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Global Dynamics of a Kawasaki Disease Vascular Endothelial Cell Injury Model with Backward Bifurcation and Hopf Bifurcation

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Abstract Kawasaki disease (KD) is an acute, febrile, systemic vasculitis that mainly affects children under five years of age. In this paper, we propose and study a class of 5-dimensional ordinary differential equation model describing the vascular endothelial cell injury in the lesion area of KD. This model exhibits forward/backward bifurcation. It is shown that the vascular injury-free equilibrium is locally asymptotically stable if the basic reproduction number $R_0 < 1$. Further, we obtain two types of sufficient conditions for the global asymptotic stability of the vascular injury-free equilibrium, which can be applied to both the forward and backward bifurcation cases. In addition, the local and global asymptotic stability of the vascular injury equilibria and the presence of Hopf bifurcation are studied. It is also shown that the model is permanent if the basic reproduction number $R_0 > 1$, and some explicit analytic expressions of ultimate lower bounds of the solutions of the model are given. Our results suggest that the control of vascular injury in the lesion area of KD is not only correlated with the basic reproduction number R_0, but also with the growth rate of normal vascular endothelial cells promoted by the vascular endothelial growth factor.

Keywords Kawasaki disease model; backward bifurcation; Hopf bifurcation; global stability; permanence
2020 MR Subject Classification 34D23; 34C23; 92B05

1 Introduction

Kawasaki disease (KD), also known as mucocutaneous lymph node syndrome (MCLS), is an acute, febrile, systemic vasculitis that mainly affects children under five years of age[26]. KD has been occurring in many countries and its incidence has been increasing[1, 11, 19, 21, 26]. To better prevent and control KD, national epidemiological surveys are regularly conducted in some countries, such as Japan and Korea, which have high rates of the disease[1, 21]. Over the past 50 years since the discovery of KD by Tomisaku Kawasaki in [20], many important advances have been made by researchers worldwide in the search for the cause of KD and its pathogenesis[30]. Nevertheless, there are still many gaps in the etiology and pathogenesis of KD. In developed countries, KD is the most common cause of acquired heart disease in children[26].

KD can be divided into complete KD and incomplete KD, depending on the number of principal clinical features[23]. In patients with incomplete KD, the paucity of clinical symptoms makes early diagnosis difficult and makes it easy to miss and misdiagnose. Untimely treatment leads to increased risk of coronary artery aneurysms in patients with KD. In untreated cases, the incidence of coronary artery aneurysms occurs in around 20–30%[6]. Currently, the most effective anti-inflammatory treatment for KD is early intravenous immunoglobulin (IVIG), which

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reduces the systemic inflammatory response and is effective in reducing the incidence of coronary artery aneurysms. However, about 10-28% of patients are still resistant to IVIG treatment and additional complex treatment is needed for this group of patients[6, 26]. Prompt prevention, diagnosis and treatment of KD can go a long way towards reducing the damage the disease can do to your child's body.

Although the cause of KD remains unknown, many scholars have studied the pathogenesis of KD and the understanding of its pathogenesis is increasing. Epidemiological studies suggest the presence of infectious triggers in the pathogenesis of KD. A variety of pathogenic organisms have been reported to be associated with the development of KD, including viruses, bacteria and fungi[18, 27]. Many researchers believe that KD is caused by one or more unknown pathogenic factors that trigger the disruption of the body's immune system and the abnormal expression of various cytokines, resulting in acute systemic vasculitis[6, 30]. Cytokines are critical in the pathogenesis, diagnosis and treatment of KD[8]. In recent years, based on the interaction mechanism between some important cytokines (vascular endothelial growth factors, adhesion molecules/chemokines and inflammatory cytokines) and normal endothelial cells in the lesion area of patients with KD, Qiang et al.[28] constructed the following ordinary differential equation model to describe the inflammatory response of KD:

$$\begin{cases} \dot{E}_N(t) = s + \dfrac{\alpha E_N(t)V(t)}{1+V(t)} - \beta E_N(t)P(t) - d_N E_N(t), \\ \dot{V}(t) = \beta_1 E_N(t)P(t) - d_v V(t), \\ \dot{C}(t) = \beta_2 E_N(t)P(t) + \eta V(t) - d_c C(t), \\ \dot{P}(t) = \delta C(t) - d_p P(t). \end{cases} \tag{1.1}$$

In Model (1.1), $E_N(t)$, $V(t)$, $C(t)$ and $P(t)$ denote concentrations of normal endothelial cells, vascular endothelial growth factors, activated adhesion molecules/chemokines and inflammatory cytokines in the lesion area at time t, respectively. The constants $s > 0$ and $d_N > 0$ denote the rates of proliferation and apoptosis of normal endothelial cells, respectively. The constant $\alpha > 0$ denotes proliferation rate of normal endothelial cells promoted by vascular endothelial growth factors. The vascular endothelial growth factor promotes normal endothelial cells proliferation following the saturated functional response ($\alpha E_N(t)V(t)/(1+V(t))$[22]). The constant $\beta > 0$ is the rate of injury of normal endothelial cells caused by inflammatory cytokines. The constants $\beta_1 > 0$ and $\beta_2 > 0$ denote the production rates of vascular endothelial growth factors and activated adhesion molecules/chemokines caused by inflammatory cytokines, respectively. The constant $\eta > 0$ denotes the production rate of adhesion molecules/chemokines induced by vascular endothelial growth factors. The constant $\delta > 0$ denotes the production rate of inflammatory cytokines by increasing of abnormally activated immune cells. The constants $d_v > 0$, $d_c > 0$ and $d_p > 0$ denote hydrolytic rates of vascular endothelial growth factors, activated adhesion molecules/chemokines and inflammatory cytokines, respectively. Model (1.1) exhibits forward/backward bifurcation. In [14, 28], in order to ensure that the solution of Model (1.1) is bounded, the authors assume that $\alpha < d_N$ holds and study the local and global stability of the equilibria of Model (1.1). Moreover, in [12, 15], Guo et al. further considered the effect of time delays and nonautonomous factors on the inflammatory response in KD.

In the acute phase of KD, the concentrations of many inflammatory cytokines (such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β) are elevated[8]. Inflammatory cytokines can injure endothelial cells and disrupt the barrier function of endothelial cells, and can further induce injured endothelial cells to express adhesion molecules, chemokines, etc[25, 28, 29]. Therefore, it is more reasonable to divide the endothelial cells into normal endothelial cells and injured endothelial cells in the construction of the model. We use $E_I(t)$ to denote the concentration of injured endothelial cells in the lesion area of patients with KD at time t. Based on

the above discussion and [28], we can obtain a diagram of the mechanism of action between normal endothelial cells, injured endothelial cells, vascular endothelial growth factors, activated adhesion factors/chemokines, and inflammatory cytokines in lesion area of KD (see Figure 1.1). This derives the following ordinary differential equation model describing endothelial cell injury in the lesion area of KD:

$$\begin{cases} \dot{E}_N(t) = s - d_N E_N(t) + rE_N(t)\Big(1 - \dfrac{E_N(t)}{K}\Big) + \dfrac{\alpha E_N(t)V(t)}{1+V(t)} - \beta E_N(t)P(t), \\ \dot{E}_I(t) = \beta E_N(t)P(t) - d_I E_I(t), \\ \dot{V}(t) = \gamma_1 E_I(t) - d_v V(t), \\ \dot{C}(t) = \gamma_2 E_I(t) + \eta V(t) - d_c C(t), \\ \dot{P}(t) = \delta C(t) - d_p P(t). \end{cases} \tag{1.2}$$

In Model (1.2), normal endothelial cells growth is assumed to also satisfy logistic growth $rE_N(t)(1 - \frac{E_N(t)}{K})$, where the constant $r > 0$ is the intrinsic growth rate, and the constant $K > 0$ is carrying capacity of the logistic mitosis. The constant $d_I > 0$ denotes the apoptosis rate of injured endothelial cells. The constants $\gamma_1 > 0$ and $\gamma_2 > 0$ denote the production rates of endothelial growth factor and activated adhesion molecules/chemokines resulting from endothelial cell injury, respectively. The biological meanings of the remaining parameters in Model (1.2) are the same as in Model (1.1).

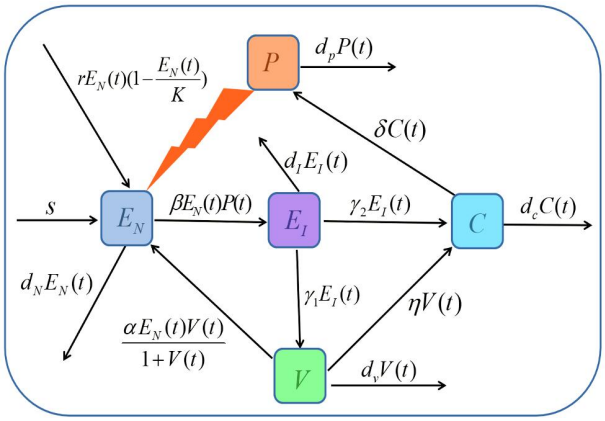


Figure 1.1. Schematic diagram of Model (1.2).

We find that Model (1.2) has a backward bifurcation within a certain range of parameters, which means that Model (1.2) has positive equilibria even if the basic reproduction number is less than 1. Also, it is interesting to observe that the parameter α can cause the appearance of the Hopf bifurcation at the vascular injury equilibrium (positive equilibrium), and that the vascular injury equilibrium is always unstable when the α is relatively large. Although, the later calculations show that the expression for the basic reproduction number of Model (1.2) is independent of the parameter α, this also suggests that the control of KD vasculitis is closely related to the parameter α. The presence of backward bifurcation and Hopf bifurcation in Model (1.2) under some conditions may cause difficulties in the study of the global dynamics of Model (1.2), in particular the global stability of the equilibria of Model (1.2). In this paper, we will study the global stability of the vascular injury-free equilibrium (boundary equilibrium) and the vascular injury equilibrium (positive equilibrium) of Model (1.2) by constructing appropriate

Lyapunov functions (e.g., some construction techniques of Lyapunov functions can be found in [2–4, 7, 13, 24] and the references therein). Moreover, we will consider the permanence of Model (1.2) through some analytical techniques (see e.g., [10, 13, 15, 16, 32, 33] and the references therein). Some explicit expressions are given for the ultimate lower bounds for the components of any positive solution of Model (1.2) if the basic reproduction number is greater than 1. These explicit expressions can be used to estimate the lower bounds of the concentrations of injured vascular endothelial cells, vascular endothelial growth factors, adhesion molecules/chemokines and inflammatory cytokines.

The rest of this paper is organized as follows. The well-posedness, dissipativeness and classification of equilibria of Model (1.2) are obtained in Section 2. Section 3 studies the local and global stability of the vascular injury-free equilibrium of Model (1.2). Section 4 studies the permanence of Model (1.2) when the basic reproduction number is greater than 1. Section 5 studies the local stability of the vascular injury equilibria, the existence of Hopf bifurcation caused by the parameter α, and the global stability of the vascular injury equilibrium when the basic reproduction number is greater than 1. Some numerical simulations are given in Section 6. The last section concludes the paper.

2 Preliminaries

The initial condition of Model (1.2) is given as follows:

$$E_N(0) \geq 0, \quad E_I(0) \geq 0, \quad V(0) \geq 0, \quad C(0) \geq 0, \quad P(0) \geq 0. \tag{2.1}$$

Here $E_N(0)$, $E_I(0)$, $V(0)$, $C(0)$ and $P(0)$ denote the initial concentrations of normal vascular endothelial cells, injured vascular endothelial cells, vascular endothelial growth factors, adhesion molecules/chemokines and inflammatory cytokines in the lesion area. For convenience, we define $\Phi(t) = (E_N(t), E_I(t), V(t), C(t), P(t))$.

2.1 The Well-posedness and Dissipativeness

Unlike papers [14, 28], we do not need to limit $\alpha < d_N$ in the paper. It can also be obtained that any solution of Model (1.2) satisfying the initial condition (2.1) is ultimately bounded.

Theorem 2.1. *The solution $\Phi(t)$ of Model (1.2) with the initial condition (2.1) is existent, unique and nonnegative on $[0, +\infty)$, and satisfies*

$$\begin{aligned}
&\limsup_{t\to+\infty} E_N(t) \leq \frac{K}{2r}\Big[r - d_N + \alpha + \sqrt{(r - d_N + \alpha)^2 + \frac{4rs}{K}}\Big] := M_1,\\
&\limsup_{t\to+\infty} E_I(t) \leq \frac{s + (\alpha + r)M_1}{\min\{d_N, d_I\}} := M_2,\\
&\limsup_{t\to+\infty} V(t) \leq \frac{\gamma_1}{d_v} M_2 := M_3,\\
&\limsup_{t\to+\infty} C(t) \leq \frac{\gamma_2 M_2 + \eta M_3}{d_c} := M_4,\\
&\limsup_{t\to+\infty} P(t) \leq \frac{\delta}{d_p} M_4 := M_5.
\end{aligned} \tag{2.2}$$

Proof. By using the standard theory of ordinary differential equations (see [17]), we can easily prove that the solution $\Phi(t)$ of Model (1.2) with the initial condition (2.1) is existent, unique and nonnegative on $[0, +\infty)$. Next, let us prove that any solution of Model (1.2) is ultimately bounded.

