the second equation of model (2), we have \(\dot{V}(t) \geq -d_2V(t)\) for \(t \geq 0\), then integrating from \(t\) to \(t + \tau\), we have

\[V(t + \tau) \geq V(t)\exp\left(-\int_t^{t+\tau} d_2 ds\right) = V(t)e^{-d_d \tau} .\]

The proof is completed.

3. Stability of the inflammatory factors-free equilibrium.

3.1. Local stability of the inflammatory factors-free equilibrium. For any equilibria \(Q(\bar{E}, \bar{V}, \bar{C}, \bar{P})\) of model (2), the associated transcendental characteristic equation of model (2) at \(Q(\bar{E}, \bar{V}, \bar{C}, \bar{P})\) is

\[
\begin{vmatrix}
\lambda - \left(k_5\bar{V} - k_1\bar{P} - d_1\right) & -\frac{k_4\bar{V}}{(1+\bar{V})^2} & 0 & k_1\bar{E} \\
-k_5\bar{P}e^{-\lambda\tau} & \lambda + d_2 & 0 & -k_2\bar{E}e^{-\lambda\tau} \\
-k_4\bar{P}e^{-\lambda\tau} & -k_4 & \lambda + d_3 & -k_3\bar{E}e^{-\lambda\tau} \\
0 & 0 & -k_5 & \lambda + d_4 \\
\end{vmatrix}
= 0. \tag{6}
\]

Then, for the local stability of the inflammatory factors-free equilibrium \(Q_0\), we have the following theorem.

Theorem 3.1. The following statements hold:

(i) If \(R_0 < 1\), then the inflammatory factors-free equilibrium \(Q_0\) is locally asymptotically stable for any \(\tau \geq 0\).

(ii) If \(R_0 = 1\), then the inflammatory factors-free equilibrium \(Q_0\) is linearly stable for any \(\tau \geq 0\).

(iii) If \(R_0 > 1\), then the inflammatory factors-free equilibrium \(Q_0\) is unstable for any \(\tau \geq 0\).

Proof. By (6), the associated transcendental characteristic equation of model (2) at the inflammatory factors-free equilibrium \(Q_0\) can be expressed as follows,

\[L_0(\lambda, \tau) \equiv (\lambda + d_1)[\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0 + e^{-\lambda\tau}(b_1\lambda + b_0)] = 0, \tag{7}\]

where

\[a_2 = d_2 + d_3 + d_4, \quad a_1 = d_2d_3 + d_2d_4 + d_3d_4, \quad a_0 = d_2d_3d_4,\]

\[b_1 = -k_3k_5E_0, \quad b_0 = -d_3k_5E_0 - k_2k_4k_5E_0.\]

It is clear that (7) has a root \(\lambda = -d_1 < 0\), and let

\[L_1(\lambda, \tau) = \lambda^3 + a_2\lambda^2 + a_1\lambda + a_0 + e^{-\lambda\tau}(b_1\lambda + b_0) = 0. \tag{8}\]
From [28], we know that all roots of (8) with \( \tau = 0 \) have negative real parts if \( R_0 < 1 \). Now, we suppose (8) has a purely imaginary root \( \lambda = iv_0 (v_0 > 0) \) for some \( \tau > 0 \). Substituting \( \lambda = iv_0 \) into (8) and separating the real and imaginary parts, we have

\[
\begin{aligned}
    b_0 \cos v_0 \tau + b_1 v_0 \sin v_0 \tau &= a_2 v_0^2 - a_0, \\
    b_1 v_0 \cos v_0 \tau - b_0 \sin v_0 \tau &= v_0^3 - a_1 v_0,
\end{aligned}
\]

from which it has

\[
v_0^6 + (a_2^2 - 2a_1)v_0^4 + (a_1^2 - 2a_0a_2 - b_1^2)v_0^2 + a_0^2 - b_0^2 = 0. \tag{9}
\]

By calculation, we have

\[

d_2^2 - 2a_1 = d_3^2 + d_4^2 + d_5^2 > 0,
\]

\[
    a_1^2 - 2a_0a_2 - b_1^2 = d_2^2(d_3^2 + d_4^2) + (d_3d_4 + k_3k_5E_0)(d_3d_4 - k_3k_5E_0) > 0,
\]

\[
    a_0^2 - b_0^2 = d_2d_3d_4(d_3d_4 + k_3k_5E_0 + k_2k_4k_5E_0)(1 - R_0) > 0,
\]

where \( d_3d_4 - k_3k_5E_0 = d_3d_4(1 - R_0) + \frac{k_2k_4k_5E_0}{d_3d_4} \) and \( R_0 < 1 \) are used. Thus, (9) does not hold. This shows that all roots of (7) have negative real parts for any \( \tau \geq 0 \) if \( R_0 < 1 \). Hence, the inflammatory factors-free equilibrium \( Q_0 \) is locally asymptotically stable for any \( \tau \geq 0 \).

When \( R_0 = 1 \), similar to the previous argument, it is easy to obtain that \( \lambda = 0 \) is a single root of (7), and all other roots of (7) have negative real parts. Hence, the inflammatory factors-free equilibrium \( Q_0 \) is linearly stable for any \( \tau \geq 0 \).

When \( R_0 > 1 \), note that \( L_1(\lambda, \tau) \) is continuous for \( \lambda, \tau \geq 0 \), and for any given \( \tau \geq 0 \),

\[
    L_1(0, \tau) = d_2d_3d_4(1 - R_0) < 0, \quad \lim_{\lambda \to \infty} L_1(\lambda, \tau) = \infty.
\]

It follows from the intermediate value theorem that there exists \( \lambda = \overline{\lambda}(\tau) > 0 \) such that \( L_1(\overline{\lambda}(\tau), \tau) = 0 \) (i.e., \( L_1(\lambda, \tau) = 0 \), has a positive root \( \lambda = \overline{\lambda}(\tau) \)). Hence, the inflammatory factors-free equilibrium \( Q_0 \) is unstable for any \( \tau \geq 0 \).

The proof is completed. \( \square \)

Theorem 3.1 indicates that the time delay \( \tau \) does not affect the local stability of the inflammatory factors-free equilibrium \( Q_0 \) (this is also called that the time delay \( \tau \) is harmless [17]). For the case of forward or backward bifurcation, the inflammatory factors-free equilibrium \( Q_0 \) is always locally asymptotically stable for any \( \tau \geq 0 \), if the basic reproduction number \( R_0 \) is less than 1. In biology, the local asymptotic stability of the inflammatory factors-free equilibrium \( Q_0 \) implies that, for suitable initial state values, the inflammation in the lesion area of patients will eventually become disappeared. However, it has great limitations in predicting the progression of the inflammatory by local asymptotic stability of the inflammatory factors-free equilibrium \( Q_0 \). Especially, for the case of backward bifurcation, different initial state values may lead to completely different trends of the progression of the inflammatory. Therefore, we will further investigate the global asymptotic stability of the inflammatory factors-free equilibrium \( Q_0 \) in the following Subsection 3.2.

3.2. Global stability of the inflammatory factors-free equilibrium. In this subsection, we will study the global stability of the inflammatory factors-free equilibrium \( Q_0 \), by Barbalat’s lemma and constructing suitable Lyapunov functionals.
If \( rk_2k_6 \leq d_1d_2k_1 \) (i.e. \( d_2k_1 \geq k_2k_6E_0 \), the case of forward bifurcation), we define

\[
\mathcal{Y} = \max\{\mathcal{Y}_1, \mathcal{Y}_2, \mathcal{Y}_3\} > 1, \quad \mathcal{Y}_1 = \frac{k_1(d_1 + d_2)^2}{4E_0\Lambda_1}(e^{d_2\tau} - 1)^2 + e^{d_2\tau},
\]

\[
\mathcal{Y}_2 = \frac{k_1(2d_1 + 2d_2 - k_6)^2}{4E_0\Lambda_2} + 1, \quad \mathcal{Y}_3 = \frac{k_1(d_1 + d_2 - k_6)^2}{4E_0\Lambda_2} + e^{d_2\tau},
\]

\[
\Lambda_1 = \frac{d_1[k_1(d_1 + d_2) - k_2k_6E_0]}{E_{\text{max}} + \epsilon} + k_2k_6(d_1 - k_6) > 0,
\]

\[
\Lambda_2 = \frac{d_1[k_1(d_1 + d_2) - k_2k_6E_0]}{E_0} + k_2k_6(d_1 - k_6) > 0.
\]

Then, we have the following result.

**Theorem 3.2.** If \( d_2k_1 > \mathcal{Y}k_2k_6E_0 \) and \( R_0 < 1 \), then the inflammatory factors-free equilibrium \( Q_0 \) is globally asymptotically stable.

**Proof.** By Theorem 3.1, when \( R_0 < 1 \), the inflammatory factors-free equilibrium \( Q_0 \) is locally asymptotically stable. Thus, we only need to show that the inflammatory factors-free equilibrium \( Q_0 \) is globally attractive.

Let \( (E(t), V(t), C(t), P(t))^T \) be any solution of model (2) that satisfies the initial condition (3), and assume \( d_2k_1 > \mathcal{Y}k_2k_6E_0 \) holds. Thus, there exists a sufficiently small \( \epsilon > 0 \), such that \( d_2k_1 > \mathcal{Y}(\epsilon)k_2k_6E_0 \), where

\[
\mathcal{Y}_1(\epsilon) = \frac{k_1(d_1 + d_2)^2}{4E_0\Lambda_1(\epsilon)}(e^{d_2\tau} - 1)^2 + e^{d_2\tau},
\]

\[
\Lambda_1(\epsilon) = \frac{d_1[k_1(d_1 + d_2) - k_2k_6E_0]}{E_{\text{max}} + \epsilon} + k_2k_6(d_1 - k_6).
\]

By Lemma 2.1, we have that for the above \( \epsilon \), there exists a sufficiently large \( T > 0 \) such that for \( t \geq T, E(t) < E_{\text{max}} + \epsilon, P(t) < P_{\text{max}} + \epsilon \). Then, according to the first equation of model (2), for \( t \geq T \), we have

\[
\dot{E}(t) \geq r - [k_1(P_{\text{max}} + \epsilon) + d_1]E(t),
\]

from which it has, for \( t \geq T + \tau + 1 \),

\[
E(t) \geq \frac{r}{k_1(P_{\text{max}} + \epsilon) + d_1} + \left( E(T) - \frac{r}{k_1(P_{\text{max}} + \epsilon) + d_1} \right) e^{-[k_1(P_{\text{max}} + \epsilon) + d_1](t-T)}
\]

\[
\geq \frac{r}{k_1(P_{\text{max}} + \epsilon) + d_1} \left[ 1 - e^{-[k_1(P_{\text{max}} + \epsilon) + d_1](t-T)} \right]
\]

\[
\geq \frac{r}{k_1(P_{\text{max}} + \epsilon) + d_1} \left[ 1 - e^{-[k_1(P_{\text{max}} + \epsilon) + d_1](\tau+1)} \right]
\]

\[
:= E_{\text{min}}(\epsilon).
\]

Let us define a differentiable function \( N_1(t) \) on \( [T + \tau + 1, \infty) \) as follows,

\[
N_1(t) = k_2[k_1(d_1 + d_2) - k_2k_6E_0]U_1(t) + k_6U_2(t),
\]

where

\[
U_1(t) = E(t) - E_0 - E_0 \ln \frac{E(t)}{E_0} + k_1 \int_{t-\tau}^{t} E(s)P(s)ds
\]

\[
+ \frac{k_1}{k_2k_4 + d_2k_3} \left( k_4V(t) + d_2C(t) + \frac{d_2d_3}{k_5}P(t) \right),
\]

\[
U_2(t) = \frac{1}{2}[k_2(E(t) - E_0) + k_1V(t + \tau)]^2.
\]
Note that \( d_2 k_1 - k_2 k_6 E_0 > (\gamma - 1) k_2 k_6 E_0 > 0 \) and \( E(t) \geq E_{\min}(\varepsilon) > 0 \), then by Lemma 2.1, it has \( N_1(t) \) is positive and bounded.

Let us calculate the derivative of \( U_1(t) \) and \( U_2(t) \), respectively. For \( t \geq T + \tau + 1 \), we have

\[
\dot{U}_1(t) = \left(1 - \frac{E_0}{E(t)}\right) (r - d_1 E(t)) + k_6 \frac{(E(t) - E_0) V(t)}{1 + V(t)} + k_1 E_0 P(t) - k_1 E(t - \tau) P(t - \tau) + \frac{k_1}{k_2 k_4 + d_2 k_3} \left[(k_2 k_4 + d_2 k_3) E(t - \tau) P(t - \tau) - \frac{d_2 d_3 d_4}{k_5} P(t)\right] = - \frac{d_1}{E(t)} (E(t) - E_0)^2 + k_6 \frac{(E(t) - E_0) V(t)}{1 + V(t)} + k_1 E_0 \left(1 - \frac{1}{R_0}\right) P(t),
\]

\[
\dot{U}_2(t) = [k_2 (E(t) - E_0) + k_1 V(t + \tau)] \times \left[k_2 \left(d_1 - \frac{k_6 V(t)}{1 + V(t)}\right) (E_0 - E(t)) + k_2 k_6 E_0 \frac{V(t)}{1 + V(t)} - d_2 k_1 V(t + \tau)\right] = - \frac{k_2^2}{k_2} \left(d_1 - \frac{k_6 V(t)}{1 + V(t)}\right) (E(t) - E_0)^2 - d_2 k_1^2 V^2(t + \tau)
\]

\[
+ k_2^2 k_6 E_0 \frac{(E(t) - E_0) V(t)}{1 + V(t)} + k_1 k_2 k_6 E_0 \frac{V(t) V(t + \tau)}{1 + V(t)} - k_1 k_2 [(d_1 + d_2) + (d_1 + d_2 - k_6) V(t)] \frac{(E(t) - E_0) V(t + \tau)}{1 + V(t)}.
\]

By (10), we have

\[
\dot{N}_1(t) = - \Lambda(t) k_2 (E(t) - E_0)^2 - d_2 k_1^2 k_5 V^2(t + \tau) + k_1 k_2 k_6 E_0 \frac{V(t) V(t + \tau)}{1 + V(t)} + k_1 k_2 k_6 (d_1 + d_2) \frac{(E(t) - E_0) (V(t) - V(t + \tau))}{1 + V(t)}
\]

\[
- k_1 k_2 k_6 (d_1 + d_2 - k_6) \frac{V(t)}{1 + V(t)} (E(t) - E_0) V(t + \tau) + k_1 k_2 E_0 [k_1 (d_1 + d_2) - k_2 k_6 E_0] \left(1 - \frac{1}{R_0}\right) P(t),
\]

where

\[
\Lambda(t) = \frac{d_1 k_1 (d_1 + d_2) - k_2 k_6 E_0}{E(t)} + k_2 k_6 \left[d_1 - \frac{k_6 V(t)}{1 + V(t)}\right] > 0.
\]

Now, the following four cases need to be considered.

Case (i) \( E(t) \geq E_0 \) and \( V(t) \leq V(t + \tau) \).

In this case, we can easily obtain that if \( R_0 \leq 1 \),

\[
\dot{N}_1(t) \leq - \Lambda(t) k_2 (E(t) - E_0)^2 - k_1 k_6 \left(d_2 k_1 - \frac{k_2 k_6 E_0}{1 + V(t + \tau)}\right) V^2(t + \tau) \leq 0,
\]

and \( \dot{N}_1(t) = 0 \) implies \( E(t) = E_0 \) and \( V(t + \tau) = 0 \).

Case (ii) \( E(t) \geq E_0 \) and \( V(t) \geq V(t + \tau) \).

Note that \( d_2 k_1 > \gamma(\varepsilon) k_2 k_6 E_0 \) implies that

\[
2 \sqrt{\Lambda(\varepsilon)}(d_2 k_1 - k_2 k_6 E_0 e^{d_2 \tau}) > \sqrt{k_1 k_2 k_6 (d_1 + d_2) (e^{d_2 \tau} - 1)} \geq 0.
\]
By Lemma 2.4, it has $V(t + \tau) \geq V(t)e^{-d_{2}\tau}$. Then, by (11) and $R_0 \leq 1$, we have

$$
\dot{N}_1(t) \leq -k_2A_1(\varepsilon)(E(t) - E_0)^2 - k_1k_6(d_2k_1 - k_2k_6E_0e^{d_{2}\tau})V^2(t + \tau) + k_1k_2k_6(d_1 + d_2)(e^{d_{2}\tau} - 1)(E(t) - E_0)V(t + \tau)
$$

$$
\leq -k_2A_1(\varepsilon) \left[ 1 - \frac{\sqrt{k_1k_2k_6(d_1 + 2d_2)A_1(\varepsilon)}}{2\Lambda_1(\varepsilon)(d_2k_1 - k_2k_6E_0e^{d_{2}\tau})} \right] (E(t) - E_0)^2
$$

$$
- k_1k_6(d_2k_1 - k_2k_6E_0e^{d_{2}\tau}) \left[ 1 - \frac{\sqrt{k_1k_2k_6(d_1 + 2d_2)A_1(\varepsilon)}}{2\Lambda_1(\varepsilon)(d_2k_1 - k_2k_6E_0e^{d_{2}\tau})} \right] V^2(t + \tau)
$$

\leq 0,

and $\dot{N}_1(t) = 0$ implies $E(t) = E_0$ and $V(t + \tau) = 0$.

**Case (iii) $E(t) \leq E_0$ and $V(t) \leq V(t + \tau)$.

Note that $d_2k_1 > \Lambda_2k_2k_6E_0$ implies that

$$
2\sqrt{A_2(d_2k_1 - k_2k_6E_0)} > \sqrt{k_1k_2k_6(2d_1 + 2d_2 - k_6)} > 0. \tag{12}
$$

By (12) and $R_0 \leq 1$, we have

$$
\dot{N}_1(t) \leq -k_2A_2(E(t) - E_0)^2 - k_1k_6(d_2k_1 - k_2k_6E_0)V^2(t + \tau)
-k_1k_2k_6(2d_1 + 2d_2 - k_6)(E(t) - E_0)V(t + \tau)
$$

$$
\leq -k_2A_2 \left[ 1 - \frac{\sqrt{k_1k_2k_6(d_1 + 2d_2 - k_6)}}{2\Lambda_2(d_2k_1 - k_2k_6E_0)} \right] (E(t) - E_0)^2
$$

$$
- k_1k_6(d_2k_1 - k_2k_6E_0) \left[ 1 - \frac{\sqrt{k_1k_2k_6(2d_1 + 2d_2 - k_6)}}{2\Lambda_2(d_2k_1 - k_2k_6E_0)} \right] V^2(t + \tau)
$$

\leq 0,

and $\dot{N}_1(t) = 0$ implies $E(t) = E_0$ and $V(t + \tau) = 0$.

**Case (iv) $E(t) \leq E_0$ and $V(t) \geq V(t + \tau)$.

Note that $d_2k_1 > \Lambda_3k_2k_6E_0$ implies that

$$
2\sqrt{A_2(d_2k_1 - k_2k_6E_0e^{d_{2}\tau})} > \sqrt{k_1k_2k_6(1 + d_2 - k_6)} > 0. \tag{13}
$$

By Lemma 2.4, it has $V(t + \tau) \geq V(t)e^{-d_{2}\tau}$. Then, by (13) and $R_0 \leq 1$, we can obtain

$$
\dot{N}_1(t) \leq -k_2A_2(E(t) - E_0)^2 - k_1k_6(d_2k_1 - k_2k_6E_0e^{d_{2}\tau})V^2(t + \tau)
-k_1k_2k_6(1 + d_2 - k_6)(E(t) - E_0)V(t + \tau)
$$

$$
\leq -k_2A_2 \left[ 1 - \frac{\sqrt{k_1k_2k_6(d_1 + d_2 - k_6)}}{2\Lambda_2(d_2k_1 - k_2k_6E_0e^{d_{2}\tau})} \right] (E(t) - E_0)^2
$$

$$
- k_1k_6(d_2k_1 - k_2k_6E_0e^{d_{2}\tau}) \left[ 1 - \frac{\sqrt{k_1k_2k_6(1 + d_2 - k_6)}}{2\Lambda_2(d_2k_1 - k_2k_6E_0e^{d_{2}\tau})} \right] V^2(t + \tau)
$$

\leq 0,

and $\dot{N}_1(t) = 0$ implies $E(t) = E_0$ and $V(t + \tau) = 0$.

Hence, we show that when $t \geq T + \tau + 1$, $\dot{N}_1(t)$ is monotonically decreasing and has a lower bound. Thus, there exists a constant $N_1^* \geq 0$ such that $N_1(t) \to N_1^*$ as $t \to \infty$. In addition, it is not difficult to show that when $t \geq T + \tau + 1$, $\dot{N}_1(t)$ is
bounded, then follow from Lemma 2.2 (Barbalat’s lemma), we have $\dot{N}_1(t) \to 0$ as $t \to \infty$. According to the previous argument, we can obtain $E(t) \to E_0$ as $t \to \infty$ and $V(t) \to 0$ as $t \to \infty$. In addition, note that when $t \geq T + \tau + 1$, $\dot{V}(t)$ and $\dot{P}(t)$ are bounded, then according to the second and last equations of model (2), we can also obtain $P(t) \to 0$ as $t \to \infty$ and $C(t) \to 0$ as $t \to \infty$. Therefore, the inflammatory factors-free equilibrium $Q_0$ is globally attractive.

The proof is completed. $\square$

**Remark 1.** If $d_2 k_1 > \Upsilon k_2 k_6 E_0$ and $R_0 \leq 1$, then the inflammatory factors-free equilibrium $Q_0$ is globally attractive.

**Remark 2.** Let $\Pi(k_6) = d_2 k_1 - \Upsilon k_2 k_6 E_0$, then from $\Pi(0) = d_2 k_1 > 0$, we have that there exists a positive constant $k_6^* < d_1$ such that $\Pi(k_6) > 0$ for $k_6 < k_6^*$.

From Theorem 3.2 and Remarks 1 and 2, we have the following Corollary 1.

**Corollary 1.** If $k_6 < k_6^*$ and $R_0 < 1$ ($R_0 = 1$), then the inflammatory factors-free equilibrium $Q_0$ is globally asymptotically stable (globally attractive).

Theorem 3.2 gives sufficient conditions for the global asymptotic stability of the inflammatory factors-free equilibrium $Q_0$ in the case of forward bifurcation. In the following, we will give a class of different sufficient conditions for the global asymptotic stability of the inflammatory factors-free equilibrium $Q_0$, which can be applied to the cases of both forward bifurcation and backward bifurcation.

Let $\omega^* = E_0/E_{\max} = 1 - k_6/d_1 < 1$ and

$$\Omega = \{ \phi = (\phi_1, \phi_2, \phi_3, \phi_4) \in \mathbb{C}^+ : 0 \leq \|\phi_1\| \leq E_{\max} \}.$$  

We have the following result.

**Theorem 3.3.** If $R_0 < \omega^*$, then the inflammatory factors-free equilibrium $Q_0$ is globally asymptotically stable for any $\tau \geq 0$ in $\Omega$.

**Proof.** It is easy show that the set $\Omega$ is positively invariant with respect to model (2) and attracts any solution of model (2) with $\phi \in \Omega$. By Theorem 3.1, when $R_0 < \omega^* < 1$, the inflammatory factors-free equilibrium $Q_0$ is locally asymptotically stable. Thus, we only need to show that $Q_0$ is globally attractive.