We define

$$\widetilde{M_1} = \frac{K}{2r}\Big[(r - d_N + \alpha) - \sqrt{(r - d_N + \alpha)^2 + \frac{4rs}{K}}\Big] < 0.$$

From the first equation of Model (1.2), we have, for $t \geq 0$,

$$\begin{aligned}\dot{E}_N(t) \leq & s - d_N E_N(t) + rE_N(t)\Big(1 - \frac{E_N(t)}{K}\Big) + \alpha E_N(t)\\ = & -\frac{r}{K}(E_N(t) - \widetilde{M_1})(E_N(t) - M_1),\end{aligned}$$

which implies that

$$\limsup_{t\to+\infty} E_N(t) \leq M_1. \tag{2.3}$$

By (2.3), we see that, for any $\varepsilon > 0$, there exits a $\bar{t} > 0$, such that $E_N(t) \leq M_1 + \varepsilon$ for $t > \bar{t}$. We define

$$G(t) = E_N(t) + E_I(t).$$

Calculating the derivative of $G(t)$ along the solution of Model (1.2), it follows that, for $t \geq 0$,

$$\begin{aligned}\dot{G}(t) = & s - d_N E_N(t) + rE_N(t)\Big(1 - \frac{E_N(t)}{K}\Big) + \frac{\alpha E_N(t)V(t)}{1 + V(t)} - d_I E_I(t)\\ \leq & s + (r + \alpha)E_N(t) - d_N E_N(t) - d_I E_I(t).\end{aligned}$$

Then, we have, for $t > \bar{t}$,

$$\dot{G}(t) \leq s + (r + \alpha)(M_1 + \varepsilon) - \min\{d_N, d_I\}G(t),$$

which implies that

$$\limsup_{t\to+\infty} G(t) \leq \frac{s + (r + \alpha)(M_1 + \varepsilon)}{\min\{d_N, d_I\}}. \tag{2.4}$$

Since (2.4) holds for any $\varepsilon > 0$, we have $\limsup_{t\to+\infty} G(t) \leq M_2$. Thus, we can obtain $\limsup_{t\to+\infty} E_I(t) \leq M_2$. Similarly, we can obtain $\limsup_{t\to+\infty} V(t) \leq M_3$, $\limsup_{t\to+\infty} C(t) \leq M_4$ and $\limsup_{t\to+\infty} P(t) \leq M_5$. □

Theorem 2.1 indicates that the concentrations of normal vascular endothelial cells, injured vascular endothelial cells, vascular endothelial growth factors, adhesion molecules/chemokines and inflammatory cytokines in the lesion area of the patients with KD changes within some limited ranges.

From Theorem 2.1, it is not difficult to obtain the following result; we omit the proof.

Lemma 2.2. *The solution $\Phi(t)$ of Model (1.2) with the initial condition (2.1) satisfies*

$$\liminf_{t\to+\infty} E_N(t) \geq \frac{K}{2r}\Big[r - d_N - \beta M_5 + \sqrt{(r - d_N - \beta M_5)^2 + \frac{4rs}{K}}\Big] := m_1.$$

Moreover, the following bounded set

$$\begin{aligned}\Omega_1 := \big\{&(E_N, E_I, V, C, P)^T \in \mathbb{R}^5_+ : m_1 \leq E_N \leq M_1,\ E_N + E_I \leq M_2,\\ &V \leq M_3,\ C \leq M_4,\ P \leq M_5\big\}\end{aligned}$$

is positively invariant and attractive with respect to Model (1.2).

2.2 Basic Reproduction Number and the Equilibria

Obviously, Model (1.2) always has a vascular injury-free equilibrium (boundary equilibrium) $Q_0 = (E_0, 0, 0, 0, 0)$, where

$$E_0 = \frac{K}{2r}\Big[(r - d_N) + \sqrt{(r - d_N)^2 + \frac{4sr}{K}}\Big].$$

Except for Q_0, Model (1.2) has no other boundary equilibria.

First, we define the following matrices:

$$\hat{\mathcal{F}} = \begin{pmatrix} 0 & 0 & 0 & \beta E_0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}, \qquad \hat{\mathcal{V}} = \begin{pmatrix} d_I & 0 & 0 & 0 \\ -\gamma_1 & d_v & 0 & 0 \\ -\gamma_2 & -\eta & d_c & 0 \\ 0 & 0 & -\delta & d_p \end{pmatrix}.$$

By using the method of the next generation matrix (see [9, 31]), we can derive the expression of the basic reproduction number of Model (1.2) is

$$R_0 = \rho(\hat{\mathcal{F}}\hat{\mathcal{V}}^{-1}) = \frac{E_0\beta\delta(\gamma_1\eta + \gamma_2 d_v)}{d_I d_v d_c d_p} = \frac{K}{2r}\Big[(r - d_N) + \sqrt{(r - d_N)^2 + \frac{4sr}{K}}\Big]\frac{\beta\delta(\gamma_1\eta + \gamma_2 d_v)}{d_I d_v d_c d_p},$$

where $\rho(\hat{\mathcal{F}}\hat{\mathcal{V}}^{-1})$ is the spectral radius of the matrix $\hat{\mathcal{F}}\hat{\mathcal{V}}^{-1}$. Here, R_0 denotes the number of normal vascular endothelial cells injured by an injured vascular endothelial cell in its life span.

Suppose (E_N, E_I, V, C, P) is any vascular injury equilibrium (positive equilibrium) of Model (1.2). From the last 3 equations of Model (1.2), we have

$$E_I = \frac{d_v}{\gamma_1}V, \qquad C = \frac{\gamma_1\eta + \gamma_2 d_v}{d_v d_c}E_I = \frac{\gamma_1\eta + \gamma_2 d_v}{\gamma_1 d_c}V, \qquad P = \frac{\delta}{d_p}C = \frac{\delta(\gamma_1\eta + \gamma_2 d_v)}{\gamma_1 d_c d_p}V. \tag{2.5}$$

Then, from the second equation of Model (1.2), we have

$$E_N = \frac{d_I E_I}{\beta P} = \frac{d_I d_v d_c d_p}{\delta\beta(\gamma_1\eta + \gamma_2 d_v)}. \tag{2.6}$$

Note that $R_0 = \frac{E_0}{E_N}$, then we have

$$\begin{aligned} s - d_N E_N + rE_N\Big(1 - \frac{E_N}{K}\Big) &= -\frac{r}{K}(E_N + E_1)(E_N - E_0) \\ &= -\frac{rE_N}{KR_0}(E_0 + E_1 R_0)(1 - R_0) := \Lambda, \end{aligned}$$

where

$$E_1 = -\frac{K}{2r}\Big[(r - d_N) - \sqrt{(r - d_N)^2 + \frac{4sr}{K}}\Big] > 0.$$

For convenience, we define the function

$$\begin{aligned} \Delta(x) &= \Lambda_1^2(x) + 4\alpha^* x\Big[\frac{r}{K}(E_0 + E_1 x)(x - 1)\Big], \\ \Lambda_1(x) &= (\alpha^* - \alpha)x - \frac{r}{K}(E_0 + E_1 x)(x - 1), \end{aligned}$$

where

$$\alpha^* = \frac{\delta\beta(\gamma_1\eta + \gamma_2 d_v)}{d_c d_p \gamma_1}.$$

From (2.5), (2.6) and the first equation of Model (1.2), we have

$$\frac{\Lambda}{E_N}+\frac{\alpha V}{1+V}-\beta P=\frac{\Lambda}{E_N}+\frac{\alpha V}{1+V}-\alpha^* V=0, \tag{2.7}$$

which leads to

$$F(V):=\alpha^* R_0 V^2+\Lambda_1(R_0)V-\frac{r}{K}(E_0+E_1R_0)(R_0-1)=0. \tag{2.8}$$

We consider the existence of positive roots of $F(V)=0$ in two cases.

Case (i). Assume that $\alpha\le\alpha^*$.

When $R_0>1$, it is clear that $F(V)=0$ has a unique positive root

$$V=\frac{-\Lambda_1(R_0)+\sqrt{\Delta(R_0)}}{2\alpha^* R_0}:=V_1^*>0.$$

Note that if $R_0\le 1$, then $\Lambda_1(R_0)\ge 0$; thus, $F(V)=0$ has no positive roots.

Case (ii). Assume that $\alpha>\alpha^*$.

When $R_0\ge 1$, it is clear that $F(V)=0$ has a unique positive root $V=V_1^*$.

Note that

$$E_0E_1=\frac{sK}{r},\qquad E_0-E_1=\frac{K}{r}(r-d_N),$$

then the function $\Lambda_1(x)$ can be rewritten as

$$\begin{aligned}\Lambda_1(x)&=-\frac{r}{K}E_1x^2-\Big[\frac{r}{K}(E_0-E_1)-\alpha^*+\alpha\Big]x+\frac{r}{K}E_0\\&=-\frac{s}{E_0}x^2-(r-d_N-\alpha^*+\alpha)x+\frac{r}{K}E_0.\end{aligned}$$

Clearly, $\Lambda_1(x)=0$ has a unique positive root

$$x=\frac{E_0}{2s}\Big[-(r-d_N-\alpha^*+\alpha)+\sqrt{(r-d_N-\alpha^*+\alpha)^2+\frac{4sr}{K}}\Big]:=w^+.$$

Note that $\Lambda_1(0)=\frac{r}{K}E_0>0$, $\Lambda_1(1)=\alpha^*-\alpha<0$. Thus, we have

$$0<w^+<1.$$

If $0<R_0\le w^+$, then $\Lambda_1(R_0)\ge 0$; thus, $F(V)=0$ has no positive roots.

If $w^+<R_0<1$, then $\Lambda_1(R_0)<0$. We rewrite the function $\Delta(x)$ as follows:

$$\begin{aligned}\Delta(x)&=\Big[\frac{s}{E_0}x^2+(r-d_N-\alpha^*+\alpha)x-\frac{r}{K}E_0\Big]^2+4\alpha^*x\Big[\frac{s}{E_0}x^2+(r-d_N)x-\frac{rE_0}{K}\Big]\\&:=A_1x^4+A_2x^3+A_3x^2+A_4x+A_5,\end{aligned}$$

where

$$\begin{aligned}&A_1=\frac{s^2}{E_0^2}>0,\qquad A_2=2\frac{s}{E_0}(r-d_N+\alpha^*+\alpha),\\&A_3=(r-d_N-\alpha^*+\alpha)^2-2\frac{sr}{K}+4\alpha^*(r-d_N),\\&A_4=-2\frac{r}{K}E_0(r-d_N+\alpha^*+\alpha),\qquad A_5=\frac{r^2}{K^2}E_0^2>0.\end{aligned}$$

Note that

$$\Delta(0)=\frac{r^2}{K^2}E_0^2>0,\qquad \Delta(1)=\Lambda^2(1)=(\alpha-\alpha^*)^2>0,$$
$$\Delta(w^+)=4\alpha^* w^+\Big[\frac{r}{K}(E_0+E_1w^+)(w^+-1)\Big]<0.$$

Thus, $\Delta(x)=0$ has at least two unequal positive roots on $(0,1)$.

If $A_2\geq 0$, then $A_4\leq 0$, by using Descartes' rule of signs, we have $\Delta(x)=0$ has at most two positive roots on $(0,1)$. Thus, $\Delta(x)=0$ has one and only two unequal positive roots on $(0,1)$. Similarly, when $A_2<0$, we can also prove that $\Delta(x)=0$ has one and only two unequal positive roots on $(0,1)$.

In summary, there exits a constant $\omega\in(w^+,1)$ such that $\Delta(\omega)=0$, $\Delta(R_0)<0$ for $w^+<R_0<\omega$ and $\Delta(R_0)>0$ for $\omega<R_0<1$. Thus, when $w^+<R_0<\omega$, $F(V)=0$ has no positive roots; when $R_0=\omega$, $F(V)=0$ has a unique positive root

$$V=\frac{-\Lambda_1(R_0)}{2\alpha^*R_0}=V_1^*;$$

when $\omega<R_0<1$, $F(V)=0$ has two positive roots $V=V_1^*>0$, $V=V_2^*>0$, where

$$V_2^*=\frac{-\Lambda_1(R_0)-\sqrt{\Delta(R_0)}}{2\alpha^*R_0}>0.$$

Then, we have the following results.