Let

$$u_t = (E_t, V_t, C_t, P_t)^T = (E(t + \theta), V(t + \theta), C(t + \theta), P(t + \theta))^T (\tau \leq \theta \leq 0)$$

be any solution of model (2) with $\phi \in \Omega$. Define a Lyapunov functional $N_2$ on $\Omega$ as follows,

$$N_2(\phi) = k_4 \phi_2(0) + d_2 \phi_3(0) + \frac{d_2 d_4}{k_5} \phi_4(0) + (k_2 k_4 + d_2 k_3) \int_{-\tau}^0 \phi_1(\theta) \phi_4(\theta) d\theta.$$  

The derivative of $N_2$ along the solution $u_t$ of model (2) for $t \geq 0$ is given by

$$\dot{N}_2(u_t) = (k_2 k_4 + d_2 k_3) E(t) P(t) - \frac{d_2 d_4}{k_5} P(t)$$

$$\leq (k_2 k_4 + d_2 k_3) E_0 \left( \frac{E_{\max}}{E_0} - \frac{1}{R_0} \right) P(t)$$

$$= (k_2 k_4 + d_2 k_3) E_0 \left( \frac{1}{\omega^*} - \frac{1}{R_0} \right) P(t).$$

(14)
Note that $R_0 < \omega^*$, then $\dot{N}_2(u_t) \leq 0$, this shows that $N_2$ is a Lyapunov functional on $\Omega$. Define
\[ E = \{ \phi = (\phi_1, \phi_2, \phi_3, \phi_4) \in \Omega : \dot{N}_2(\phi) = 0 \} \]
\[ \subset \{ \phi = (\phi_1, \phi_2, \phi_3, \phi_4) \in \Omega : \phi_4(0) = 0 \}. \]

Let $M$ be the largest set in $E$ which is invariant with respect to model (2). Clearly, $M$ is not empty since $Q_0 \in M$. We have from model (2) and the invariance of $M$ that $M = \{ Q_0 \}$. Thus, by the classical Lyapunov-LaSalle theorem (see [11, 17]), we obtain that the inflammatory factors-free equilibrium $Q_0$ is globally attractive.

The proof is completed.

**Remark 3.** It is not difficult to show that, if $r k_2 k_6 > d_1 d_2 k_1$ (the case of backward bifurcation), then $\omega^* < \omega < 1$.

In biology, the global asymptotic stability of the inflammatory factors-free equilibrium $Q_0$ implies that, for any initial state value, the inflammation in the lesion area of patients will eventually become disappeared and hence the inflammation can be always controlled. For the case of forward bifurcation, the conditions $k_6 < k_6^*$ and $R_0 < 1$ in Corollary 1 actually imply some strategy for the control of the inflammation. For the cases of both forward bifurcation and backward bifurcation, the condition $R_0 < w^* = 1 - k_6/d_1$ (i.e., $R_0 + k_6/d_1 < 1$) in Theorem 3.3 gives another strategy for the control of the inflammation.

4. **Uniform persistence.** In this section, we will study the uniform persistence of model (2) while $R_0 > 1$, and give some explicit analytic expressions of eventual lower bounds of the concentrations of normal endothelial cells, vascular endothelial growth factors, activated adhesion factors/chemokines, inflammatory factors.

Note that $R_0 = E_0/E^* > 1$, then according to the first equation of model (2), it has
\[ \frac{r}{d_1} = E_0 > E^* = \frac{r}{d_1 + k_1 P^* - \frac{k_6 V^*}{1 + V^*}}, \]
which implies $k_1 P^* - \frac{k_6 V^*}{1 + V^*} > 0$. Thus, there exists a $\delta \in (0, 1)$, such that
\[ \delta k_1 P^* < k_1 P^* - \frac{k_6 V^*}{1 + V^*} \]
holds. For convenience, we define the following parameters
\[ b(\delta) = \delta k_1 P^* + d_1, \ E^{(0)}(\delta) = \frac{r}{b(\delta)} > E^*, \ q_1(\delta) = \sqrt{\frac{E^{(0)}(\delta)}{E^*}} > 1, \]
\[ E^{(1)}(\delta) = q_1(\delta) E^* > E^*, \ q_2(\delta) = \sqrt{\frac{E^{(0)}(\delta)}{E^{(1)}(\delta)}} > 1, \ E^{(2)}(\delta) = q_2(\delta) E^* > E^*, \]
\[ q_3(\delta) = \sqrt{\frac{E^{(1)}(\delta)}{E^{(2)}(\delta)}} > 1, \ E^{(3)}(\delta) = q_3(\delta) E^* > E^*. \]
It is easy to see that
\[ q_1(\delta) > q_2(\delta) > q_3(\delta) > 1, \ E^0(\delta) > E^{(1)}(\delta) > E^{(2)}(\delta) > E^{(3)}(\delta) > E^*. \]
**Theorem 4.1.** If $R_0 > 1$, then model (2) is uniformly persistent in $\mathbb{C}^+$, and the solution $(E(t), V(t), C(t), P(t))^T$ of model (2) with any $\phi \in \mathbb{C}^+$ satisfies

\[
\liminf_{t \to \infty} E(t) \geq \frac{rd_2d_4\nu}{rk_3(2k_2k_4 + d_2k_3) + \nu d_1d_2d_4} \equiv \nu_1, \\
\liminf_{t \to \infty} V(t) \geq \frac{k_2\nu_1}{d_2} \delta P^* e^{-d_4(T_1 + T_2 + T_3 + \tau)} \equiv \nu_2(\delta), \\
\liminf_{t \to \infty} C(t) \geq \frac{(d_2k_3 + k_2k_4)\nu_1}{d_2d_3} \delta P^* e^{-d_4(T_1 + T_2 + T_3 + \tau)} \equiv \nu_3(\delta), \\
\liminf_{t \to \infty} P(t) \geq \delta P^* e^{-d_4(T_1 + T_2 + T_3 + \tau)} \equiv \nu_4(\delta),
\]

where

\[
T_1 = \frac{1}{b(\delta)} \ln\left(\frac{q_1(\delta)}{q_1(\delta) - 1}\right), \quad T_2 = \frac{1}{d_2} \ln\left(\frac{q_1(\delta)}{q_1(\delta) - q_2(\delta)}\right), \quad T_3 = \frac{1}{d_3} \ln\left(\frac{q_2(\delta)}{q_2(\delta) - q_3(\delta)}\right).
\]

**Proof.** By Lemmas 2.1 and 2.3, we can easily obtain that $\mathbb{C}^+$ is positively invariant for model (2), and we only need to show that (15) holds.

Let $(E(t), V(t), C(t), P(t))^T$ be the solution of model (2) with any $\phi \in \mathbb{C}^+$. By Lemma 2.1, for any sufficiently small $\varepsilon > 0$, there exists a sufficiently large constant $T' > 0$ such that, $P(t) \leq P_{max} + \varepsilon$ for $t > T'$. From the first equation of model (2), it has that,

\[
\dot{E}(t) \geq r - [k_1(P_{max} + \varepsilon) + d_1] E(t)
\]

for $t > T'$, from which it has

\[
\liminf_{t \to \infty} E(t) \geq \frac{r}{k_1(P_{max} + \varepsilon) + d_1} = \nu_1.
\]

Considering that the above formula holds for arbitrary $\varepsilon > 0$, it has that

\[
\liminf_{t \to \infty} E(t) \geq \frac{r}{k_1P_{max} + d_1} = \nu_1.
\]

Next, let us show that $\liminf_{t \to \infty} P(t) \geq \nu_4(\delta)$.

**Claim** For any $t_0 > \tau + 1$, it is impossible to satisfy $P(t) \leq \delta P^*$ for all $t \geq t_0$.

If the claim would not hold, then there exists a $t_0 > \tau + 1$ such that $P(t) \leq \delta P^*$ for all $t \geq t_0$. It follows from the first equation of model (2) that, for $t \geq t_0$,

\[
\dot{E}(t) \geq r - k_1E(t)P(t) - d_1E(t) \geq r - (\delta k_1P^* + d_1)E(t) = r - b(\delta)E(t),
\]

which implies

\[
E(t) \geq e^{-b(\delta)(t-t_0)} \left[ E(t_0) + r \int_{t_0}^{t} e^{b(\delta)(s-t_0)} ds \right] \geq \frac{r}{b(\delta)} \left[ 1 - e^{-b(\delta)(t-t_0)} \right].
\]

Hence, it has

\[
E(t) \geq \frac{r}{b(\delta)} (1 - e^{-b(\delta)T_1}) = E^{(1)}(\delta) > E^* \quad (16)
\]

for $t \geq t_0 + T_1$. Define

\[
t_m = t_0 + T_1 + \tau, \quad V_m = \min_{\theta \in [-\tau, 0]} V(t_0 + \tau + 2\theta), \\
C_m = \min_{\theta \in [-\tau, 0]} C(t_0 + \tau + 2\theta), \quad P_m = \min_{\theta \in [-\tau, 0]} P(t_0 + \tau + 2\theta), \\
S_m(\delta) = \min \left\{ \frac{d_2V_m}{k_2E^{(1)}(\delta)}, \frac{d_2d_3C_m}{(k_2k_4 + d_2k_3)E^{(1)}(\delta)}, P_m \right\} > 0.
\]
Now, we shall show that \( P(t) \geq S_m(\delta) > 0 \) for \( t \geq t_m \). If not, there exists a \( \tilde{t} \geq 0 \) such that \( P(t) \geq S_m(\delta) \) for \( t_m \leq t \leq t_m + \tau + \tilde{t} \), \( P(t_m + \tau + \tilde{t}) = S_m(\delta) \) and \( \dot{P}(t_m + \tau + \tilde{t}) \leq 0 \). From the second equation of model (2), it has

\[
\dot{V}(t) \geq k_2 E^{(1)}(\delta) S_m(\delta) - d_2 V(t)
\]

for \( t_m \leq t \leq t_m + \tau + \tilde{t} \), from which we obtain

\[
V(t) \geq \frac{k_2 E^{(1)}(\delta) S_m(\delta)}{d_2} + \left[ V(t_m) - \frac{k_2 E^{(1)}(\delta) S_m(\delta)}{d_2} \right] e^{-d_2(t-t_m)} \geq \frac{k_2 E^{(1)}(\delta) S_m(\delta)}{d_2} \geq \frac{k_2 E^{(1)}(\delta) S_m(\delta)}{d_2} + [V(t_m) - V_m] e^{-d_2(t-t_m)}
\]

(17)

for \( t_m \leq t \leq t_m + \tau + \tilde{t} \). Then, from the third equation of model (2) and (17), it has

\[
\hat{C}(t) \geq k_3 E^{(1)}(\delta) S_m(\delta) + \frac{k_2 k_4 E^{(1)}(\delta) S_m(\delta)}{d_2} - d_3 C(t)
\]

for \( t_m \leq t \leq t_m + \tau + \tilde{t} \), from which we obtain

\[
C(t) \geq \frac{d_2 k_3 + k_2 k_4}{d_2 d_3} E^{(1)}(\delta) S_m(\delta) + \left[ C(t_m) - \frac{d_2 k_3 + k_2 k_4}{d_2 d_3} E^{(1)}(\delta) S_m(\delta) \right] e^{-d_3(t-t_m)} \geq \frac{d_2 k_3 + k_2 k_4}{d_2 d_3} E^{(1)}(\delta) S_m(\delta) + [C(t_m) - C_m] e^{-d_3(t-t_m)} \geq \frac{d_2 k_3 + k_2 k_4}{d_2 d_3} E^{(1)}(\delta) S_m(\delta)
\]

(18)

for \( t_m \leq t \leq t_m + \tau + \tilde{t} \). By (18) and \( E^* = \frac{d_3 d_4}{k_5 (d_2 k_4 + d_2 k_3)} \), it has

\[
P(t_m + \tau + \tilde{t}) = k_5 C(t_m + \tau + \tilde{t}) - d_4 P(t_m + \tau + \tilde{t}) \geq \frac{k_5 (d_2 k_3 + k_2 k_4)}{d_2 d_3} E^{(1)}(\delta) S_m(\delta) - d_4 S_m(\delta) = d_4 S_m(\delta) \left( \frac{E^{(1)}(\delta)}{E^*} - 1 \right) > 0.
\]

This leads a contradiction to \( \dot{P}(t_m + \tau + \tilde{t}) \leq 0 \). Thus, \( P(t) \geq S_m(\delta) > 0 \) for \( t \geq t_m \). Let

\[
G(t) = k_4 V(t) + d_2 C(t) + \frac{d_2 d_3}{k_5} P(t) + (k_2 k_4 + d_2 k_3) \int_{t-\tau}^{t} E(s) P(s) ds,
\]

for \( t \geq t_m \), we have

\[
\dot{G}(t) = (k_2 k_4 + d_2 k_3) E(t) P(t) - \frac{d_2 d_3 d_4}{k_5} P(t) = (k_2 k_4 + d_2 k_3) E^* \left( \frac{E(t)}{E^*} - 1 \right) P(t) \geq (k_2 k_4 + d_2 k_3) E^* \left( \frac{E^{(1)}(\delta)}{E^*} - 1 \right) S_m(\delta) > 0,
\]

\[
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\]

\[
\]
which means that \( \lim_{t \to \infty} G(t) = \infty \). However, by Lemma 2.1, it holds that

\[
\limsup_{t \to \infty} G(t) \leq k_4 V_{\text{max}} + d_2 C_{\text{max}} + \frac{d_2 d_3 P_{\text{max}}}{k_5} + (k_2 k_4 + d_2 k_3) E_{\text{max}} P_{\text{max}} \tau < \infty.
\]

This is a contradiction. Hence, the claim is proved.