Theorem 2.3. *The following statements are valid.*
(i) *Model (1.2) always has a vascular injury-free equilibrium* $Q_0=(E_0,0,0,0,0)$.
(ii) *If* $\alpha\leq\alpha^*=\frac{\delta\beta(\gamma_1\eta+\gamma_2d_v)}{d_cd_p\gamma_1}$ *and* $R_0>1$ *(Model (1.2) undergoes a forward bifurcation, see Figure 2.1 (a)), then Model (1.2) has a unique vascular injury equilibrium* $Q_1^*=(E_{N_1}^*,E_{I_1}^*,V_1^*,C_1^*,P_1^*)$, *where*

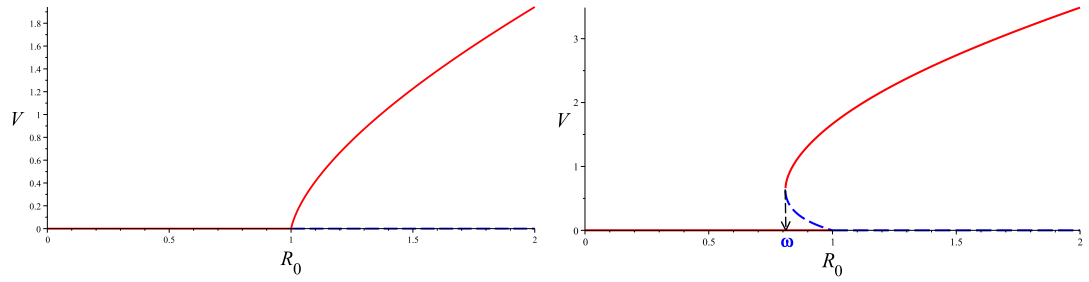
$$E_{N_1}^*=\frac{d_Id_vd_cd_p}{\delta\beta(\gamma_1\eta+\gamma_2d_v)},\ E_{I_1}^*=\frac{d_v}{\gamma_1}V_1^*,\ C_1^*=\frac{\gamma_1\eta+\gamma_2d_v}{\gamma_1d_c}V_1^*,\ P_1^*=\frac{\delta(\gamma_1\eta+\gamma_2d_v)}{\gamma_1d_cd_p}V_1^*.\quad(2.9)$$

(iii) *If* $\alpha>\alpha^*=\frac{\delta\beta(\gamma_1\eta+\gamma_2d_v)}{d_cd_p\gamma_1}$, *there are the following three subcases (Model (1.2) undergoes a backward bifurcation, see Figure 2.1 (b)).*
(iii)$_1$ *If* $R_0\geq 1$, *then Model (1.2) has a unique vascular injury equilibrium* $Q_1^*=(E_{N_1}^*,E_{I_1}^*,V_1^*,C_1^*,P_1^*)$.
(iii)$_2$ *If* $\omega<R_0<1$, *then Model (1.2) has two vascular injury equilibria* $Q_1^*=(E_{N_1}^*,E_{I_1}^*,V_1^*,C_1^*,P_1^*)$ *and* $Q_2^*=(E_{N_2}^*,E_{I_2}^*,V_2^*,C_2^*,P_2^*)$, *where*

$$E_{N_2}^*=\frac{d_Id_vd_cd_p}{\delta\beta(\gamma_1\eta+\gamma_2d_v)},\ E_{I_2}^*=\frac{d_v}{\gamma_1}V_2^*,\ C_2^*=\frac{\gamma_1\eta+\gamma_2d_v}{\gamma_1d_c}V_2^*,\ P_2^*=\frac{\delta(\gamma_1\eta+\gamma_2d_v)}{\gamma_1d_cd_p}V_2^*.\quad(2.10)$$

(iii)$_3$ *If* $R_0=\omega$, *then Model (1.2) has a unique vascular injury equilibrium* $Q_\omega^*=(E_{N_1}^*,E_{I_1}^*,V_1^*,C_1^*,P_1^*)$.
(iv) *Model (1.2) has no vascular injury equilibria if* $\alpha\leq\alpha^*$, $R_0\leq 1$ *or* $\alpha>\alpha^*$, $R_0<\omega$.

Note that R_0 is independent of α, and that both α^* and ω are independent of d_I. Thus, in the case of forward bifurcation or backward bifurcation, we can change the size of R_0 by changing d_I. We fix some parameters $s=1$, $d_N=1$, $r=1$, $K=2$, $\beta=0.25$, $\gamma_1=1$, $d_v=2$, $\gamma_2=1$, $\eta=1$, $d_c=1$, $\delta=1$, $d_p=1$. Then, we can obtain the following forward and backward bifurcation graphs (see Figure 2.1).



(a) Forward bifurcation ($\alpha \le \alpha^*$) (b) Borward bifurcation ($\alpha > \alpha^*$)

Figure 2.1. (a) Here $\alpha = 0.6 < \alpha^* = 0.75$. (b) Here $\alpha = 2 > \alpha^* = 0.75$ and $\omega \approx 0.8098$.

Remark 2.4. Let $f(x) = \sqrt{\frac{4sr}{K} + x^2} + x$ ($x \in \mathbb{R}$). Note that $f'(x) = \frac{x}{\sqrt{\frac{4sr}{K}+x^2}} + 1 > 0$ for $x \in \mathbb{R}$, which implies that $f(x)$ is strictly monotonically increasing with respect to x on $\mathbb{R}$. Thus, we have $M_1 \ge E_0 > m_1$.

3 Stability of the vascular injury-free equilibrium

In this section, we will study the local and global stability of the vascular injury-free equilibrium Q_0.

Suppose $\overline{Q} = (\overline{E_N}, \overline{E_I}, \overline{V}, \overline{C}, \overline{P})$ is an arbitrary equilibrium of Model (1.2). Then, the characteristic equation of Model (1.2) at $\overline{Q}$ is

$$\begin{vmatrix} \lambda + d_N - r + \frac{2r}{K}\overline{E_N} - \frac{\alpha\overline{V}}{1+\overline{V}} + \beta\overline{P} & 0 & -\frac{\alpha\overline{E_N}}{(1+\overline{V})^2} & 0 & \beta\overline{E_N} \\ -\beta\overline{P} & \lambda + d_I & 0 & 0 & -\beta\overline{E_N} \\ 0 & -\gamma_1 & \lambda + d_v & 0 & 0 \\ 0 & -\gamma_2 & -\eta & \lambda + d_c & 0 \\ 0 & 0 & 0 & -\delta & \lambda + d_p \end{vmatrix} = 0. \quad (3.1)$$

3.1 Local Stability of the Vascular Injury-free Equilibrium

For the local stability of the vascular injury-free equilibrium, we obtain the following theorem.

Theorem 3.1. *The vascular injury-free equilibrium Q_0 is locally asymptotically stable if $R_0 < 1$, is unstable if $R_0 > 1$.*

Proof. By (3.1), the characteristic equation of Model (1.2) at Q_0 can be expressed as

$$\big(\lambda + d_N - r + \frac{2r}{K}E_0\big)(\lambda^4 + b_1\lambda^3 + b_2\lambda^2 + b_3\lambda + b_4) = 0, \quad (3.2)$$

where

$$\begin{aligned} b_1 =& d_I + d_v + d_c + d_p > 0, \\ b_2 =& d_I(d_v + d_c + d_p) + d_v d_c + d_v d_p + d_c d_p > 0, \\ b_3 =& d_I(d_v d_c + d_v d_p + d_c d_p) + d_v d_c d_p - \beta\delta\gamma_2 E_0 \\ =& d_I(d_v d_c + d_v d_p) + d_v d_c d_p + d_I d_c d_p(1 - R_0) + \frac{\beta\delta\gamma_1\eta E_0}{d_v}, \end{aligned}$$

$$b_4 = d_I d_v d_c d_p - \beta\delta E_0(\gamma_1\eta + \gamma_2 d_v) = d_I d_v d_c d_p(1 - R_0).$$

Obviously, (3.2) always has a negative real root

$$\lambda = -\Big(d_N - r + \frac{2r}{K}E_0\Big) = -\sqrt{(r - d_N)^2 + \frac{4sr}{K}} < 0.$$

When $R_0 < 1$, we have $b_2 > 0$, $b_3 > 0$,

$$\begin{aligned} &b_1 b_2 - b_3 > d_I^2(d_v + d_c + d_p) + d_I(d_v + d_c + d_p)^2 := Z > 0,\\ &(b_1 b_2 - b_3)b_3 - b_1^2 b_4 > Z(d_I d_c d_p + d_v d_c d_p)(1 - R_0) - b_1^2 b_4\\ =&[d_I(d_I + d_v + d_c + d_p)(d_c + d_p)]d_I d_c d_p(1 - R_0) > 0. \end{aligned}$$

Then, it follows from the Routh-Hurwitz stability criterion that all roots of (3.2) have negative real parts. Thus, Q_0 is locally asymptotically stable if $R_0 < 1$.

When $R_0 > 1$, we have $b_4 < 0$. Then, it is clear that (3.2) has at least one positive real root. Thus, Q_0 is unstable if $R_0 > 1$. □

3.2 Global Stability of the Vascular Injury-free Equilibrium

In this subsection, we consider the global stability of the vascular injury-free equilibrium Q_0 by constructing some appropriate Lyapunov functions. From the local stability results of the vascular injury-free equilibrium Q_0, we only need to discuss the global stability of the vascular injury-free equilibrium Q_0 in two cases: (i) $\alpha \le \alpha^*$, $R_0 \le 1$; (ii) $\alpha > \alpha^*$, $R_0 < \omega(< 1)$.

For convenience of presentation, we define the following parameters

$$\begin{aligned} &\theta = \frac{[d_I + \frac{r}{K}(E_0 + E_1)]^2}{2\frac{r}{K}d_I(E_0 + E_1)} = 1 + \frac{K^2 d_I^2 + r^2(E_0 + E_1)^2}{2rK(E_0 + E_1)d_I},\\ &a_{11} = \frac{r}{K}[\theta(E_0 + E_1) + m_1 + E_1], \qquad \widehat{a}_{11} = \frac{r}{K}\Big[\theta E_0 + \frac{\theta E_0 E_1}{M_1} + E_0 + E_1\Big],\\ &a_{12} = \frac{1}{2}\Big[\frac{r}{K}(E_0 + E_1) + d_I\Big], \qquad a_{13} = \frac{1}{2}\alpha(\theta E_0 + M_1), \qquad a_{22} = d_I,\\ &a_{23} = \frac{1}{2}\Big(\alpha E_0 + \frac{d_I d_v}{\gamma_1}\Big), \qquad \widehat{a}_{23} = \frac{1}{2}\Big(\alpha M_1 + \frac{d_I d_v}{\gamma_1}\Big), \qquad a_{33} = \frac{d_I d_v^2}{\gamma_1^2}. \end{aligned}$$

We define the condition

$$(H) \quad a_{22}a_{33} \ge \max\Big\{a_{23}^2 + \frac{a_{33}}{a_{11}}a_{12}^2,\ \ \widehat{a}_{23}^2 + \frac{a_{22}}{\widehat{a}_{11}}a_{13}^2\Big\} := \Pi(\alpha),$$

then we have the following result.

Theorem 3.2. *If $R_0 \le 1$ and condition* (H) *holds, then the vascular injury-free equilibrium Q_0 is globally asymptotically stable in Ω_1.*

Proof. We define the following Lyapunov function on Ω_1,

$$L(t) = \theta E_0 L_1(t) + L_2(t) + L_3(t),$$

where

$$L_1(t) = E_N(t) - E_0 - E_0 \ln\frac{E_N(t)}{E_0} + E_I(t) + \frac{d_I}{\gamma_1\eta + \gamma_2 d_v}\Big(\eta V(t) + d_v C(t) + \frac{d_v d_c}{\delta}P(t)\Big),$$

$$L_2(t)=\frac{1}{2}\big(E_N(t)-E_0+E_I(t)\big)^2,\qquad L_3(t)=\frac{d_Id_v}{2\gamma_1^2}V^2(t).$$

It is clear that $L(t)$ is continuous on Ω_1 and positive definite with respect to Q_0.