By the claim, there are two cases need to be discussed.

(i) \( P(t) \geq \delta P^* \) for all sufficiently large \( t \).

(ii) \( P(t) \) oscillates about \( \delta P^* \) for all sufficiently large \( t \).

Obviously, we only need to consider the case (ii). Let \( t_1 \) and \( t_2 \) be sufficiently large such that \( P(t_1) = P(t_2) = \delta P^* \), and \( P(t) < \delta P^* \) for \( t_1 < t < t_2 \).

If \( t_2 - t_1 \leq T_1 + T_2 + T_3 + \tau \), from the last equation of model (2), it has \( \dot{P}(t) \geq -d_4 P(t) \). Hence, for \( t_1 \leq t \leq t_2 \), we have

\[
P(t) \geq P(t_1) e^{-d_4(t-t_1)} \geq \delta P^* e^{-d_4(t_2-t_1)} \geq \delta P^* e^{-d_4(T_1+T_2+T_3+\tau)} = \nu_4(\delta).
\]

If \( t_2 - t_1 > T_1 + T_2 + T_3 + \tau \), it is easily obtained that \( P(t) \geq \nu_4(\delta) \) for \( t_1 \leq t \leq t_1 + T_1 + T_2 + T_3 + \tau \). Then, let us show that \( P(t) \geq \nu_4(\delta) \) for \( t_1 + T_1 + T_2 + T_3 + \tau < t \leq t_2 \). In fact, if not, there exists a \( T_4 \geq 0 \) such that \( P(t) \geq \nu_4(\delta) \) for \( t_1 \leq t \leq t^* \), \( P(t^*) = \nu_4(\delta) \) and \( \dot{P}(t^*) \leq 0 \), where \( t^* = t_1 + T_1 + T_2 + T_3 + T_4 + \tau \). Using the previous similar argument to (16), we have \( E(t) \geq E^{(1)}(\delta) > E^* \) for \( t_1 + T_1 \leq t \leq t_2 \). Hence, we have

\[
\dot{V}(t) = k_2 E(t - \tau) P(t - \tau) - d_2 V(t) \geq k_2 E^{(1)}(\delta) \nu_4(\delta) - d_2 V(t)
\]

for \( t_1 + T_1 + \tau \leq t \leq t^* \), from which we have

\[
V(t) \geq \frac{k_2 E^{(1)}(\delta) \nu_4(\delta)}{d_2} + \left[ V(t_1 + T_1 + \tau) - \frac{k_2 E^{(1)}(\delta) \nu_4(\delta)}{d_2} \right] e^{-d_2(t-t_1-T_1-\tau)} \tag{19}
\]

for \( t_1 + T_1 + \tau \leq t \leq t^* \). By (19), we have

\[
V(t) \geq \frac{k_2 E^{(1)}(\delta) \nu_4(\delta)}{d_2} [1 - e^{-d_2(t-t_1-T_1-\tau)}]
\]

\[
\geq \frac{k_2 E^{(1)}(\delta) \nu_4(\delta)}{d_2} [1 - e^{-d_2 T_2}]
\]

\[
= \frac{k_2 E^{(2)}(\delta) \nu_4(\delta)}{d_2}
\]

for \( t_1 + T_1 + T_2 + \tau \leq t \leq t^* \). Next, from the third equation of model (2), we have

\[
\dot{C}(t) = k_3 E(t - \tau) P(t - \tau) + k_4 V(t) - C(t)
\]

\[
\geq k_3 E^{(1)}(\delta) \nu_4(\delta) + \frac{k_2 k_4 E^{(2)}(\delta) \nu_4(\delta)}{d_2} - d_3 C(t),
\]

\[
\geq k_3 E^{(2)}(\delta) \nu_4(\delta) + \frac{k_2 k_4 E^{(2)}(\delta) \nu_4(\delta)}{d_2} - d_3 C(t)
\]

for \( t_1 + T_1 + T_2 + \tau \leq t \leq t^* \), from which we have

\[
C(t) \geq \left( \frac{d_2 k_3 + k_2 k_4}{d_2 d_3} \right) E^{(2)}(\delta) \nu_4(\delta)
\]

\[
+ \left[ C(t_1 + T_1 + T_2 + \tau) - \left( \frac{d_2 k_3 + k_2 k_4}{d_2 d_3} \right) E^{(2)}(\delta) \nu_4(\delta) \right] e^{-d_3(t-t_1-T_1-T_2-\tau)} \tag{20}
\]
for \( t_1 + T_1 + T_2 + \tau \leq t \leq t^* \). By (20), we have

\[
C(t) \geq \left( \frac{d_2 k_3 + k_2 k_4}{d_2 d_3} \right) E^{(2)}(\delta)v_4(\delta)[1 - e^{-d_3(t - t_1 - T_1 - T_2 - \tau)}] \\
\geq \left( \frac{d_2 k_3 + k_2 k_4}{d_2 d_3} \right) E^{(2)}(\delta)v_4(\delta)[1 - e^{-d_3 T_3}] \\
= \left( \frac{d_2 k_3 + k_2 k_4}{d_2 d_3} \right) E^{(3)}(\delta)v_4(\delta)
\]

for \( t_1 + T_1 + T_2 + T_3 + \tau \leq t \leq t^* \). According to the last equation of model (2), we have

\[
\dot{P}(t^*) = k_5 C(t^*) - d_4 P(t^*) \\
\geq k_5 \left( \frac{d_2 k_3 + k_2 k_4}{d_2 d_3} \right) E^{(3)}(\delta)v_4(\delta) - d_4 v_4(\delta) \\
= d_4 v_4(\delta) \left( \frac{E^{(3)}(\delta)}{E^*} - 1 \right) \\
> 0,
\]

which is a contradiction to \( \dot{P}(t^*) \leq 0 \). Thus, \( P(t) \geq v_4(\delta) \) for \( t_1 \leq t \leq t_2 \). Since the interval \( t_1 \leq t \leq t_2 \) is arbitrary chosen, we conclude that \( P(t) \geq v_4(\delta) \) holds for all sufficiently large \( t \). Hence, \( \liminf_{t \to \infty} P(t) \geq v_4(\delta) \).

Moreover, according to model (2), it easily has that

\[
\liminf_{t \to \infty} V(t) \geq \frac{k_2 \nu_1 v_4(\delta)}{d_2} = \nu_2(\delta) \\
\liminf_{t \to \infty} C(t) \geq \frac{k_3 \nu_1 v_4(\delta) + k_4 \nu_2(\delta)}{d_3} = \frac{(d_2 k_3 + k_2 k_4) \nu_1 v_4(\delta)}{d_2 d_3} = \nu_3(\delta).
\]

The proof is completed. \( \square \)

We would like to mention that, although model (2) undergoes a forward bifurcation or a backward bifurcation under some conditions, the conclusion of uniform persistence in Theorem 4.1 implies that, if the basic reproduction number \( R_0 > 1 \), the inflammation in the lesion area of patients can not be removed and will exist forever. Furthermore, the explicit expressions of \( \nu_1, \nu_2(\delta), \nu_3(\delta) \) and \( \nu_4(\delta) \) in Theorem 4.1 also give feasible estimations of the concentrations of normal endothelial cells, vascular endothelial growth factors, activated adhesion factors/chemokines and inflammatory factors when the time \( t \) is sufficiently large.

5. Stability of the inflammatory factors-existent equilibria and Hopf bifurcation analysis.

5.1. Local stability of the inflammatory factors-existent equilibria and Hopf bifurcation analysis. Without loss of generality, we assume that \( Q(E, V, C, \overline{P}) \) is any positive equilibrium of model (2). By (4), (5) and \( R_0 = \frac{r}{d_1 E} \) we have

\[
d_1 + k_1 \overline{P} - \frac{k_6 V}{1 + V} = \frac{r}{E} = d_1 R_0, \quad \overline{P} = \frac{k_5}{d_4} \frac{E}{C} = \frac{k_5 (k_2 k_4 + d_2 k_3)}{d_3 d_4 k_2} V = \frac{d_1 d_2 R_0}{r k_2} V. \quad (21)
\]
By (21), (6) can be rewritten as

\[
\begin{vmatrix}
\lambda + d_1R_0 & -\frac{r_k}{d_1R_0e^{-\lambda\tau}} & 0 & \frac{r_k}{d_1R_0} \\
-\frac{d_kR_0}{d_1R_0}e^{-\lambda\tau} & \lambda + d_2 & 0 & -\frac{r_k}{d_1R_0}e^{-\lambda\tau} \\
-\frac{d_kR_0}{r_k} & -k_4 & \lambda + d_3 & -\frac{r_k}{d_1R_0}e^{-\lambda\tau} \\
0 & 0 & -k_5 & \lambda + d_4
\end{vmatrix} = 0.
\]

(22)

By calculation, the associated transcendental characteristic equation of model (2) at \(Q(E, V, C, P)\) can be expressed as follows,

\[L_2(\lambda, \tau) \equiv \lambda^4 + A_3\lambda^3 + A_2\lambda^2 + A_1\lambda + A_0 + e^{-\lambda\tau}(B_2\lambda^2 + B_1\lambda + B_0) = 0,\]

(23)

where

\[
\begin{align*}
A_3 &= d_1R_0 + d_2 + d_3 + d_4, \\
A_2 &= d_2d_3d_4 + d_1R_0(d_2 + d_3 + d_4), \\
A_1 &= d_2d_3d_4 + d_1R_0(d_2 + d_3 + d_4), \\
A_0 &= d_1d_2d_3d_4R_0,
\end{align*}
\]

\[
\begin{align*}
B_2 &= -\frac{d_2k_4V}{(1 + V)^2} - \frac{r_kk_5}{d_1R_0}, \\
B_1 &= -rk_3k_5 - d_2d_3d_4 - \frac{d_2(d_3 + d_4)k_6V}{(1 + V)^2} + \frac{d_2k_1k_3k_5V}{k_2}, \\
B_0 &= -d_1d_2d_3d_4R_0 + d_2k_1k_4k_5V + \frac{d_2k_1k_3k_5V}{k_2} - \frac{d_2d_3d_4k_6V}{(1 + V)^2}.
\end{align*}
\]

Let us first consider the local stability of the inflammatory factors-existent equilibrium \(Q^*(E^*, V^*, C^*, P^*)\). Through the proof process of Theorem 4.4 in \[28\], we have

\[A_0 + B_0 = d_2k_1k_4k_5V^* + \frac{d_2k_1k_3k_5V^*}{k_2} - \frac{d_2d_3d_4k_6V^*}{(1 + V^*)^2} < 0.\]

Note that \(L_2(\lambda, \tau)\) is continuous for \(\lambda, \tau\), and for any given \(\tau \geq 0\),

\[L_2(0, \tau) = A_0 + B_0 < 0, \quad \lim_{\lambda \to \infty} L_2(\lambda, \tau) = \infty.\]

Hence, similar to the argument in Theorem 3.1, we can obtain the inflammatory factors-existent equilibrium \(Q^*\) is unstable for any \(\tau \geq 0\).