Note that

$$s-d_NE_N(t)+rE_N(t)\Big(1-\frac{E_N(t)}{K}\Big)=-\frac{r}{K}(E_N(t)+E_1)(E_N(t)-E_0).$$

Calculating the derivatives of $L_1(t)$, $L_2(t)$ and $L_3(t)$ along the solution of Model (1.2), we have, for $t\geq 0$,

$$\begin{aligned}\dot{L}_1(t)=&\Big(1-\frac{E_0}{E_N(t)}\Big)\dot{E}_N(t)+\dot{E}_I(t)+\frac{d_I}{\gamma_1\eta+\gamma_2d_v}\Big(\eta\dot{V}(t)+d_v\dot{C}(t)+\frac{d_vd_c}{\delta}\dot{P}(t)\Big)\\
=&-\frac{r}{K}\Big(1+\frac{E_1}{E_N(t)}\Big)(E_N(t)-E_0)^2+\frac{\alpha V(t)}{1+V(t)}(E_N(t)-E_0)+\beta E_0P(t)-d_IE_I(t)\\
&+\frac{d_I}{\gamma_1\eta+\gamma_2d_v}\Big[(\gamma_1\eta+\gamma_2d_v)E_I(t)-\frac{d_vd_cd_p}{\delta}P(t)\Big]\\
=&-\frac{r}{K}\Big(1+\frac{E_1}{E_N(t)}\Big)(E_N(t)-E_0)^2+\frac{\alpha}{1+V(t)}(E_N(t)-E_0)V(t)\\
&+\beta E_0P(t)\Big(1-\frac{1}{R_0}\Big),\end{aligned}\tag{3.3}$$

$$\begin{aligned}\dot{L}_2(t)=&(E_N(t)-E_0+E_I(t))\Big[-\frac{r}{K}(E_N(t)+E_1)(E_N(t)-E_0)+\frac{\alpha E_N(t)V(t)}{1+V(t)}-d_IE_I(t)\Big]\\
=&-\frac{r}{K}(E_N(t)+E_1)(E_N(t)-E_0)^2-d_IE_I^2(t)\\
&-\Big[\frac{r}{K}(E_N(t)+E_1)+d_I\Big](E_N(t)-E_0)E_I(t)\\
&+\frac{\alpha E_N(t)}{1+V(t)}(E_N(t)-E_0)V(t)+\frac{\alpha E_N(t)}{1+V(t)}E_I(t)V(t),\end{aligned}\tag{3.4}$$

$$\dot{L}_3(t)=\frac{d_Id_v}{\gamma_1}E_I(t)V(t)-\frac{d_Id_v^2}{\gamma_1^2}V^2(t).\tag{3.5}$$

Note that, by (3.3) and the Lyapunov-LaSalle invariance principle (see [17]), it is not difficult to prove that Q_0 is globally asymptotically stable if $\alpha=0$ and $R_0\leq 1$. In the following discussion, we assume that $\alpha>0$.

Then, by (3.3), (3.4) and (3.5), we have, for $t\geq 0$,

$$\begin{aligned}\dot{L}(t)=&-a_{11}(t)(E_N(t)-E_0)^2-a_{22}E_I^2(t)-a_{33}V^2(t)+\theta\beta E_0^2P(t)\Big(1-\frac{1}{R_0}\Big)\\
&-2a_{12}(t)(E_N(t)-E_0)E_I(t)+2a_{13}(t)(E_N(t)-E_0)V(t)+2a_{23}(t)E_I(t)V(t),\end{aligned}\tag{3.6}$$

where

$$\begin{aligned}a_{11}(t)=&\frac{r}{K}\Big[\theta E_0+\frac{\theta E_0E_1}{E_N(t)}+E_N(t)+E_1\Big],\\
a_{12}(t)=&\frac{1}{2}\Big[\frac{r}{K}(E_N(t)+E_1)+d_I\Big],\\
a_{13}(t)=&\frac{1}{2}\Big[\frac{\theta E_0\alpha}{1+V(t)}+\frac{\alpha E_N(t)}{1+V(t)}\Big],\\
a_{23}(t)=&\frac{1}{2}\Big[\frac{\alpha E_N(t)}{1+V(t)}+\frac{d_Id_v}{\gamma_1}\Big].\end{aligned}$$

When $E_N(t) \leq E_0$, we have

$$\begin{aligned}\dot{L}(t) \leq & -a_{11}(E_N(t)-E_0)^2 - a_{22}E_I^2(t) - a_{33}V^2(t) + \theta\beta E_0^2 P(t)\Big(1-\frac{1}{R_0}\Big)\\ & -2a_{12}(E_N(t)-E_0)E_I(t) + 2a_{23}E_I(t)V(t) + 2a_{13}(t)(E_N(t)-E_0)V(t)\\ = & -(E_0-E_N(t), E_I(t), V(t))J_1(E_0-E_N(t), E_I(t), V(t))^T\\ & +\theta\beta E_0^2 P(t)\Big(1-\frac{1}{R_0}\Big) + 2a_{13}(t)(E_N(t)-E_0)V(t), \end{aligned} \tag{3.7}$$

where

$$J_1 = \begin{pmatrix} a_{11} & -a_{12} & 0\\ -a_{12} & a_{22} & -a_{23}\\ 0 & -a_{23} & a_{33}\end{pmatrix}.$$

If condition (H) holds, then $a_{11}a_{22}a_{33} - a_{11}a_{23}^2 - a_{33}a_{12}^2 \geq 0$, which implies that matrix J_1 is positive semi-definite. Thus, if $R_0 \leq 1$, then we have

$$\dot{L}(t) \leq 2a_{13}(t)(E_N(t)-E_0)V(t) \leq 0.$$

We claim that, if $\dot{L}(t) = 0$, then $V(t) = 0$. If not, we have that, if $\dot{L}(t) = 0$, then $V(t) > 0$ and $E_N(t) = E_0$. Note that, if condition (H) holds, then $\sqrt{a_{22}a_{33}} > a_{23}$. When $V(t) > 0$ and $E_N(t) = E_0$, by (3.7), we have

$$\begin{aligned}\dot{L}(t) \leq & -a_{22}E_I^2(t) - a_{33}V^2(t) + 2a_{23}E_I(t)V(t)\\ \leq & -\Big(1-\frac{a_{23}}{\sqrt{a_{22}a_{33}}}\Big)(a_{22}E_I^2(t) + a_{33}V^2(t))\\ <& 0.\end{aligned}$$

Thus, the claim holds.

When $E_N(t) > E_0$, we have

$$\begin{aligned}\dot{L}(t) \leq & -\widehat{a}_{11}(E_N(t)-E_0)^2 - a_{22}E_I^2(t) - a_{33}V^2(t) + \theta\beta E_0^2 P(t)\Big(1-\frac{1}{R_0}\Big)\\ & -2a_{12}(E_N(t)-E_0)E_I(t) + 2a_{13}(E_N(t)-E_0)V(t) + 2\widehat{a}_{23}E_I(t)V(t)\\ = & -(E_N(t)-E_0, E_I(t), V(t))J_2(E_N(t)-E_0, E_I(t), V(t))^T\\ & +\theta\beta E_0^2 P(t)\Big(1-\frac{1}{R_0}\Big) - 2a_{12}(E_N(t)-E_0)E_I(t), \end{aligned} \tag{3.8}$$

where

$$J_2 = \begin{pmatrix} \widehat{a}_{11} & 0 & -a_{13}\\ 0 & a_{22} & -\widehat{a}_{23}\\ -a_{13} & -\widehat{a}_{23} & a_{33}\end{pmatrix}.$$

If condition (H) holds, then $\widehat{a}_{11}a_{22}a_{33} - \widehat{a}_{11}\widehat{a}_{23}^2 - a_{22}a_{13}^2 \geq 0$, which implies that matrix J_2 is positive semi-definite. Thus, if $R_0 \leq 1$, then we have

$$\dot{L}(t) \leq -2a_{12}(E_N(t)-E_0)E_I(t) \leq 0.$$

When $E_I(t) > 0$, it is clear that $\dot{L}(t) < 0$. Note that, if condition (H) holds, then $\sqrt{\widehat{a}_{11}a_{33}} > a_{13}$. When $E_I(t) = 0$, then by (3.8), we have

$$\dot{L}(t) \leq -\widehat{a}_{11}(E_N(t)-E_0)^2 - a_{33}V^2(t) + 2a_{13}(t)(E_N(t)-E_0)V(t)$$

$$\begin{aligned}&\leq -\Big(1-\frac{a_{13}}{\sqrt{\widehat{a}_{11}a_{33}}}\Big)[\widehat{a}_{11}(E_N(t)-E_0)^2+a_{33}V^2(t)]\\&<0.\end{aligned}$$

In summary, if $R_0 \leq 1$ and condition (H) holds, then we have $\dot{L}(t) \leq 0$, and $\dot{L}(t) = 0$ implies that $V(t) = 0$. This shows that $L(t)$ is a Lyapunov function on Ω_1. Thus, Q_0 is stable (see [17]). Let M be the largest invariant set in Γ_0, where

$$\Gamma_0 = \big\{(E_N, E_I, V, C, P) \in \overline{\Omega}_1 : \ \dot{L}(t) = 0\big\} \subset \big\{(E_N, E_I, V, C, P) \in \overline{\Omega}_1 : \ V = 0\big\}.$$

From Model (1.2) and the invariance of M, we can obtain $M = \{Q_0\}$. Then, it follows from the Lyapunov-LaSalle invariance principle (see [17]) that Q_0 is globally attractive. Thus, Q_0 is globally asymptotically stable. □

Remark 3.3. By Remark 2.4, it is clear that M_1 is increasing with respect to α, and m_1 is decreasing with respect to α. Then, we state the following two facts:

(i) Note that R_0, a_{22}, a_{33}, a_{12} and θ are independent of α; a_{11} and $\widehat{a}_{11}$ are decreasing with respect to α; a_{13}, a_{23} and $\widehat{a}_{23}$ are increasing with respect to α. Thus, $\Pi(\alpha)$ is increasing with respect to α.

(ii) Note that $a_{11} > \frac{r}{K}\theta(E_0 + E_1) = \frac{2a_{12}^2}{d_I}$, then we have

$$\begin{aligned}&a_{22}a_{33} - \Pi(0) = \frac{d_I^2 d_v^2}{\gamma_1^2} - \frac{d_I^2 d_v^2}{4\gamma_1^2} - \frac{d_I d_v^2}{\gamma_1^2}\frac{a_{12}^2}{a_{11}} > \frac{d_I^2 d_v^2}{4\gamma_1^2} > 0,\\&\lim_{\alpha\to+\infty}\Pi(\alpha) = +\infty.\end{aligned}$$

From (i) and (ii), for a fixed $R_0 \leq 1$, there exits a positive constant $\widehat{\alpha}(R_0) > 0$, such that $a_{22}a_{33} = \Pi(\widehat{\alpha}(R_0))$, $a_{22}a_{33} \geq \Pi(\alpha)$ for $0 \leq \alpha \leq \widehat{\alpha}(R_0)$, $a_{22}a_{33} < \Pi(\alpha)$ for $\alpha > \widehat{\alpha}(R_0)$.

From Theorem 3.2 and Remark 3.3, we have the following corollary.

Corollary 3.4. *If $R_0 \leq 1$ and $0 \leq \alpha \leq \widehat{\alpha}(R_0)$, then the vascular injury-free equilibrium Q_0 is globally asymptotically stable in Ω_1.*

Next, we will give another type of sufficient condition for the global stability of the vascular injury-free equilibrium Q_0. We define

$$\omega^* = \frac{E_0}{M_1} = \frac{(r-d_N) + \sqrt{(r-d_N)^2 + \frac{4sr}{K}}}{r - d_N + \alpha + \sqrt{(r-d_N+\alpha)^2 + \frac{4sr}{K}}} \leq 1.$$

Then, we have the following result.

Theorem 3.5. *If $R_0 < \omega^*$, then the vascular injury-free equilibrium Q_0 is globally asymptotically stable in Ω_1.*

Proof. By Theorem 3.1, we know that Q_0 is locally asymptotically stable if $R_0 < \omega^* \leq 1$. Thus, we only need to prove that Q_0 is globally attractive. We define the following Lyapunov function on Ω_1,

$$W(t) = E_I(t) + \frac{d_I}{\gamma_1\eta + \gamma_2 d_v}\Big(\eta V(t) + d_v C(t) + \frac{d_v d_c}{\delta}P(t)\Big). \tag{3.9}$$

Computing the derivative of $W(t)$ along the solution of Model (1.2) gives

$$\dot{W}(t) = \beta E_N(t)P(t) - d_I E_I(t) + \frac{d_I}{\gamma_1\eta + \gamma_2 d_v}\Big[(\gamma_1\eta + \gamma_2 d_v)E_I(t) - \frac{d_v d_c d_p}{\delta}P(t)\Big]$$

$$\begin{aligned}&\leq \beta M_1 P(t) - \frac{d_I d_v d_c d_p}{\delta(\gamma_1\eta + \gamma_2 d_v)} P(t)\\ &= \beta E_0\Big(\frac{1}{\omega^*} - \frac{1}{R_0}\Big) P(t) \leq 0. \end{aligned} \tag{3.10}$$

It is easy to prove that the largest invariant set in $\Gamma_1 := \{(E_N, E_I, V, C, P) \in \overline{\Omega}_1 : \dot{W} = 0\}$ is the singleton $\{Q_0\}$. It follows from the Lyapunov-LaSalle invariance principle (see [17]) that Q_0 is globally attractive. □

Remark 3.6. Theorem 3.2 and Theorem 3.5 can be applied to both forward bifurcation and backward bifurcation cases (see Figure 6.1 in Section 6). By Remark 2.4, it is easy to see that, if $\alpha > \alpha^*$ (the case of backward bifurcation), then $\omega^* < w^+ < \omega < 1$.

4 Permanence

To obtain the main results of this section, we need the following preparations.

In this section, we assume that $R_0 > 1$. Note that $R_0 = \frac{E_0}{E^*_{N_1}} > 1$, then we have

$$E_0 = \frac{K}{2r}\Big[(r - d_N) + \sqrt{(r - d_N)^2 + \frac{4sr}{K}}\Big] > E^*_{N_1}. \tag{4.1}$$

By Remark 2.4, we can see that there exists some constant $\vartheta \in (0, 1)$ such that

$$B := \frac{K}{2r}\Big[r - d_N - \vartheta\beta P^*_1 + \sqrt{(r - d_N - \vartheta\beta P^*_1)^2 + \frac{4sr}{K}}\Big] > E^*_{N_1}.$$

Clearly, the equation

$$s - d_N x + rx\Big(1 - \frac{x}{K}\Big) - \vartheta\beta P^*_1 x = 0$$

has two roots $x = B$ and $x = -\widehat{B}$, where

$$\widehat{B} = -\frac{K}{2r}\Big[r - d_N - \vartheta\beta P^*_1 - \sqrt{(r - d_N - \vartheta\beta P^*_1)^2 + \frac{4sr}{K}}\Big] > 0.$$

For any $\theta_i > 0$ $(i = 1, 2, 3)$ and $n_1 > 1$, we define

$$\begin{aligned} &B_1 = E^*_{N_1} + \theta_1(B - E^*_{N_1}) \in (E^*_{N_1}, B), \qquad B_2 = E^*_{N_1} + \theta_2(B_1 - E^*_{N_1}) \in (E^*_{N_1}, B_1),\\ &B_3 = E^*_{N_1} + \theta_3(B_2 - E^*_{N_1}) \in (E^*_{N_1}, B_2), \qquad m_1(n_1) = m_1\Big(1 - \frac{1}{n_1}\Big) < m_1 < E^*_{N_1}. \end{aligned}$$

Clearly, $B > B_1 > B_2 > B_3 > E^*_{N_1} > m_1 > m_1(n_1)$. Then, we have the following result.

Theorem 4.1. *If $R_0 > 1$, then Model (1.2) is permanent in $X := \{(E_N, E_I, V, C, P) \in \mathbb{R}^5_+ : P > 0\}$, and the solution $\Phi(t)$ of Model (1.2) with any initial value $\Phi(0) \in X$ satisfies*

$$\begin{aligned} &\liminf_{t\to+\infty} E_I(t) \geq \frac{\beta m_1}{d_I}\vartheta P^*_1 e^{-d_p(T_1+T_2+T_3+T_4)} := m_2,\\ &\liminf_{t\to+\infty} V(t) \geq \frac{\beta\gamma_1 m_1}{d_I d_v}\vartheta P^*_1 e^{-d_p(T_1+T_2+T_3+T_4)} := m_3,\\ &\liminf_{t\to+\infty} C(t) \geq \frac{\beta(\gamma_1\eta + \gamma_2 d_v)m_1}{d_I d_v d_c}\vartheta P^*_1 e^{-d_p(T_1+T_2+T_3+T_4)} := m_4,\\ &\liminf_{t\to+\infty} P(t) \geq \vartheta P^*_1 e^{-d_p(T_1+T_2+T_3+T_4)} := m_5, \end{aligned} \tag{4.2}$$

where

$$T_1 = \frac{K}{r(B+\widehat{B})}\ln\Big(\frac{1}{\rho_1}\Big), \qquad \rho_1 = \frac{(B-B_1)(\widehat{B}+m_1(n_1))}{(B-m_1(n_1))(\widehat{B}+B_1)} \in (0,1),$$
$$T_2 = \frac{1}{d_I}\ln\Big(\frac{1}{\rho_2}\Big), \qquad \rho_2 = 1-\frac{B_2}{B_1} \in (0,1),$$
$$T_3 = \frac{1}{d_v}\ln\big(\frac{1}{\rho_3}\big), \qquad \rho_3 = 1-\frac{B_3}{B_2} \in (0,1),$$
$$T_4 = \frac{1}{d_c}\ln\big(\frac{1}{\rho_4}\big), \qquad \rho_4 = 1-\frac{(\gamma_2 d_v+\eta\gamma_1)E^*_{N_1}}{\gamma_2 d_v B_2+\eta\gamma_1 B_3} \in (0,1).$$

Proof. It is easy to prove that, for $t>0$, the solution $\Phi(t)$ of Model (1.2) with any initial value $\Phi(0)\in X$ is positive and X is positively invariant with respect to Model (1.2). By Theorem 2.1 and Lemma 2.2, we only need to prove that (4.2) holds.

From Lemma 2.2, we can see that there exits a $\widetilde{t}>0$ such that $E_N(t)>m_1(n_1)$ for $t\geq\widetilde{t}$. To prove $\liminf\limits_{t\to+\infty}P(t)\geq m_5$, we first give two important claims.

Claim (i) $\liminf\limits_{t\to+\infty}E_N(t)\leq E^*_{N_1}$.

If not, there exits a $\widetilde{E^*_{N_1}}>E^*_{N_1}$ such that $\liminf\limits_{t\to+\infty}E_N(t)=\widetilde{E^*_{N_1}}$. Let $\epsilon_0=\frac{1}{2}(\widetilde{E^*_{N_1}}-E^*_{N_1})>0$, then there exits a $T(\epsilon_0)>0$ such that, for $t>T(\epsilon_0)$,

$$E_N(t)>\widetilde{E^*_{N_1}}-\epsilon_0=\frac{1}{2}(\widetilde{E^*_{N_1}}+E^*_{N_1})=E^*_{N_1}+\epsilon_0.$$

From (3.9) and (3.10), we have, for $t\geq T(\epsilon_0)$,

$$\begin{aligned}\dot{W}(t)=&\beta E_N(t)P(t)-\frac{d_I d_v d_c d_p}{\delta(\gamma_1\eta+\gamma_2 d_v)}P(t)\\ \geq&\beta(E^*_{N_1}+\epsilon_0)P(t)-\frac{d_I d_v d_c d_p}{\delta(\gamma_1\eta+\gamma_2 d_v)}P(t)\\ =&\beta\epsilon_0 P(t)\geq 0,\end{aligned}$$

which shows that $W(t)$ is monotonically increasing on $[T(\epsilon_0),+\infty)$. From Theorem 2.1, we can see that $W(t)$ is bounded. Thus, there exits a constant

$$W^*\geq\frac{d_I d_v d_c}{(\gamma_1\eta+\gamma_2 d_v)\delta}P(T(\epsilon_0))>0$$

such that $\lim\limits_{t\to+\infty}W(t)=W^*$. Moreover, from Theorem 2.1, it is not difficult to prove that $\dot{W}(t)$ is uniformly continuous on $[T(\epsilon_0),+\infty)$. Accordingly, it follows from Barbalat's lemma[5] that $\lim\limits_{t\to+\infty}\dot{W}(t)=0$, which leads to $\lim\limits_{t\to+\infty}P(t)=0$. Further, from Model (1.2), it is easy to obtain that $\lim\limits_{t\to+\infty}E_I(t)=\lim\limits_{t\to+\infty}V(t)=\lim\limits_{t\to+\infty}C(t)=0$. Thus, $\lim\limits_{t\to+\infty}W(t)=0$, which contradicts $\lim\limits_{t\to+\infty}W(t)=W^*>0$. This proves the claim.

Claim (ii) For any $t_0\geq\widetilde{t}$, it is impossible to satisfy $P(t)\leq\vartheta P^*$ for all $t>t_0$.

If not, then there exits a $t_0\geq\widetilde{t}$ such that $P(t)\leq\vartheta P^*$ for $t>t_0$. From the first equation of Model (1.2), we have, for $t>t_0$,

$$\begin{aligned}\dot{E}_N(t)\geq&s-d_N E_N(t)+rE_N(t)\Big(1-\frac{E_N(t)}{K}\Big)-\beta\vartheta P^* E_N(t)\\ =&-\frac{r}{K}(E_N(t)+\widehat{B})(E_N(t)-B),\end{aligned}\tag{4.3}$$

which implies that $\liminf_{t\to+\infty} E_N(t) \geq B > E^*_{N_1}$. This contradicts **Claim (i)**. Thus, **Claim (ii)** holds.

By **Claim (ii)**, there are two cases to be considered.

From **Claim (ii)**, we only need to consider the following two cases: (i) $P(t) \geq \vartheta P^*$ for all sufficiently large t; (ii) $P(t)$ oscillates about ϑP^* for all sufficiently large t.

Clearly, we only need to consider case (ii). Let $t_1, t_2 > \widetilde{t}$ be sufficiently large such that $P(t_1) = P(t_2) = \vartheta P^*$, $P(t) < \vartheta P^*$ for $t_1 < t < t_2$.

If $t_2 - t_1 \leq T_1 + T_2 + T_3 + T_4 := \hat{\Pi}_1$, then from the last equation of Model (1.2), we have $\dot{P}(t) \geq -d_p P(t)$. Thus, we have, for $t_1 \leq t \leq t_2$,

$$P(t) \geq P(t_1)e^{-d_p(t-t_1)} \geq \vartheta P^* e^{-d_p(t_2-t_1)} \geq \vartheta P^* e^{-d_p\hat{\Pi}_1} = m_5.$$

If $t_2 - t_1 > \hat{\Pi}_1$, then it is easy to obtain that $P(t) \geq m_5$ for $t_1 \leq t \leq t_1 + \hat{\Pi}_1$. Then, we will prove that $P(t) \geq m_5$ for $t_1 + \hat{\Pi}_1 < t \leq t_2$. In fact, if not, there exists a $T_5 \geq 0$ such that $P(t) \geq m_5$ for $t_1 \leq t \leq t^*$, $P(t^*) = m_5$ and $\dot{P}(t^*) \leq 0$, where $t^* = t_1 + \hat{\Pi}_1 + T_5$. Similarly, by (4.3), we have, for $t_1 \leq t \leq t_2$,

$$\dot{E}_N(t) \geq -\frac{r}{K}(E_N(t) + \widehat{B})(E_N(t) - B),$$

which implies that, for $t_1 \leq t \leq t_2$,

$$\begin{aligned} E_N(t) \geq & \frac{B + \widehat{B}\big(\frac{E_N(t_1)-B}{E_N(t_1)+\widehat{B}}\big)e^{-\frac{r}{K}(B+\widehat{B})(t-t_1)}}{1 - \big(\frac{E_N(t_1)-B}{E_N(t_1)+\widehat{B}}\big)e^{-\frac{r}{K}(B+\widehat{B})(t-t_1)}} \\ \geq & \frac{B - \widehat{B}\big(\frac{B-m_1(n_1)}{m_1(n_1)+\widehat{B}}\big)e^{-\frac{r}{K}(B+\widehat{B})(t-t_1)}}{1 + \big(\frac{B-m_1(n_1)}{m_1(n_1)+\widehat{B}}\big)e^{-\frac{r}{K}(B+\widehat{B})(t-t_1)}}. \end{aligned} \tag{4.4}$$

From (4.4), we have, for $t_1 + T_1 \leq t \leq t_2$,

$$E_N(t) \geq \frac{B - \widehat{B}\big(\frac{B-m_1(n_1)}{m_1(n_1)+\widehat{B}}\big)e^{-\frac{r}{K}(B+\widehat{B})T_1}}{1 + \big(\frac{B-m_1(n_1)}{m_1(n_1)+\widehat{B}}\big)e^{-\frac{r}{K}(B+\widehat{B})T_1}} = B_1. \tag{4.5}$$

From (4.5) and the second equation of Model (1.2), we have, for $t_1 + T_1 \leq t \leq t^*$,

$$\dot{E}_I(t) \geq \beta B_1 m_5 - d_I E_I(t),$$

which implies that, for $t_1 + T_1 \leq t \leq t^*$,

$$\begin{aligned} E_I(t) \geq & \frac{\beta B_1 m_5}{d_I} + \Big[E_I(t_1 + T_1) - \frac{\beta B_1 m_5}{d_I}\Big]e^{-d_I(t-t_1-T_1)} \\ \geq & \frac{\beta B_1 m_5}{d_I}\big[1 - e^{-d_I(t-t_1-T_1)}\big]. \end{aligned} \tag{4.6}$$