Next, let us consider the local stability of the inflammatory factors-existent equilibrium \(Q^*(E^*, V^*, C^*, P^*)\). From \[28\], we know that each root of (23) has negative real part for \(\tau = 0\). Then, we suppose (23) has a purely imaginary root \(\lambda = \imath u\) \((u > 0)\) for some \(\tau > 0\). Substituting \(\lambda = \imath u\) into (23) and separating the real and imaginary parts, we have

\[
\begin{align*}
(B_2u^2 - B_0)\cos u\tau - B_1u\sin u\tau &= u^4 - A_2u^2 + A_0, \\
(B_2u^2 - B_0)\sin u\tau + B_1u\cos u\tau &= A_3u^3 - A_1u.
\end{align*}
\]

(24)

Squaring and adding the two equations of (24), it follows that

\[u^8 + pu^6 + qu^4 + lu^2 + \eta = 0,\]

(25)

where

\[
\begin{align*}
p &= A_3^2 - 2A_2 = d_2^2R_0^2 + d_4^2 + d_3^2 + d_2^2 > 0, \\
q &= A_2^2 - 2A_1A_3 - B_2^2 + 2A_0, \\
l &= A_2^2 - 2A_0A_2 + 2B_0B_2 - B_1^2, \\
\eta &= A_0^2 - B_0^2.
\end{align*}
\]
Now, let us show that \( q > 0 \) and \( \eta > 0 \). By Lemma 4.1 and the proof process of Theorem 4.3 in [28], we have

\[
V^* < \frac{r_k k}{d_2 k_1}, \quad d_2 k_1 k_4 k_5 V^* + \frac{d_2^2 k_1 k_3 k_5 V^*}{k_2} > \frac{d_2 d_3 d_4 k_6 V^*}{(1 + V^*)^2}. \tag{26}
\]

Then, by (26), we have

\[
d_1 d_2 d_3 d_4 R_0 = r k_3 k_2 k_4 + r k_3 d_2 k_3 > d_2 k_1 k_4 k_5 V^* + \frac{d_2^2 k_1 k_3 k_5 V^*}{k_2} > \frac{d_2 d_3 d_4 k_6 V^*}{(1 + V^*)^2}. \tag{27}
\]

By (27) and note that \( d_3 d_4 - \frac{r k k}{d_1 R_0} = \frac{r k k}{d_2 R_0} > 0 \), we have

\[
q = d_1^2 R_0^2 (d_2^2 + d_3^2 + d_4^2) + d_2^2 d_3^2 + d_2^2 + d_3^2 > \left( \frac{d_2 k_6 V^*}{(1 + V^*)^2} + \frac{r k_3 k_5}{d_1 R_0} \right)^2
\]

\[
- d_1 R_0 (d_2^2 + d_3^2 + d_4^2) + d_2^2 d_3^2 + d_2^2 + d_3^2 - (d_1 d_2 R_0 + d_3 d_4)^2
\]

\[
= d_1^2 R_0^2 + d_2^2 d_3^2 + (d_1 d_3 R_0 - d_2 d_4)^2 > 0,
\]

\[
\eta = (d_1 d_2 d_3 d_4 R_0)^2 - \left( d_1 d_2 d_3 d_4 R_0 - d_2 k_1 k_4 k_5 V^* - \frac{d_2^2 k_1 k_3 k_5 V^*}{k_2} + \frac{d_2 d_3 d_4 k_6 V^*}{(1 + V^*)^2} \right)^2
\]

\[
= \left( d_2 k_1 k_4 k_5 V^* + \frac{d_2^2 k_1 k_3 k_5 V^*}{k_2} - \frac{d_2 d_3 d_4 k_6 V^*}{(1 + V^*)^2} \right)
\]

\[
\times \left( (2 d_1 d_2 d_3 d_4 R_0 - d_2 k_1 k_4 k_5 V^* - \frac{d_2^2 k_1 k_3 k_5 V^*}{k_2} + \frac{d_2 d_3 d_4 k_6 V^*}{(1 + V^*)^2} \right) > 0.
\]

The sign of \( l \) cannot be determined, and the numerical simulation in the last section will give an explanation.

Letting \( v = w^2 > 0 \), (25) can be written as

\[
h(v) \equiv v^4 + pv^3 + qv^2 + lv + \eta = 0. \tag{28}
\]

Then we have

\[
h'(v) = 4v^3 + 3pv^2 + 2qv + l.
\]

If \( l < 0 \), there exists a unique \( v^* \) such that \( h'(v^*) = 0 \). Then, it is easy to obtain the following conclusions.

**Lemma 5.1.** The following statements hold:

(i) If \( l \geq 0 \), (28) has no positive root.

(ii) If \( l < 0 \) and \( h(v^*) > 0 \), (28) has no positive root.

(iii) If \( l < 0 \) and \( h(v^*) \leq 0 \), (28) has two positive roots (assumed to be \( v_1^* \) and \( v_2^* \)).

**Proof.** Obviously, if \( l \geq 0 \), (28) has no positive root. If \( l < 0 \) and note that \( p, q > 0 \), hence, \( h(v) \) takes the minimum value \( h(v_0) \) at \( v = v^* \). If \( h(v^*) > 0 \), we can also obtain that (28) has no positive root. If \( h(v^*) \leq 0 \), by Descartes’ rule of signs, we can obtain that (28) has two positive roots, \( v_1^* \) and \( v_2^* \).

The proof is completed.

**Remark 4.** If \( l < 0 \) and \( h(v^*) = 0 \), then (28) has a double positive root \( v = v^* = v_1^* = v_2^* \) and \( h'(v^*) = 0 \).
Below, let us consider the case of \( l < 0 \) and \( h'(v^*) \leq 0 \). Without loss of generality, we assume that \( v_1^* \geq v_2^* \), then we have \( h'(v_1^*) \geq 0 \) and \( h'(v_2^*) \leq 0 \). Then, (25) has positive roots \( u_k = \sqrt{\nu_k^2} \) \((k = 1, 2)\). From (24), we have

\[
\begin{align*}
\cos u_k \tau &= \frac{(u_k^4 - A_2u_k^2 + A_0)(B_2u_k^2 - B_0) + B_1u_k(A_3u_k^3 - A_1u_k)}{B_1^2u_k^2 + (B_2u_k^2 - B_0)^2} \equiv F_c(u_k), \\
\sin u_k \tau &= \frac{-B_1u_k(u_k^4 - A_2u_k^2 + A_0) + (B_2u_k^2 - B_0)(A_3u_k^3 - A_1u_k)}{B_1^2u_k^2 + (B_2u_k^2 - B_0)^2} \equiv F_s(u_k).
\end{align*}
\]

Let

\[
\tau_k^{(j)} = \begin{cases} 
\arccos \frac{u_k}{A_2u_k^2 + A_0} + \frac{2j\pi}{2\pi - \arccos \frac{u_k}{A_2u_k^2 + A_0}}, & F_s(u_k) \geq 0, \\
\frac{2\pi - \arccos \frac{u_k}{A_2u_k^2 + A_0} + 2j\pi}{2\pi - \arccos \frac{u_k}{A_2u_k^2 + A_0}}, & F_s(u_k) < 0, \\
\end{cases} \quad k = 1, 2, \ j = 0, 1, 2, \ldots
\]

Let \( \lambda(\tau) = \alpha(\tau) + iu(\tau) \) be the root of (23) satisfying \( \alpha(\tau_k^{(j)}) = 0 \) and \( u(\tau_k^{(j)}) = u_k \) \((k = 1, 2, \ j = 0, 1, 2, \ldots)\). Then we have the following conclusion.

**Lemma 5.2.** If \( l < 0 \) and \( h(v^*) < 0 \), then \( \alpha'(\tau_1^{(j)}) > 0 \) and \( \alpha'(\tau_2^{(j)}) < 0 \).

**Proof.** Differentiating the two sides of (23) with respect to \( \tau \) and noticing that \( \lambda \) is a function of \( \tau \), it follows that

\[
\left( \frac{d\lambda(\tau)}{d\tau} \right)^{-1} = \frac{4\lambda^3 + 3A_2\lambda^2 + 2A_2\lambda + A_1}{\lambda e^{-\lambda\tau}(B_2\lambda^2 + B_1\lambda + B_0)} - \frac{\tau}{\lambda} + \frac{2B_2\lambda + B_1}{\lambda(B_2\lambda^2 + B_1\lambda + B_0)}.
\]

Then, by direct calculation, we have

\[
\left[ \frac{d(\text{Re}\lambda(\tau))}{d\tau} \right]_{\tau = \tau_k^{(j)}}^{-1} = -\frac{(3A_3u_k^2 + A_1)(A_3u_k^3 - A_1) + (u_k^4 - A_2u_k^2 + A_0)(-4u_k^2 + 2A_2)}{(u_k^4 - A_2u_k^2 + A_0)^2 + (A_3u_k^3 - A_1u_k)^2} + \frac{A_2^2u_k^2 + B_2(B_0 - B_2u_k^2)}{(B_2u_k^2 - B_0)^2 + B_1^2u_k^2}.
\]

By (24), we have

\[
(B_2u_k^2 - B_0)^2 + B_1^2u_k^2 = (u_k^4 - A_2u_k^2 + A_0)^2 + (A_3u_k^3 - A_1u_k)^2,
\]

from which (31) can be rewritten as

\[
\left[ \frac{d(\text{Re}\lambda(\tau))}{d\tau} \right]_{\tau = \tau_k^{(j)}}^{-1} = \frac{4u_k^2 + 3pu_k^2 + 2qu_k^2 + l}{(B_2u_k^2 - B_0)^2 + B_1^2u_k^2} = \frac{h'(v_k^*)}{(B_2u_k^2 - B_0)^2 + B_1^2u_k^2}.
\]

Hence, it follows that

\[
sign\{\alpha'(\tau_k^{(j)})\} = sign\left\{ \frac{d(\text{Re}\lambda(\tau))}{d\tau} \right\}_{\tau = \tau_k^{(j)}}^{-1} = sign\left\{ \frac{d(\text{Re}\lambda(\tau))}{d\tau} \right\}_{\tau = \tau_k^{(j)}}^{-1} = sign\{h'(v_k^*)\}.
\]

Note that \( h(v^*) < 0 \) implies \( v_1^* > v_2^* \), then we have \( h'(v_1^*) > 0 \) and \( h'(v_2^*) < 0 \). Therefore, we have \( \alpha'(\tau_1^{(j)}) > 0 \) and \( \alpha'(\tau_2^{(j)}) < 0 \).

The proof is completed. \( \square \)
Remark 5. It is not difficult to show that, if $l < 0$ and $h(v^*) = 0$, then $\alpha'(\tau_1^{(j)}) = 0$.

If $l < 0$ and $h(v^*) < 0$, then according to the definition of $\{\tau_1^{(j)}\}$ and $\{\tau_2^{(j)}\}$ in (30), for all $j \in N$, we have

$$
\tau_1^{(j)} < \tau_1^{(j+1)}, \ \tau_2^{(j)} < \tau_2^{(j+1)}, \ \lim_{j \to \infty} \tau_k^{(j)} = \infty.
$$

In addition, since the multiplicity of roots with positive real parts cannot become negative, then by Lemma 5.2, we have $\tau_1^{(0)} < \tau_2^{(0)}$. Furthermore, by $u_1 > u_2$ and (30), we have $\tau_1^{(j+1)} - \tau_1^{(j)} < \tau_2^{(j+1)} - \tau_2^{(j)}$ and $\tau_1^{(j)} < \tau_2^{(j)}$. Therefore, there exists a $\widehat{j} \in N$, such that $\tau_1^{(j+1)} < \tau_2^{(j)}$, then we have

$$
0 < \tau_1^{(0)} < \tau_1^{(1)} < \tau_2^{(1)} < \cdots < \tau_1^{(\widehat{j}-1)} < \tau_1^{(\widehat{j}+1)} < \tau_2^{(\widehat{j})}.
$$

By Lemmas 5.1 and 5.2, and applying the local stability theory and Hopf bifurcation theorem for DDEs (see [11, 17]), then we have the following results.

Theorem 5.3. If $r k_2 k_5 \leq d_1 d_2 k_1$ (the case of forward bifurcation) and $R_0 > 1$, or $r k_2 k_5 > d_1 d_2 k_1$ (the case of backward bifurcation) and $R_0 > \omega$, then the inflammatory factors-existent equilibrium $Q^*$ exists. Then, the following results hold:

(i) If $l \geq 0$, or $l < 0$ and $h(v^*) > 0$, then the inflammatory factors-existent equilibrium $Q^*$ is locally asymptotically stable for any $\tau \geq 0$.