From (4.6), we have, for $t_1 + T_1 + T_2 \leq t \leq t^*$,

$$E_I(t) \geq \frac{\beta B_1 m_5}{d_I}\big[1 - e^{-d_I T_2}\big] = \frac{\beta B_2 m_5}{d_I}. \tag{4.7}$$

From (4.7) and the third equation of Model (1.2), we have, for $t_1 + T_1 + T_2 \leq t \leq t^*$,

$$\dot{V}(t) \geq \frac{\gamma_1 \beta B_2 m_5}{d_I} - d_v V(t),$$

which implies that, for $t_1+T_1+T_2\le t\le t^*$,

$$\begin{aligned}V(t)\ge&\frac{\gamma_1\beta B_2m_5}{d_Id_v}+\Big[V(t_1+T_1+T_2)-\frac{\gamma_1\beta B_2m_5}{d_Id_v}\Big]e^{-d_v(t-t_1-T_1-T_2)}\\ \ge&\frac{\gamma_1\beta B_2m_5}{d_Id_v}\big[1-e^{-d_v(t-t_1-T_1-T_2)}\big].\end{aligned}\tag{4.8}$$

From (4.8), we have, for $t_1+T_1+T_2+T_3\le t\le t^*$,

$$V(t)\ge\frac{\gamma_1\beta B_2m_5}{d_Id_v}\big[1-e^{-d_vT_3}\big]=\frac{\gamma_1\beta B_3m_5}{d_Id_v}.\tag{4.9}$$

Further, from the fourth equation of Model (1.2), (4.7) and (4.9), we have, for $t_1+T_1+T_2+T_3\le t\le t^*$,

$$\dot C(t)\ge\gamma_2\frac{\beta B_2m_5}{d_I}+\eta\frac{\gamma_1\beta B_3m_5}{d_Id_v}-d_cC(t),$$

which implies that, for $t_1+T_1+T_2+T_3\le t\le t^*$,

$$\begin{aligned}C(t)\ge&B_{23}+[C(t_1+T_1+T_2+T_3)-B_{23}]e^{-d_c(t-t_1-T_1-T_2-T_3)}\\ >&B_{23}\big[1-e^{-d_c(t-t_1-T_1-T_2-T_3)}\big],\end{aligned}\tag{4.10}$$

where

$$B_{23}=\Big(\frac{\gamma_2B_2}{d_Id_cB_3}+\frac{\eta\gamma_1}{d_Id_vd_c}\Big)\beta B_3m_5.$$

From (4.10), we have, for $t_1+T_1+T_2+T_3+T_4\le t\le t^*$,

$$C(t)>B_{23}\big[1-e^{-d_cT_4}\big]=\Big(\frac{\gamma_2d_v+\eta\gamma_1}{d_Id_vd_c}\Big)\beta E^*_{N_1}m_5.$$

Finally, from the last equation of Model (1.2), we have

$$\dot P(t^*)=\delta C(t^*)-d_pP(t^*)>\delta\Big(\frac{\gamma_2d_v+\eta\gamma_1}{d_Id_vd_c}\Big)\beta E^*_{N_1}m_5-d_pm_5=0,$$

which is a contradiction to $\dot P(t^*)\le0$. Thus, $P(t)\ge m_5$ for $t_1\le t\le t_2$. Since the interval $t_1\le t\le t_2$ is arbitrary chosen, we have that $P(t)\ge m_5$ holds for all sufficiently large t. Thus, we have $\liminf\limits_{t\to+\infty}P(t)\ge m_5$.

Moreover, from Model (1.2) and Lemma 2.2, we have

$$\liminf_{t\to+\infty}E_I(t)\ge\frac{\beta m_1m_5}{d_I}=m_2,\ \liminf_{t\to+\infty}V(t)\ge\frac{\gamma_1m_2}{d_v}=m_3,\ \liminf_{t\to+\infty}P(t)\ge\frac{\gamma_2m_2+\eta m_3}{d_c}=m_4.$$

□

Remark 4.2. In Theorem 4.1, it is easy to see that ρ_1 is monotonically increasing with respect to $n_1>1$ and T_1 is monotonically decreasing with respect to $n_1>1$. Note that $n_1>1$ is chosen arbitrarily. Let

$$\widetilde T_1=\lim_{n_1\to+\infty}T_1=\frac{K}{r(B+\widehat B)}\ln\Big(\frac{1}{\widetilde\rho_1}\Big),\qquad\widetilde\rho_1=\frac{(B-B_1)(\widehat B+m_1)}{(B-m_1)(\widehat B+B_1)}\in(0,1).$$

By Theorem 4.1, we can obtain the following better estimations:

$$\begin{aligned}
&\liminf_{t\to+\infty} E_I(t) \geq \frac{\beta m_1}{d_I}\vartheta P_1^* e^{-d_p(\widetilde{T}_1+T_2+T_3+T_4)} := \widetilde{m}_2,\\
&\liminf_{t\to+\infty} V(t) \geq \frac{\beta\gamma_1 m_1}{d_I d_v}\vartheta P_1^* e^{-d_p(\widetilde{T}_1+T_2+T_3+T_4)} := \widetilde{m}_3,\\
&\liminf_{t\to+\infty} C(t) \geq \frac{\beta(\gamma_1\eta+\gamma_2 d_v)m_1}{d_I d_v d_c}\vartheta P_1^* e^{-d_p(\widetilde{T}_1+T_2+T_3+T_4)} := \widetilde{m}_4,\\
&\liminf_{t\to+\infty} P(t) \geq \vartheta P_1^* e^{-d_p(\widetilde{T}_1+T_2+T_3+T_4)} := \widetilde{m}_5.
\end{aligned} \tag{4.11}$$

Theorem 4.1 shows that if the basic reproduction number $R_0 > 1$, then the vascular injury and inflammation in the KD lesion area will persist, and KD is uncontrollable.

5 Stability of the Vascular Injury Equilibria and Hopf Bifurcation

5.1 Local Stability of the Vascular Injury Equilibria and Hopf Bifurcation

Without loss of generality, we assume that $\overline{Q} = (\overline{E_N}, \overline{E_I}, \overline{V}, \overline{C}, \overline{P})$ is an arbitrary vascular injury equilibrium of Model (1.2). Using the first equation of Model (1.2) and (2.5), we have

$$d_N - r + \frac{2r}{K}\overline{E_N} - \frac{\alpha\overline{V}}{1+\overline{V}} + \beta\overline{P} = \frac{s}{\overline{E_N}} + \frac{r}{K}\overline{E_N}, \qquad \beta\overline{P} = \alpha^*\overline{V}. \tag{5.1}$$

Then, the characteristic equation (3.1) of Model (1.2) at $\overline{Q}$ can be rewritten as

$$\begin{vmatrix}
\lambda+\Psi_1 & 0 & -\Psi_2(\overline{V}) & 0 & \Psi_3\\
-\alpha^*\overline{V} & \lambda+d_I & 0 & 0 & -\Psi_3\\
0 & -\gamma_1 & \lambda+d_v & 0 & 0\\
0 & -\gamma_2 & -\eta & \lambda+d_c & 0\\
0 & 0 & 0 & -\delta & \lambda+d_p
\end{vmatrix} = 0, \tag{5.2}$$

where

$$\Psi_1 = \frac{s}{\overline{E_N}} + \frac{r}{K}\overline{E_N}, \quad \Psi_2(\overline{V}) = \frac{\alpha\overline{E_N}}{(1+\overline{V})^2}, \quad \Psi_3 = \beta\overline{E_N}, \qquad \overline{E_N} = \frac{d_I d_v d_c d_p}{\delta\beta(\gamma_1\eta+\gamma_2 d_v)}.$$

We define

$$\begin{aligned}
p(\overline{V}) &= \Psi_1 d_I d_v - \Psi_2(\overline{V})\gamma_1\alpha^*\overline{V} = d_I d_v\Big(\Psi_1 - \frac{\alpha\overline{V}}{(1+\overline{V})^2}\Big),\\
q &= d_I d_c d_p - \Psi_3\delta\gamma_2 = d_I d_c d_p\frac{\gamma_1\eta}{\gamma_1\eta+\gamma_2 d_v} > 0.
\end{aligned}$$

By (5.2), direct calculations lead to

$$\Xi(\lambda) := \lambda^5 + D_1\lambda^4 + D_2\lambda^3 + D_3(\overline{V})\lambda^2 + D_4(\overline{V})\lambda + D_5(\overline{V}) = 0, \tag{5.3}$$

where

$$\begin{aligned}
&D_1 = \Psi_1 + d_I + d_v + d_c + d_p > 0,\\
&D_2 = \Psi_1(d_I + d_v + d_c + d_p) + d_I(d_v + d_c + d_p) + d_v(d_c + d_p) + d_c d_p > 0,
\end{aligned}$$

$$D_3(\overline{V}) = \Psi_1(d_I d_c + d_I d_p + d_v d_c + d_v d_p + d_c d_p) + d_I d_v(d_c + d_p) + d_v d_c d_p + p(\overline{V}) + q,$$
$$D_4(\overline{V}) = \Psi_1 d_v d_c d_p + (d_c + d_p)p(\overline{V}) + \Psi_1 q + \Psi_3 \delta\gamma_2\alpha^*\overline{V},$$
$$D_5(\overline{V}) = \alpha^*\overline{V}[\Psi_3\delta(\eta\gamma_1 + \gamma_2 d_v) - \Psi_2(\overline{V})\gamma_1 d_c d_p] = \frac{d_I d_v d_c d_p \overline{V}}{(1+\overline{V})^2}(\alpha^*(1+\overline{V})^2 - \alpha).$$

In fact, through numerical simulations, we find that the sign of $p(\overline{V})$ is indefinite. Moreover, $D_3(\overline{V})$ and $D_4(\overline{V})$ are negative within a certain range of parameters. In order to determine the sign of $D_5(\overline{V})$, we give the following lemma.

Lemma 5.1. *The following statements are valid.*
(i) *Assume that* $0 \le \alpha \le \alpha^*$ *(the case of forward bifurcation). Then* $\alpha^*(1+V_1^*)^2 - \alpha > 0$ *if* $R_0 > 1$.
(ii) *Assume that* $\alpha > \alpha^*$ *(the case of backward bifurcation). Then* $\alpha^*(1+V_1^*)^2 - \alpha > 0$ *if* $R_0 > \omega$, $\alpha^*(1+V_2^*)^2 - \alpha < 0$ *if* $\omega < R_0 < 1$, $\alpha^*(1+V_1^*)^2 - \alpha = 0$ *if* $R_0 = \omega$.

Proof. If $\alpha \le \alpha^*$, $R_0 > 1$, or $\alpha > \alpha^*$, $R_0 > \omega$, then the vascular injury equilibrium Q_1^* exits ($V_1^* > 0$). Applying Vedda's theorem to the equation (2.8), we have

$$(V_1^*)^2 > \frac{-\frac{r}{K}(E_0 + E_1 R_0)(R_0 - 1)}{\alpha^* R_0} := \chi_1,$$
$$2V_1^* > \frac{-(\alpha^* - \alpha)R_0 + \frac{r}{K}(E_0 + E_1 R_0)(R_0 - 1)}{\alpha^* R_0} := \chi_2.$$

Thus,

$$\alpha^*(1+V_1^*)^2 - \alpha = \alpha^*[(V_1^*)^2 + 2V_1^* + 1] - \alpha > \alpha^*(\chi_1 + \chi_2) + \alpha^* - \alpha = 0.$$

Similarly, we can prove that $(V_2^*)^2 < \chi_1$, $2V_2^* < \chi_2$ and $\alpha^*(1+V_2^*)^2 - \alpha < 0$ if $\alpha > \alpha^*$ and $\omega < R_0 < 1$; $(V_1^*)^2 = \chi_1$, $2V_1^* = \chi_2$ and $\alpha^*(1+V_1^*)^2 - \alpha = 0$ if $\alpha > \alpha^*$ and $R_0 = \omega$. □

Let us first consider the stability of Q_2^*. By Lemma 5.1, we have $D_5(V_2^*) < 0$. Then, it is easy to see that the characteristic equation (5.3) at Q_2^* has at least one positive real root. Thus, Q_2^* is unstable if it exists.