(ii) If $l < 0$ and $h(v^*) < 0$, then model (2) undergoes a Hopf bifurcation at the inflammatory factors-existent equilibrium $Q^*$ when $\tau = \tau_k^{(j)}$ $(k = 1, 2, j = 0, 1, 2, \ldots)$. Furthermore, the inflammatory factors-existent equilibrium $Q^*$ is locally asymptotically stable for

$$
\tau \in (0, \tau_1^{(0)}) \cup (\tau_2^{(0)}, \tau_1^{(1)}) \cup \cdots \cup (\tau_2^{(\widehat{j}-1)}, \tau_1^{(\widehat{j})})
$$

and is unstable for

$$
\tau \in (\tau_2^{(0)}, \tau_1^{(0)}) \cup \cdots \cup (\tau_1^{(\widehat{j}-1)}, \tau_2^{(\widehat{j}-1)}) \cup (\tau_2^{(\widehat{j})}, \infty),
$$

that is, the stability of the inflammatory factors-existent equilibrium $Q^*$ will switch $2j + 1$ times.

(iii) If $l < 0$ and $h(v^*) = 0$, then the inflammatory factors-existent equilibrium $Q^*$ is locally asymptotically stable for $\tau \in (0, \tau_1^{(0)})$

Theorem 5.4. If $r k_2 k_5 \geq d_1 d_2 k_1$ (the case of backward bifurcation) and $\omega < R_0 < 1$, then the inflammatory factors-existent equilibrium $Q^*$ is unstable for any $\tau \geq 0$.

As pointed out in Section 4, for any case of forward bifurcation and backward bifurcation, the conclusion of uniform persistence in Theorem 4.1 implies that, if the basic reproduction number $R_0 > 1$, the inflammation in the lesion area of patients can not be removed and will exist forever for any time delay $\tau$. The conclusion (i) in Theorem 5.3 further indicates that the time delay $\tau$ may be harmless for the local asymptotic stability of the inflammatory factors-existent equilibrium $Q^*$ of model (2). That is, when the value of the initial function $\phi$ is chosen in the neighbourhood of $Q^*$, with the increase of the time $t$, the concentrations of normal endothelial cells, vascular endothelial growth factors, activated adhesion factors/chemokines and inflammatory factors will ultimately tend to some constant values. However, the conclusion (ii) in Theorem 5.3 indicates the time delay $\tau$ may be no longer harmless.
for the local asymptotic stability of the inflammatory factors-existent equilibrium \( Q^* \) and lead to the existence of periodic solutions of model (2). In biology, this means that, for larger time delay \( \tau \), the concentrations of normal endothelial cells, vascular endothelial growth factors, activated adhesion factors/chemokines and inflammatory factors will become oscillatory in some ranges. In addition, for the case of backward bifurcation, the conclusions in Theorems 3.1, 5.3 and 5.4 show that, if \( \omega < R_0 < 1 \), whether the inflammation can be cleared or not will also depend on the choice of the value of the initial function \( \phi \) of model (2).

5.2. Global stability of the inflammatory factors-existent equilibrium. In this subsection, we will further consider the global stability of the inflammatory factors-existent equilibrium \( Q^* \) while \( R_0 > 1 \), by Barbalat’s lemma.

Define

\[
\delta_1 = k_1(d_1 + d_2)(1 + V^*) - k_2k_6e^*, \quad \delta_2 = k_1(d_1 + d_2 - k_6)(1 + V^*) > 0.
\]

From the first two equations of model (2), we have

\[
r - d_1V^* = \frac{d_2k_1V^* - k_6V^*e^*}{1 + V^*},
\]

then by \( R_0 = \frac{r}{d_1V^*} > 1 \), we have

\[
\delta_1 > (1 + V^*)(d_2k_1 - \frac{k_2k_6V^*}{1 + V^*}) = \frac{k_2(1 + V^*)(r - d_1V^*)}{V^*} > 0.
\]

For simplicity of presentation, for any sufficiently small \( \varepsilon > 0 \) and any \( \theta_1 \in [0, 1] \), we define

\[
M_0(\varepsilon) = (k_5 + d_4)(E_{\text{max}} + \varepsilon) + \left[ \frac{r}{E^*} + \left( \frac{k_6}{1 + V^*} + k_1 \right)(E_{\text{max}} + \varepsilon) \right] (P_{\text{max}} + \varepsilon),
\]

\[
M_{11}(\varepsilon) = \frac{k_2(\delta_1 + \delta_2V^*)}{E_{\text{max}} + \varepsilon} \left( d_1 - \frac{k_6V^*}{1 + V^*} + k_2k_6 \left( d_1 - k_6 \frac{V_{\text{max}} + \varepsilon}{1 + V_{\text{max}} + \varepsilon} \right) \right)
- \frac{k_1k_2k_6}{2E^*} [k_2E^*M_0(\varepsilon) + r(k_1 + k_2)(P_{\text{max}} + \varepsilon)] \tau,
\]

\[
\tilde{M}_{11}(\varepsilon) = \frac{k_2(\delta_1 + \delta_2V^*)}{E^*} \left( d_1 - \frac{k_6V^*}{1 + V^*} + k_2k_6 \left( d_1 - k_6 \frac{V_{\text{max}} + \varepsilon}{1 + V_{\text{max}} + \varepsilon} \right) \right)
- \frac{k_1k_2k_6}{2E^*} [k_2E^*M_0(\varepsilon) + r(k_1 + k_2)(P_{\text{max}} + \varepsilon)] \tau,
\]

\[
M_{12}(\varepsilon, \theta_1) = \frac{(1 - \theta_1)k_2k_6d_2}{1 + V^*} \max \left\{ V^*, \frac{V_{\text{max}} + \varepsilon - V^*}{V_{\text{max}} + \varepsilon + 1} \right\},
\]

\[
M_{22}(\varepsilon, \theta_1) = \frac{\theta_1k_1k_5k_6d_2(\varepsilon - \nu_1 + \varepsilon)}{1 + V^*},
\]

\[
M_{22}(\varepsilon) = k_1k_6 \left( d_2k_1 - \frac{k_2k_6E^*}{1 + V^*} \right) + k_3k_6(d_2k_3 + k_2k_4)
- \frac{k_1k_2k_6}{2(1 + V^*)} [k_1M_0(\varepsilon)(1 + V^*) + (k_1 + k_2)k_6E(\varepsilon + \varepsilon)(P_{\text{max}} + \varepsilon)] \tau,
\]

\[
M_{23} = k_2k_6[(d_2 + d_3)k_3 + k_2k_4], \quad M_{34} = k_3^2k_5k_6,
\]

\[
M_{33}(\varepsilon) = d_3k_2k_6 - \frac{1}{2}k_1k_2(k_1 + k_2)k_5k_6(E_{\text{max}} + \varepsilon) \tau,
\]

\[
M_{44}(\varepsilon) = d_4k_2k_6 - \frac{1}{2}k_1k_2(k_1 + k_2)k_6d_4 + k_1(P_{\text{max}} + \varepsilon)(E_{\text{max}} + \varepsilon) \tau.
\]
Let us define two real symmetric matrices as follows,

\[
J_1(\varepsilon) = \begin{pmatrix}
M_{11}(\varepsilon) & 0 & 0 \\
0 & M_{22}(\varepsilon) & -\frac{1}{2}M_{23} \\
0 & -\frac{1}{2}M_{23} & M_{33}(\varepsilon) \\
0 & 0 & -\frac{1}{2}M_{34}
\end{pmatrix},
\]

\[
J_2(\varepsilon, \theta_1) = \begin{pmatrix}
\hat{M}_{11}(\varepsilon) & -\frac{1}{2}M_{12}(\varepsilon, \theta_1) & 0 & 0 \\
-\frac{1}{2}M_{12}(\varepsilon, \theta_1) & M_{22}(\varepsilon) - M_{22}(\varepsilon, \theta_1) & -\frac{1}{2}M_{23} & 0 \\
0 & -\frac{1}{2}M_{23} & M_{33}(\varepsilon) & -\frac{1}{2}M_{34} \\
0 & 0 & -\frac{1}{2}M_{34} & M_{44}(\varepsilon)
\end{pmatrix}.
\]

Then, we have the following result.

**Theorem 5.5.** If \( R_0 > 1 \) and the following condition holds:

\((H_1) \ J_1(0) \) and \( J_2(0, \theta_1) \) are positive definite matrices.

Then the inflammatory factors–existent equilibrium \( Q^* \) is globally attractive in \( \bar{C}^+ \).

**Proof.** Let \((E(t), V(t), C(t), P(t))^T\) be the solution of model (2) with any \( \phi \in \bar{C}^+ \).

If \( R_0 > 1 \) and the condition \((H_1)\) holds, then there exists a sufficiently small positive constant \( \varepsilon_1 < \min\{\nu_1, \nu_2(\delta), \nu_3(\delta), \nu_4(\delta)\} \) such that \( J_1(\varepsilon_1) \) and \( J_2(\varepsilon_1, \theta_1) \) are also positive definite matrices. By Lemma 2.1 and Theorem 4.1, for the above \( \varepsilon_1 \), there exists a \( T(\varepsilon_1) > 0 \) such that, for \( t \geq T(\varepsilon_1) \),

\[
\begin{align*}
0 < \nu_1 - \varepsilon_1 < E(t) < E_{\text{max}} + \varepsilon_1, \quad & 0 < \nu_2(\delta) - \varepsilon_1 < V(t) < V_{\text{max}} + \varepsilon_1, \\
0 < \nu_3(\delta) - \varepsilon_1 < C(t) < C_{\text{max}} + \varepsilon_1, \quad & 0 < \nu_4(\delta) - \varepsilon_1 < P(t) < P_{\text{max}} + \varepsilon_1.
\end{align*}
\]

Let \( g(x) = x - 1 - \ln x \). For \( t \geq T(\varepsilon_1) \), we define

\[
W(t) = k_2(\delta_1 + \delta_2 V^*)[W_1(t) + W_2(t)] + \sum_{i=3}^{9} W_i(t),
\]

where

\[
W_1(t) = E^*g \left( \frac{E(t)}{E^*} \right) + \frac{k_1k_4V^*}{k_2k_4 + d_2k_3} g \left( \frac{V(t)}{V^*} \right) + \frac{d_3k_1C^*}{k_2k_4 + d_2k_3} g \left( \frac{C(t)}{C^*} \right) + \frac{k_1E^*P^*}{d_4} g \left( \frac{P(t)}{P^*} \right),
\]

\[
W_2(t) = k_1E^*P^* \int_{t-\tau}^{t} g \left( \frac{E(\xi)P(\xi)}{E^*P^*} \right) d \xi,
\]

\[
W_3(t) = \frac{1}{2} k_6[k_2(E(t) - E^*) + k_1(V(t) - V^*)]^2,
\]

\[
W_4(t) = \frac{1}{2} k_6[k_3(V(t) - V^*) - k_2(C(t) - C^*)]^2,
\]

\[
W_5(t) = \frac{1}{2} k_2^2 k_6(P(t) - P^*)^2,
\]

\[
W_6(t) = \frac{r k_1 k_2 (k_1 + k_2) k_6 (P_{\text{max}} + \varepsilon_1)}{2E^*} \int_{t-\tau}^{t} \int_{s}^{t} [E(\xi) - E^*]^2 d \xi ds,
\]

\[
W_7(t) = \frac{k_1 k_2 (k_1 + k_2) k_6^2 (E_{\text{max}} + \varepsilon_1) (P_{\text{max}} + \varepsilon_1)}{2(1 + V^*)} \int_{t-\tau}^{t} \int_{s}^{t} [V(\xi) - V^*]^2 d \xi ds,
\]

\[
W_8(t) = \frac{k_1 k_2 (k_1 + k_2) k_5 k_6 (E_{\text{max}} + \varepsilon_1)}{2} \int_{t-\tau}^{t} \int_{s}^{t} [C(\xi) - C^*]^2 d \xi ds,
\]
\[ W_0(t) = \frac{k_1 k_2 (k_1 + k_2) k_0 [d_4 + k_1 (P_{\text{max}} + \varepsilon_1)] (E_{\text{max}} + \varepsilon_1)}{2} \int_{t-\tau}^{t} \int_{s}^{t} [P(\xi) - P^*]^2 d\xi ds. \]