In the following, we consider the stability of Q_1^*. By Lemma 5.1, we have $D_5(V_1^*) > 0$. Thus, $\lambda = 0$ is not a root of the characteristic equation (5.3). In addition, the calculation gives $\Delta_1 := D_1 > 0$,

$$\begin{aligned}\Delta_2(V_1^*) :=& D_1 D_2 - D_3(V_1^*)\\ =& (\Psi_1 + d_I)D_2 + (\Psi_1 + d_I)(d_v^2 + d_c^2 + d_p^2 + d_v d_c + d_v d_p + d_c d_p)\\ &+ d_v(d_c^2 + d_p^2 + d_v d_c + d_v d_p + 2d_c d_p) + d_c d_p(d_c + d_p) + \Psi_3\delta\gamma_2 + \Psi_2(V_1^*)\gamma_1\alpha^* V_1^*\\ >& 0.\end{aligned}$$

We define the following condition

$$\text{(H1)}\quad \begin{cases} D_3(V_1^*) > 0, \quad D_4(V_1^*) > 0,\\ \Delta_3(V_1^*) := D_3(V_1^*)[D_1 D_2 - D_3(V_1^*)] - D_1[D_1 D_4(V_1^*) - D_5(V_1^*)] > 0,\\ \Delta_4(V_1^*) := [D_1 D_2 - D_3(V_1^*)][D_3(V_1^*)D_4(V_1^*) - D_2 D_5(V_1^*)]\\ \qquad\qquad - [D_1 D_4(V_1^*) - D_5(V_1^*)]^2 > 0. \end{cases}$$

If condition (H1) holds, we have $\Delta_5(V_1^*) := D_5(V_1^*)\Delta_4(V_1^*) > 0$. Then, it follows from the Routh-Hurwitz stability criterion that Q_1^* is locally asymptotically stable.

If $\Delta_4(V_1^*) \neq 0$, it is not difficult to obtain that the characteristic equation (5.3) at Q_1^* has no pure imaginary roots. Thus, if $\Delta_4(V_1^*) \neq 0$ and condition (H1) does not hold, then the characteristic equation (5.3) has at least one root with a positive real part; thus Q_1^* is unstable.

Let $V_1^*(\alpha) = V_1^*$ and $\lambda(\alpha) = \xi_1(\alpha) + i\xi_2(\alpha)$ be the characteristic root of the characteristic equation (5.3). If $\Delta_4(V_1^*(\alpha)) = 0$, then the characteristic equation (5.3) has a pair pure imaginary roots $\pm\varpi(\alpha)i$, where

$$\varpi(\alpha) = \sqrt{\frac{D_1 D_4(V_1^*(\alpha)) - D_5(V_1^*(\alpha))}{D_1 D_2 - D_3(V_1^*(\alpha))}} > 0.$$

From (5.3), we have

$$\begin{aligned}
&\Theta(\varpi(\alpha))\\
:=&\text{sign}\Big\{\frac{d(\text{Re }\lambda(\alpha))}{d\alpha}\Big\}_{\lambda(\alpha)=\varpi(\alpha)i} = \text{sign}\Big\{\frac{d(\xi_1(\alpha))}{d\alpha}\Big\}_{\lambda(\alpha)=\varpi(\alpha)i}\\
=&\text{sign}\Big\{\text{Re}\Big[-\frac{\frac{dD_3(V_1^*(\alpha))}{d\alpha}\lambda^2(\alpha) + \frac{dD_4(V_1^*(\alpha))}{d\alpha}\lambda(\alpha) + \frac{dD_5(V_1^*(\alpha))}{d\alpha}}{5\lambda^4(\alpha) + 4D_1\lambda^3(\alpha) + 3D_2\lambda^2(\alpha) + 2D_3(V_1^*(\alpha))\lambda(\alpha) + D_4(V_1^*(\alpha))}\Big]\Big\}_{\lambda(\alpha)=\varpi(\alpha)i}\\
=&\text{sign}\Big\{\Big[\frac{dD_3(V_1^*(\alpha))}{d\alpha}\varpi^2(\alpha) - \frac{dD_5(V_1^*(\alpha))}{d\alpha}\Big]\Big[5\varpi^4(\alpha) - 3D_2\varpi^2(\alpha) + D_4(V_1^*(\alpha))\Big]\\
&+ \frac{dD_4(V_1^*(\alpha))}{d\alpha}[4D_1\varpi^2(\alpha) - 2D_3(V_1^*(\alpha))]\varpi^2(\alpha)\Big\}.
\end{aligned}$$

Note that

$$\begin{aligned}
&\frac{dD_3(V_1^*(\alpha))}{d\alpha} = -d_I d_v \Theta_1(\alpha), \quad \Theta_1(\alpha) = \frac{V_1^*(\alpha)}{(1+V_1^*(\alpha))^2} + \frac{\alpha(1-V_1^*(\alpha))}{(1+V_1^*(\alpha))^3}\frac{dV_1^*(\alpha)}{d\alpha},\\
&\frac{dD_4(V_1^*(\alpha))}{d\alpha} = -d_I d_v(d_c+d_p)\Theta_1(\alpha) + \Psi_3\delta\gamma_2\alpha^*\frac{dV_1^*(\alpha)}{d\alpha},\\
&\frac{dD_5(V_1^*(\alpha))}{d\alpha} = d_I d_v d_c d_p\Big[\alpha^*\frac{dV_1^*(\alpha)}{d\alpha} - \Theta_1(\alpha)\Big].
\end{aligned}$$

By Theorem 2 in [35], we have that Model (1.2) has a Hopf bifurcation at Q_1^* if $\Delta_4(V_1^*(\alpha)) = 0$ and $\Theta(\varpi(\alpha)) \neq 0$.

In summary, we have the following results.

Theorem 5.2. *The following statements are valid.*
(i) *If $\alpha > \alpha^*$ and $\omega < R_0 < 1$ (i.e., Q_2^* exists), then the vascular injury equilibrium Q_2^* is unstable.*
(ii) *Assume that $0 \leq \alpha \leq \alpha^*$, $R_0 > 1$, or $\alpha > \alpha^*$, $R_0 > \omega$ (i.e., Q_1^* exists). The vascular injury equilibrium Q_1^* is locally asymptotically stable if condition (H1) holds, is unstable if $\Delta_4(V_1^*) \neq 0$ and condition (H1) does not hold. Moreover, Model (1.2) has a Hopf bifurcation at the vascular injury equilibrium Q_1^* if $\Delta_4(V_1^*(\alpha)) = 0$ and $\Theta(\varpi(\alpha)) \neq 0$.*

Note that condition (H1) is complex. It is necessary to give convenient verification sufficient conditions for the local asymptotic stability of the vascular injury equilibrium Q_1^*. We define

$$\Upsilon^*(V_1^*(\alpha)) = \Upsilon_1^* - \frac{\alpha V_1^*(\alpha)}{1+V_1^*(\alpha)}, \qquad \Upsilon_1^* = d_N - r + \frac{2r}{K}E_{N_1}^*.$$

Theorem 5.3. *Assume that $0 \leq \alpha \leq \alpha^*$, $R_0 > 1$, or $\alpha > \alpha^*$, $R_0 > \omega$ (i.e. Q_1^* exists). Then, the following statements are valid.*
(i) *If $\Upsilon_1^* \geq 0$ and $\alpha = 0$, then the vascular injury equilibrium Q_1^* is locally asymptotically stable.*
(ii) *If $\Upsilon^*(V_1^*(\alpha)) \geq \min\{d_I, d_c, d_p\}$, then the vascular injury equilibrium Q_1^* is locally asymptotically stable.*

Proof. The characteristic equation (5.2) at Q_1^* can be rewritten in the following form:

$$\begin{aligned}&(\lambda+\Psi_1)(\lambda+d_I)(\lambda+d_v)(\lambda+d_c)(\lambda+d_p)\\ =&(\lambda+\Psi_1-\alpha^*V^*)\beta\delta E_{N_1}^*[\gamma_1\eta+\gamma_2(\lambda+d_v)]+\alpha^*V_1^*\Psi_2(V_1^*)\gamma_1(\lambda+d_c)(\lambda+d_p),\end{aligned}$$

the above equation is equivalent to

$$\begin{aligned}1=&\frac{\lambda+\Psi_1-\alpha^*V_1^*}{\lambda+\Psi_1}\beta\delta E_{N_1}^*\Big[\frac{\gamma_1\eta}{(\lambda+d_I)(\lambda+d_v)(\lambda+d_c)(\lambda+d_p)}+\frac{\gamma_2}{(\lambda+d_I)(\lambda+d_c)(\lambda+d_p)}\Big]\\ &+\frac{\alpha^*V_1^*\Psi_2(V_1^*)\gamma_1}{(\lambda+\Psi_1)(\lambda+d_I)(\lambda+d_v)}.\end{aligned}\tag{5.4}$$

Note that (5.4) has no zero roots. Suppose (5.4) has a root $\lambda=x+iy$, where $x\geq 0$ and $x^2+y^2>0$.

(i) Assume that $\Upsilon_1^*\geq 0$ and $\alpha=0$. Clearly, $\Psi_2(V_1^*)=0$. By (5.1), we have $\Psi_1=\beta P_1^*+\Upsilon_1^*\geq\alpha^*V_1^*$, which leads to $|\lambda+\Psi_1-\alpha^*V_1^*|<|\lambda+\Psi_1|$. Then, from (5.4), we have

$$\begin{aligned}1\leq&\frac{|\lambda+\Psi_1-\alpha^*V_1^*|}{|\lambda+\Psi_1|}\beta\delta E_{N_1}^*\Big[\frac{\gamma_1\eta}{|\lambda+d_I||\lambda+d_v||\lambda+d_c||\lambda+d_p|}+\frac{\gamma_2}{|\lambda+d_I||\lambda+d_c||\lambda+d_p|}\Big]\\ \leq&\frac{|\lambda+\Psi_1-\alpha^*V_1^*|}{|\lambda+\Psi_1|}\beta\delta E_{N_1}^*\Big[\frac{\gamma_1\eta}{d_Id_vd_cd_p}+\frac{\gamma_2}{d_Id_cd_p}\Big]\\ =&\frac{|\lambda+\Psi_1-\alpha^*V_1^*|}{|\lambda+\Psi_1|}<1.\end{aligned}$$

This is a contradiction. Thus, the conclusion (i) of Theorem 5.3 is valid.

(ii) Assume that $\Upsilon^*(V_1^*(\alpha))\geq\min\{d_I,d_c,d_p\}$. By (5.1), we have

$$\Psi_1-\alpha^*V_1^*=\Psi_1-\beta P_1^*=\Upsilon^*(V_1^*(\alpha))\geq\min\{d_I,d_c,d_p\}.$$

Then, it is easy to prove that

$$\frac{|\lambda+\Psi_1-\alpha^*V_1^*|}{|\lambda+d_I||\lambda+d_v||\lambda+d_c|}\leq\frac{\Psi_1-\alpha^*V_1^*}{d_Id_vd_c}.\tag{5.5}$$

Note that

$$\frac{\alpha^*\Psi_2(V_1^*)\gamma_1}{d_Id_v}=\frac{\alpha^*\gamma_1}{d_Id_v}\frac{\alpha E_{N_1}^*}{(1+V_1^*)^2}=\frac{\alpha}{(1+V_1^*)^2},$$

then from (5.4), (5.5) and Lemma 5.1, we have

$$\begin{aligned}1\leq&\frac{\beta\delta E_{N_1}^*}{|\lambda+\Psi_1|}\Big(\frac{\gamma_1\eta|\lambda+\Psi_1-\alpha^*V_1^*|}{|\lambda+d_I||\lambda+d_v||\lambda+d_c||\lambda+d_p|}+\frac{\gamma_2|\lambda+\Psi_1-\alpha^*V_1^*|}{|\lambda+d_I||\lambda+d_c||\lambda+d_p|}\Big)\\ &+\frac{\alpha^*V_1^*\Psi_2(V_1^*)\gamma_1}{|\lambda+\Psi_1||\lambda+d_I||\lambda+d_v|}\\ \leq&\frac{\beta\delta E_{N_1}^*}{\Psi_1}\Big[\frac{\gamma_1\eta(\Psi_1-\alpha^*V_1^*)}{d_Id_vd_cd_p}+\frac{\gamma_2(\Psi_1-\alpha^*V_1^*)}{d_Id_cd_p}\Big]+\frac{\alpha^*V_1^*\Psi_2(V_1^*)\gamma_1}{\Psi_1d_Id_v}\\ =&1-\frac{\alpha^*V_1^*}{\Psi_1}+\frac{\alpha^*V_1^*\Psi_2(V_1^*)\gamma_1}{\Psi_1d_Id_v}=1-\frac{V_1^*}{\Psi_1}\Big(\alpha^*-\frac{\alpha}{(1+V_1^*)^2}\Big)<1.\end{aligned}\tag{5.6}$$

This is a contradiction. Thus, the conclusion (ii) of Theorem 5.3 is valid. □

In the following, we consider the existence of the Hopf bifurcation at Q_1^* by choosing α as the bifurcation parameter. In the analysis of Theorem 2.3, we first fix the parameters α and α^*; let R_0 be the parameter of variation to discuss the existence of Q_1^*. For a given R_0, in order to obtain the existence of Q_1^* with respect to the variation of α, we need to give a result different from Theorem 2.3.