We now calculate the derivatives of \( W_i (i = 1, 2, \cdots, 9) \) along the solutions of model (2), respectively. Note that \( W_i (t) \) is the same as \( L_i (t) \) in [9], hence, we have omitted some tedious calculations when calculating the derivative of \( W_i (t) \). By calculation, it is not difficult to obtain, for \( t \geq T(\varepsilon_1) + \tau \),

\[
W_1(t) = -\frac{1}{E(t)} \left( d_1 - \frac{k_0 V^*}{1 + V^*} (E(t) - E^*)^2 + \frac{k_6 (E(t) - E^*) (V(t) - V^*)}{(1 + V(t)) (1 + V^*)} \right) + \frac{k_2 k_4}{k_2 k_4 + d_2 k_3} k_1 E^* P^* \left( 1 - \frac{V^*}{V(t)} \right) \left[ \frac{E(t - \tau) P(t - \tau)}{E^* P^*} - \frac{E(t) P(t)}{E^* P^*} \right] + \frac{d_2 k_3}{k_2 k_4 + d_2 k_3} k_1 E^* P^* \left( 1 - \frac{C^*}{C(t)} \right) \left[ \frac{E(t - \tau) P(t - \tau)}{E^* P^*} - \frac{E(t) P(t)}{E^* P^*} \right] + \Pi_1,
\]

\[
\dot{W}_2(t) = k_1 E^* P^* \left[ g \left( \frac{E(t) P(t)}{E^* P^*} \right) - g \left( \frac{E(t - \tau) P(t - \tau)}{E^* P^*} \right) \right] = k_1 E^* P^* (t) - k_1 E(t - \tau) P(t - \tau) + k_1 E^* P^* \ln \frac{E(t - \tau) P(t - \tau)}{E(t) P(t)},
\]

where

\[
\Pi_1 = k_1 E^* P^* \ln \frac{E(t - \tau) P(t - \tau)}{E(t) P(t)}
\]

\[
= \frac{k_2 k_4}{k_2 k_4 + d_2 k_3} k_1 E^* P^* \left[ 4 - \frac{E^*}{E(t)} - \frac{V^* (E(t) P(t))}{V(t) E^* P^*} - \frac{C^* (V(t))}{C(t) V^*} - \frac{P^* C(t)}{P(t) C^*} \right] + \frac{d_2 k_3}{k_2 k_4 + d_2 k_3} k_1 E^* P^* \left[ 3 - \frac{E^*}{E(t)} - \frac{C^* E(t) P(t)}{C(t) E^* P^*} - \frac{P^* C(t)}{P(t) C^*} \right].
\]

Using equality

\[
\Pi_2 := k_1 E^* P^* \ln \frac{E(t - \tau) P(t - \tau)}{E(t) P(t)}
\]

\[
= \frac{k_2 k_4}{k_2 k_4 + d_2 k_3} k_1 E^* P^* \ln \frac{V^* (E(t - \tau) P(t - \tau))}{V(t) E^* P^*} + \ln \frac{E^*}{E(t)} + \ln \frac{C^* (V(t))}{C(t) V^*} + \ln \frac{P^* C(t)}{P(t) C^*}
\]

we can obtain

\[
\dot{W}_1 + \dot{W}_2
\]

\[
= -\frac{1}{E(t)} \left( d_1 - \frac{k_0 V^*}{1 + V^*} (E(t) - E^*)^2 + \frac{k_6 (E(t) - E^*) (V(t) - V^*)}{(1 + V(t)) (1 + V^*)} \right) + \frac{k_4}{k_2 k_4 + d_2 k_3} k_1 E^* P^* \left[ 1 - \frac{V^* (E(t - \tau) P(t - \tau))}{V(t) E^* P^*} + \ln \frac{V^* (E(t - \tau) P(t - \tau))}{V(t) E^* P^*} \right] + \frac{d_2 k_3}{k_2 k_4 + d_2 k_3} k_1 E^* P^* \left[ 1 - \frac{E^*}{E(t)} + \ln \frac{E^*}{E(t)} \right] + \frac{d_2 k_3}{k_2 k_4 + d_2 k_3} k_1 E^* P^* \left[ 1 - \frac{C^* (V(t))}{C(t) V^*} + \ln \frac{C^* (V(t))}{C(t) V^*} \right] + \frac{d_2 k_3}{k_2 k_4 + d_2 k_3} k_1 E^* P^* \left[ 1 - \frac{P^* C(t)}{P(t) C^*} + \ln \frac{P^* C(t)}{P(t) C^*} \right].
\]
where \( Q \) is a positive equilibrium of model (2), \( \dot{E}(t) \) and \( \dot{P}(t) \) can be rewritten as

\[
\dot{E}(t) = \left( d_1 - \frac{k_6 V^*}{1 + V^*} + k_1 P^* \right) E^* - \left( d_1 - \frac{k_6 V(t)}{1 + V(t)} + k_1 P(t) \right) E(t)
\]

\[
= \frac{r}{E^*} (E^* - E(t)) + \frac{k_6 (V(t) - V^*) E(t)}{(1 + V(t))(1 + V^*)} + k_1 E(t) (P^* - P(t)),
\]

\[
\dot{P}(t) = k_5 (C(t) - C^*) + d_4 (P^* - P(t)).
\]
By (32) and (35), for \( t \geq T(\varepsilon_1) + \tau \),

\[
\Pi_3 := (E(t) - E^*) \int_{t-\tau}^t |E(s)\dot{P}(s) + P(s)\dot{E}(s)| ds \\
= (E(t) - E^*) \int_{t-\tau}^t E(s)[k_5(C(s) - C^*) + d_4(P^* - P(s))] ds \\
+ (E(t) - E^*) \int_{t-\tau}^t P(s) \left[ \frac{r}{E^*}(E^* - E(s)) + \frac{k_6(V(s) - V^*)E(s)}{(1 + V(s))(1 + V^*)} + k_1E(s)(P^* - P(s)) \right] ds \\
\leq \frac{k_5(E_{max} + \varepsilon_1)}{2} \int_{t-\tau}^t [(E(t) - E^*)^2 + (C(s) - C^*)^2] ds \\
+ \frac{d_4(E_{max} + \varepsilon_1)}{2} \int_{t-\tau}^t [(E(t) - E^*)^2 + (P(s) - P^*)^2] ds \\
+ \frac{r(P_{max} + \varepsilon_1)}{2E^*} \int_{t-\tau}^t [(E(t) - E^*)^2 + (E(s) - E^*)^2] ds \\
+ \frac{k_6(E_{max} + \varepsilon_1)(P_{max} + \varepsilon_1)}{2(1 + V^*)} \int_{t-\tau}^t [(E(t) - E^*)^2 + (V(s) - V^*)^2] ds \\
+ \frac{k_1(E_{max} + \varepsilon_1)(P_{max} + \varepsilon_1)}{2} \int_{t-\tau}^t [(E(t) - E^*)^2 + (P(s) - P^*)^2] ds \\
= \frac{1}{2}M_0(\varepsilon_1)\tau(E(t) - E^*)^2 + \frac{r(P_{max} + \varepsilon_1)}{2E^*} \int_{t-\tau}^t (E(s) - E^*)^2 ds \\
+ \frac{k_6(E_{max} + \varepsilon_1)(P_{max} + \varepsilon_1)}{2(1 + V^*)} \int_{t-\tau}^t (V(s) - V^*)^2 ds \\
+ \frac{k_5(E_{max} + \varepsilon_1)}{2} \int_{t-\tau}^t (C(s) - C^*)^2 ds \\
+ \left[ \frac{d_4(E_{max} + \varepsilon_1)}{2} + \frac{k_1(E_{max} + \varepsilon_1)(P_{max} + \varepsilon_1)}{2} \right] \int_{t-\tau}^t (P(s) - P^*)^2 ds.
\]

(36)

Similarly, it has that, for \( t \geq T(\varepsilon_1) + \tau \),

\[
\Pi_4 := (V(t) - V^*) \int_{t-\tau}^t |E(s)\dot{P}(s) + P(s)\dot{E}(s)| ds \\
\leq \frac{1}{2}M_0(\varepsilon_1)\tau(V(t) - V^*)^2 + \frac{r(P_{max} + \varepsilon_1)}{2E^*} \int_{t-\tau}^t (E(s) - E^*)^2 ds \\
+ \frac{k_6(E_{max} + \varepsilon_1)(P_{max} + \varepsilon_1)}{2(1 + V^*)} \int_{t-\tau}^t (V(s) - V^*)^2 ds \\
+ \frac{k_5(E_{max} + \varepsilon_1)}{2} \int_{t-\tau}^t (C(s) - C^*)^2 ds \\
+ \left[ \frac{d_4(E_{max} + \varepsilon_1)}{2} + \frac{k_1(E_{max} + \varepsilon_1)(P_{max} + \varepsilon_1)}{2} \right] \int_{t-\tau}^t (P(s) - P^*)^2 ds.
\]

(37)
By (36) and (37), we have, for \( t \geq T(\varepsilon_1) + \tau \),

\[
\Pi_{34} := k_1 k_2 k_6 \Pi_3 + k_1^2 k_2 k_6 \Pi_4
\]

\[
\leq \frac{1}{2} k_1 k_2 k_6 M_0(\varepsilon_1) \tau (E(t) - E^*)^2 + \frac{1}{2} k_1^2 k_2 k_6 M_0(\varepsilon_1) \tau (V(t) - V^*)^2
\]

\[
+ \frac{r k_1 k_2 (k_1 + k_2) k_6 (P_{\text{max}} + \varepsilon_1)}{2E^*} \int_{t-\tau}^{t} (E(s) - E^*)^2 ds
\]

\[
+ \frac{k_1 k_2 (k_1 + k_2) k_6^2 (E_{\text{max}} + \varepsilon_1)(P_{\text{max}} + \varepsilon_1)}{2(1 + V^*)} \int_{t-\tau}^{t} (V(s) - V^*)^2 ds
\]

\[
+ \frac{k_1 k_2 (k_1 + k_2) k_6 (E_{\text{max}} + \varepsilon_1)}{2} \int_{t-\tau}^{t} (C(s) - C^*)^2 ds
\]

\[
+ \frac{k_1 k_2 (k_1 + k_2) k_6 [d_2 + k_1 (P_{\text{max}} + \varepsilon_1)(E_{\text{max}} + \varepsilon_1)]}{2} \int_{t-\tau}^{t} (P(s) - P^*)^2 ds.
\]

(38)

By (4), we have, for \( t \geq T(\varepsilon_1) + \tau \),

\[
\dot{W}_4 = k_6 [k_3 (V(t) - V^*) - k_2 (C(t) - C^*)]
\]

\[
\times [d_4 k_3 (C(t) - C^*) - (d_2 k_3 + k_2 k_4)(V(t) - V^*)]
\]

\[
= - k_3 k_6 (d_2 k_3 + k_2 k_4)(V(t) - V^*)^2 - d_1 k_6 k_3 (C(t) - C^*)^2
\]

\[
+ k_3 k_6 [(d_2 + d_3) k_3 + k_2 k_4](V(t) - V^*)(C(t) - C^*),
\]

(39)

\[
\dot{W}_5 = k_2^2 k_6 (P(t) - P^*) [k_5 (C(t) - C^*) + d_4 (P^* - P(t))]
\]

\[
= - d_4 k_2^2 k_6 (P(t) - P^*)^2 + k_2^2 k_5 k_6 (C(t) - C^*)(P(t) - P^*).
\]

By (33), (34), (38), (39) and (40), we have, for \( t \geq T(\varepsilon_1) + \tau \),

\[
\dot{W}(t) \leq - \dot{M}_{11}(t)(E(t) - E^*)^2 - M_{22}(\varepsilon_1)(V(t) - V^*)^2 - M_{33}(\varepsilon_1)(C(t) - C^*)^2
\]

\[
- M_{44}(\varepsilon_1)(P(t) - P^*)^2 - k_2 k_6 \frac{(E(t) - E^*)(V(t) - V^*)^2}{(1 + V(t))(1 + V^*)}
\]

\[
+ M_{23}(V(t) - V^*)(C(t) - C^*) + M_{34}(C(t) - C^*)(P(t) - P^*),
\]

(41)
where
\[
\tilde{M}_{11}(t) = \frac{k_2(\delta_1 + \delta_2 V^*)}{E(t)} \left( d_1 - \frac{k_0 V^*}{1 + V^*} \right) + k_2k_0 \left( d_1 - k_0 \frac{V_{\text{max}} + \varepsilon_1}{1 + V_{\text{max}} + \varepsilon_1} \right)
- \frac{k_1k_2k_0}{2E^*} \left[ k_2E^*M_0(\varepsilon_1) + r(k_1 + k_2)(P_{\text{max}} + \varepsilon_1) \right] \tau.
\]

If \( E(t) \geq E^* \), then \( \tilde{M}_{11}(t) \geq M_{11}(\varepsilon_1) \) and
\[
- k_2k_0 \delta_2 \frac{(E(t) - E^*)(V(t) - V^*)^2}{(1 + V(t))(1 + V^*)} \leq 0,
\]
and the equal sign is established if and only if \( E(t) = E^* \), \( V(t) = V^* \), \( C(t) = C^* \), \( P(t) = P^* \).

If \( E(t) \leq E^* \), then \( \tilde{M}_{11}(t) \geq M_{11}(\varepsilon_1) \). Using inequality
\[
- k_2k_0 \delta_2 \frac{(E(t) - E^*)(V(t) - V^*)^2}{(1 + V(t))(1 + V^*)} \leq \frac{k_2k_0 \delta_2 (E^* - \nu_1 + \varepsilon_1)}{1 + V^*} (V(t) - V^*)^2
\]
and
\[
- k_2k_0 \delta_2 \frac{(E(t) - E^*)(V(t) - V^*)^2}{(1 + V(t))(1 + V^*)} \leq k_2k_0 \delta_2 \max \left\{ V^*, \frac{V_{\text{max}} + \varepsilon_1 - V^*}{1 + V_{\text{max}} + \varepsilon_1} \right\} \left| (E(t) - E^*)(V(t) - V^*) \right|,
\]
we have
\[
- k_2k_0 \delta_2 \frac{(E - E^*)(V - V^*)^2}{(1 + V)(1 + V^*)} \leq M_{22}(\varepsilon_1, \theta_1)(V - V^*)^2 + M_{12}(\varepsilon_1, \theta_1)|(E(t) - E^*)||(V(t) - V^*)|.
\]
Hence, by (43), we have, for \( t \geq T(\varepsilon_1) + \tau \),
\[
\tilde{W}(t) \leq - (|E(t) - E^*|, |V(t) - V^*|, |C(t) - C^*|, |P(t) - P^*|)J_2(\varepsilon_1, \theta_1)
\]
\[
\times (|E(t) - E^*|, |V(t) - V^*|, |C(t) - C^*|, |P(t) - P^*|)^T
\]
\[
\leq 0,
\]
and the equal sign is established if and only if \( E(t) = E^* \), \( V(t) = V^* \), \( C(t) = C^* \), \( P(t) = P^* \).

In summary, we have shown that if (H1) holds, then \( \tilde{W}(t) \leq 0 \) for \( t \geq T(\varepsilon_1) + \tau \), and the equal sign is established if and only if \( E(t) = E^* \), \( V(t) = V^* \), \( C(t) = C^* \), \( P(t) = P^* \). Hence, for \( t \geq T(\varepsilon_1) + \tau \), \( \tilde{W}(t) \) is monotonically decreasing and has a lower bound, so there exists a constant \( W^* \) such that \( W(t) \to W^* \) as \( t \to \infty \).

In addition, by (32), it is not difficult to show that for \( t \geq T(\varepsilon_1) + \tau \), \( \tilde{W}(t) \) is bounded, then follow from Lemma 2.2 (Barbalat’s lemma), we have \( \tilde{W}(t) \to 0 \) as \( t \to \infty \). According to the previous argument, we can obtain \( E(t) \to E^* \) as \( t \to \infty \), \( V(t) \to V^* \) as \( t \to \infty \), \( C(t) \to C^* \) as \( t \to \infty \), \( P(t) \to P^* \) as \( t \to \infty \). Therefore, we obtain that the inflammatory factors-existent equilibrium \( Q^* \) is globally attractive.

The proof is completed.
Corollary 2. Assume that $R_0 > 1$ and $(H_1)$ holds. If the inflammatory factors-existent equilibrium $Q^*$ is locally asymptotically stable, then the inflammatory factors-existent equilibrium $Q^*$ is also globally asymptotically stable in $\mathbb{C}^+$.

In biology, the global attractivity of the inflammatory factors-existent equilibrium $Q^*$ implies that, for any initial function $\phi \in \mathbb{C}^+$, with the increase of the time $t$, the concentrations of normal endothelial cells, vascular endothelial growth factors, activated adhesion factors/chemokines and inflammatory factors will ultimately tend to some constant values. However, we should point out here that the condition $(H_1)$ in Theorem 5.5 is actually rather complicated in its application. The main reason may be that the condition $(H_1)$ strongly relates to the construction of Lyapunov functionals and that model (2) could undergo a forward bifurcation or a backward bifurcation under some conditions as well as the existence of Hopf bifurcation caused by the time delay $\tau$.

6. Conclusions and Numerical simulations. In this paper, we propose and analyze the time-delayed dynamic model (2) of KD pathogenesis. By analyzing the characteristic equations of model (2), we performed a complete analysis on the local stability of the inflammatory factors-free equilibrium $Q_0$ and the inflammatory factors-existent equilibria $Q^*$ and $Q^{**}$, and obtain Theorems 3.1, 5.3 and 5.4. It is found that the time delay $\tau$ can cause the changes in the stability of the inflammatory factors-existent equilibrium $Q^*$ and lead to the existence of Hopf bifurcation. Moreover, in Theorems 3.2, 3.3, 5.5 and Corollary 2, some sufficient conditions are given for the global asymptotic stability of the inflammatory factors-free equilibrium $Q_0$ and the inflammatory factors-existent equilibrium $Q^*$, by constructing suitable Lyapunov functionals and combining Barbalat’s lemma and Lyapunov-LaSalle invariance principle. In Theorem 4.1, we show that model (2) is uniformly persistent for any time delay $\tau$, as long as the reproduction number $R_0 > 1$. We see that the assumptions and conclusions in our theorems have clear biological significance.

At the end of this paper, we give some numerical examples to summarize the applications of the main results.

Let us choose a set of parameter values as follows,

$$
r = 4, \ k_1 = 0.2, \ k_2 = 1, \ k_3 = 0.05, \ k_4 = 5, \ k_5 = 7.814,
\quad k_6 = 0.954, \ d_1 = 1, \ d_2 = 8, \ d_3 = 5, \ d_4 = 5.
$$

By simple calculations, we have $E_0 = r/d_1 = 4, \ d_2k_1 = 1.6 < k_2k_6E_0 = 3.816$ and $\omega \approx 0.8432094595 < R_0 = 0.843912 < 1$. Hence, the condition of backward bifurcation holds, and model (2) has three equilibria, the inflammatory factors-free equilibrium $Q_0(4,0,0,0)$, the inflammatory factors-existent equilibrium $Q^*(4.73983069, 0.732318920, 0.790904433, 1.23602545)$ and the inflammatory factors-existent equilibrium $Q^{**}(4.73983069, 0.631410948, 0.681923824, 1.06571055)$. Theorems 3.1 and 5.4 show that the inflammatory factors-free equilibrium $Q_0$ is locally asymptotically stable and the inflammatory factors-existent equilibrium $Q^{**}$ is unstable for any time delay $\tau \geq 0$. With the help of Maple software, we also have $l \approx -432.448849 < 0$, $v^* \approx 0.5424168647$ and $h(v^*) \approx -218.201807 < 0$. Hence, (25) has two positive roots $u_1 \approx 0.8791426501$ and $u_2 \approx 0.5571448480$. Finally, we have

$$
\tau_1^{(0)} \approx 6.699262191 < \tau_2^{(0)} \approx 10.85401503 < \tau_1^{(1)} \approx 13.84620849
< \tau_1^{(2)} \approx 20.99315478 < \tau_2^{(1)} \approx 22.13148684.
$$
Therefore, it follows from Theorem 5.3 that the inflammatory factors-existent equilibrium $Q^*$ is locally asymptotically stable for $\tau \in [0, \tau_1^{(0)})$, and Figure 1 is an example when $\tau = 2.8 \in [0, \tau_1^{(0)})$; model (2) undergoes Hopf bifurcation when

$\tau = \tau_1^{(0)}$ and the inflammatory factors-existent equilibrium $Q^*$ loses its stability for $\tau \in (\tau_1^{(0)}, \tau_2^{(0)})$, here Figure 2 is an example when $\tau = 7.1 \in (\tau_1^{(0)}, \tau_2^{(0)})$; the inflammatory factors-existent equilibrium $Q^*$ becomes stable for $\tau \in (\tau_2^{(0)}, \tau_1^{(0)})$, and Figure 3 is an example when $\tau = 13.6 \in (\tau_2^{(0)}, \tau_1^{(1)})$; the inflammatory factors-existent equilibrium $Q^*$ loses its stability again for $\tau \in (\tau_1^{(1)}, +\infty)$, and Figure 4 is an example when $\tau = 16 \in (\tau_1^{(1)}, +\infty)$.

Let us choose another set of parameter values as follows, $r = 4$, $k_1 = 2$, $k_2 = 1.2$, $k_3 = 0.6$, $k_4 = 5$, $k_5 = 0.15$, $d_1 = 2.4$, $d_2 = 3$, $d_3 = 4$. If we further choose $k_5 = 0.8$ and $d_4 = 0.4$, we have $R_0 \approx 2.166666667 > 1$. Hence, model (2) has a unique inflammatory factors-existent equilibrium $Q^*(0.7692307692, 0.4377959464, 0.7114184129, 1.422836826)$. Consequently, it follows from Theorem 4.1 that model (2) is uniformly persistent for any time delay $\tau \geq 0$. If we choose $\delta = (k_1P^* - \frac{k_5V^*}{1+V^*})/2k_3P^*$, it has $\delta \approx 0.4919748964$. With the help of Maple software, we further have $T_1 \approx 0.5078922213$, $T_2 \approx 0.8615662783$ and $T_3 \approx 0.8146086360$. Finally, we get $\nu_1 \approx 0.1485148514$, $\nu_2(\delta) \approx 0.01365481809$, $\nu_3(\delta) \approx 0.02218907939$ and $\nu_4(\delta) \approx 0.2298561046$ for $\tau = 0.6$. 

**Figure 1.** The phase trajectory and solution curves of model (2) with the initial value $(4.74, 0.732, 0.79, 1.236)$ and $\tau = 2.8 \in [0, \tau_1^{(0)})$. Here the inflammatory factors-existent equilibrium $Q^*$ is locally asymptotically stable.
Let us choose $k_5 = 4$ and $d_4 = 4$, we have $R_0 \approx 1.08333 > 1$ and $l \approx 3585.13406 > 0$. Hence, model (2) has a unique inflammatory factors-existent
Figure 4. The phase trajectory and solution curves of model (2) with the initial value \((4.74, 0.732, 0.79, 1.236)\) and \(\tau = 16 \in (\tau_1^{(1)}, +\infty)\). Here the inflammatory factors-existent equilibrium \(Q^*\) is unstable and periodic oscillations occur. Figure 4 (e) is a partial enlarged view of Figure 4 (a) near the inflammatory factors-existent equilibrium \(Q^*\).

Therefore, it follows from Theorem 5.3 that the inflammatory factors-existent equilibrium \(Q^*\) is locally asymptotically stable for any time delay \(\tau \geq 0\). If we choose \(\theta_1 = 0\), with the help of Maple software, it has that the matrices \(J_1(0)\) and \(J_2(0,0)\) are positive definite for \(0 \leq \tau \leq 0.02052\). Therefore, it follows from Corollary 2 that the inflammatory factors-existent equilibrium \(Q^*\) is globally asymptotically stable for \(0 \leq \tau \leq 0.02052\).

Acknowledgments. The authors would like to thank the reviewers and the editor for their careful reading, helpful comments and suggestions that greatly improved the paper.
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