In the following, we first fix all the parameters in R_0. Note that the parameters in α^* are part of R_0, and α^*, R_0, E_0 and E_1 are independent of α. We consider the following three cases.

Case (i). Assume that $R_0 > 1$.

It is not difficult to see that, for any $\alpha \geq 0$, we have that the equation (2.8) ($F(V) = 0$) has a unique positive root $V = V_1^* = V_1^*(\alpha) > 0$. Then, Model (1.2) has the vascular injury equilibrium Q_1^*.

Case (ii). Assume that $R_0 = 1$.

In this case, if $\alpha > \alpha^*$, then $F(V) = 0$ has a unique positive root $V = V_1^*(\alpha) = \frac{\alpha-\alpha^*}{\alpha^*}$. Clearly, $F(V) = 0$ has no positive roots if $0 \leq \alpha \leq \alpha^*$. Thus, if $\alpha > \alpha^*$, Model (1.2) has the vascular injury equilibrium Q_1^*.

Case (iii). Assume that $R_0 < 1$.

If

$$\alpha \leq \alpha^* + \frac{\frac{r}{K}(E_0 + E_1R_0)(1 - R_0)}{R_0} := \check{\alpha}^*,$$

then $\Lambda_1(R_0) \geq 0$, it is clear that $F(V) = 0$ has no positive roots. Thus, we assume $\alpha > \check{\alpha}^*$ in the following discussion. We need to consider the sign of $\Delta(R_0)$ as α changes. We rewrite the $\Delta(R_0)$ expression as follows

$$\begin{aligned}\Delta(R_0) =& R_0^2\alpha^2 - 2\Big[R_0\alpha^* + \frac{r}{K}(E_0 + E_1R_0)(1 - R_0)\Big]R_0\alpha \\ &+ \Big[\frac{r}{K}(E_0 + E_1R_0)(1 - R_0) - \alpha^*R_0\Big]^2.\end{aligned}$$

We define

$$\alpha^{**} = \frac{\alpha^*R_0 + \frac{r}{K}(E_0 + E_1R_0)(1 - R_0) + 2\sqrt{\alpha^*R_0\frac{r}{K}(E_0 + E_1R_0)(1 - R_0)}}{R_0} > \check{\alpha}^*.$$

Clearly, $\Delta(R_0) < 0$ if $\check{\alpha}^* < \alpha < \alpha^{**}$, $\Delta(R_0) = 0$ if $\alpha = \alpha^{**}$, $\Delta(R_0) > 0$ if $\alpha > \alpha^{**}$. Thus, $F(V) = 0$ has no positive roots if $\check{\alpha}^* < \alpha < \alpha^{**}$, $F(V) = 0$ has a unique positive root $V = V_1^*(\alpha) > 0$ if $\alpha = \alpha^{**}$, $F(V) = 0$ has two positive roots $V = V_1^*(\alpha) > 0$ and $V = V_2^* > 0$ if $\alpha > \alpha^{**}$. Then, we have that, if $\alpha > \alpha^{**}$, Model (1.2) has the vascular injury equilibrium Q_1^*.

Lemma 5.4. *The following statements are valid.*
(i) *Assume that $R_0 > 1$. For any $\alpha \geq 0$, then $V_1^*(\alpha) > 0$ and Model (1.2) has the vascular injury equilibrium Q_1^*.*
(ii) *Assume that $R_0 = 1$. For any $\alpha > \alpha^*$, then $V_1^*(\alpha) > 0$ and Model (1.2) has the vascular injury equilibrium Q_1^*.*
(iii) *Assume that $R_0 < 1$. For any $\alpha > \alpha^{**}$ ($> \alpha^*$), then $V_1^*(\alpha) > 0$ and Model (1.2) has the vascular injury equilibrium Q_1^*.*

From (2.7) and Lemma 5.4, we can easily have the following lemma.

Lemma 5.5. *The following statements are valid.*
(i) *Assume that $R_0 > 1$. For any $\alpha \geq 0$, one has $\alpha^* > \frac{\alpha}{1+V_1^*(\alpha)}$.*
(ii) *Assume that $R_0 = 1$. For any $\alpha > \alpha^*$, one has $\alpha^* = \frac{\alpha}{1+V_1^*(\alpha)}$.*
(iii) *Assume that $R_0 < 1$. For any $\alpha > \alpha^{**}$ ($> \alpha^*$), one has $\alpha^* < \frac{\alpha}{1+V_1^*(\alpha)}$.*

Lemma 5.6. *If $R_0 > 1$, $\alpha \geq 0$, or $R_0 = 1$, $\alpha > \alpha^*$, or $R_0 < 1$, $\alpha > \alpha^{**}$, then the following statements are valid.*
(i) *$V_1^*(\alpha) > 0$ is monotonically increasing with respect to α, and satisfies*

$$\lim_{\alpha\to+\infty} V_1^*(\alpha) = +\infty, \qquad \lim_{\alpha\to+\infty} \frac{\alpha}{V_1^*(\alpha)} = \lim_{\alpha\to+\infty} \frac{\alpha}{1+V_1^*(\alpha)} = \alpha^*. \tag{5.7}$$

(ii)

$$\lim_{\alpha\to+\infty} \Delta_4(V_1^*(\alpha)) = -\infty. \tag{5.8}$$

Proof. If the conditions of Lemma 5.6 are satisfied, then Q_1^* exists.

(i) From the first equation of Model (1.2) and (5.1), we have

$$\frac{s}{E_{N_1}^*} - d_N + r\Big(1 - \frac{E_{N_1}^*}{K}\Big) = \beta P_1^* - \frac{\alpha V_1^*}{1+V_1^*} = \alpha^* V_1^*(\alpha) - \frac{\alpha V_1^*(\alpha)}{1+V_1^*(\alpha)}.$$

Note that $E_{N_1}^*$ is independent of α, we have

$$0 = \frac{dV_1^*(\alpha)}{d\alpha}\Big(\alpha^* - \frac{\alpha}{(1+V_1^*(\alpha))^2}\Big) - \frac{V_1^*(\alpha)}{1+V_1^*(\alpha)}.$$

Then, similar to the proof of Lemma 5.1, we have

$$\frac{dV_1^*(\alpha)}{d\alpha} = \frac{(1+V_1^*(\alpha))V_1^*(\alpha)}{\alpha^*(1+V_1^*(\alpha))^2 - \alpha} > 0.$$

Thus, $V_1^*(\alpha)$ is monotonically increasing with respect to α. By the expression $V_1^*(\alpha)$, it is easy to obtain that (5.7) holds.

(ii) By (5.7), we have

$$\begin{aligned}
&\lim_{\alpha\to+\infty} p(V_1^*(\alpha)) = d_I d_v(\Psi_1 - \alpha^*),\\
&\lim_{\alpha\to+\infty} D_3(V_1^*(\alpha)) = D_3^*,\\
&\lim_{\alpha\to+\infty} D_1D_2 - D_3(V_1^*(\alpha)) = D_1D_2 - D_3^* > 0,\\
&\lim_{\alpha\to+\infty} \frac{D_4(V_1^*(\alpha))}{\alpha} = \Psi_3\delta\gamma_2 > 0,\\
&\lim_{\alpha\to+\infty} \frac{D_1D_4(V_1^*(\alpha)) - D_5(V_1^*(\alpha))}{\alpha} = D_1\Psi_3\delta\gamma_2 - d_I d_v d_c d_p,
\end{aligned} \tag{5.9}$$

where

$$D_3^* = \Psi_1(d_Id_c + d_Id_p + d_vd_c + d_vd_p + d_cd_p) + d_Id_v(d_c + d_p + \Psi_1 - \alpha^*) + d_vd_cd_p + q.$$

We rewrite $\Delta_4(V_1^*(\alpha))$ as follows:

$$\begin{aligned}
\Delta_4(V_1^*(\alpha)) = &-[D_1D_2 - D_3(V_1^*(\alpha))]^2 D_4(V_1^*(\alpha))\\
&+ D_2[D_1D_2 - D_3(V_1^*(\alpha))][D_1D_4(V_1^*(\alpha)) - D_5(V_1^*(\alpha))]\\
&- [D_1D_4(V_1^*(\alpha)) - D_5(V_1^*(\alpha))]^2.
\end{aligned}$$

By (5.9), we can obtain

$$\begin{cases}
\lim\limits_{\alpha\to+\infty} \dfrac{\Delta_4(V_1^*(\alpha))}{\alpha^2} = -(D_1\Psi_3\delta\gamma_2 - d_Id_vd_cd_p)^2 < 0, & \text{if } D_1\Psi_3\delta\gamma_2 \neq d_Id_vd_cd_p,\\
\lim\limits_{\alpha\to+\infty} \dfrac{\Delta_4(V_1^*(\alpha))}{\alpha} = -(D_1D_2 - D_3^*)^2\Psi_3\delta\gamma_2 < 0, & \text{if } D_1\Psi_3\delta\gamma_2 = d_Id_vd_cd_p.
\end{cases}$$

Thus, we have $\lim\limits_{\alpha\to+\infty} \Delta_4(V_1^*(\alpha)) = -\infty$. □

Remark 5.7. Assume that $R_0 = 1$. Note that $\lim\limits_{\alpha\to(\alpha^*)^+} V_1^*(\alpha) = 0$, then we have

$$\begin{aligned}
&\lim_{\alpha\to(\alpha^*)^+} D_5(V_1^*(\alpha)) = 0,\\
&\lim_{\alpha\to(\alpha^*)^+} [D_1D_2 - D_3(V_1^*(\alpha))] > \Psi_1(d_I + d_v + d_c + d_p)(\Psi_1 + d_I + d_v + d_c + d_p) := \Delta_{31},\\
&\lim_{\alpha\to(\alpha^*)^+} D_3(V_1^*(\alpha)) > \Psi_1(d_Id_v + d_cd_p) + d_Id_v(d_c + d_p) + d_vd_cd_p + q := \Delta_{32}.
\end{aligned}$$

Further, we have

$$\begin{aligned}
\lim_{\alpha\to(\alpha^*)^+} \Delta_3(V_1^*(\alpha)) =& \lim_{\alpha\to(\alpha^*)^+} [(D_1D_2 - D_3(V_1^*(\alpha)))D_3(V_1^*(\alpha)) - D_1^2D_4(V_1^*(\alpha))]\\
>&\Delta_{31}\Delta_{32} - D_1^2[d_vd_cd_p + d_Id_v(d_c + d_p) + q]\Psi_1\\
=&\Psi_1^2(\Psi_1 + d_I + d_v + d_c + d_p)[(d_I + d_v)d_Id_v + d_cd_p(d_c + d_p) + \Psi_3\delta\gamma_2]\\
:=&\widehat{\Delta}_3 > 0,\\
\lim_{\alpha\to(\alpha^*)^+} \Delta_4(V_1^*(\alpha)) =& \lim_{\alpha\to(\alpha^*)^+} [(D_1D_2 - D_3(V_1^*(\alpha)))D_3(V_1^*(\alpha)) - D_1^2D_4(V_1^*(\alpha))]D_4(V_1^*(\alpha))\\
>&\widehat{\Delta}_3[d_vd_cd_p + q]\Psi_1 > 0.
\end{aligned}$$

Then, it follows from Lemma 5.6 that $D_4(V_1^*(\alpha)) = 0$ has at least one positive root on $(\alpha^*, +\infty)$.

Through the above discussions and Remark 5.7, we can get the following results.

Theorem 5.8. *The following statements are valid.*
(i) *Assume that $R_0 > 1$. There exists some $\alpha_1 \geq 0$ such that, if $\alpha > \alpha_1$, then the vascular injury equilibrium Q_1^* is unstable. If $\Delta_4(V_1^*(0)) > 0$, then there exists some $h_1 > 0$ such that $\Delta_4(V_1^*(h_1)) = 0$, and Model (1.2) has a Hopf bifurcation at the vascular injury equilibrium Q_1^* when $\Delta_4(V_1^*(h_1)) = 0$ and $\Theta(\varpi(h_1)) \neq 0$.*
(ii) *Assume that $R_0 = 1$. There exists some $\alpha_2 > \alpha^*$ such that, if $\alpha > \alpha_2$, then the vascular injury equilibrium Q_1^* is unstable. There exists some $h_2 > \alpha^*$ such that $\Delta_4(V_1^*(h_2)) = 0$, and Model (1.2) has a Hopf bifurcation at the vascular injury equilibrium Q_1^* when $\Delta_4(V_1^*(h_2)) = 0$ and $\Theta(\varpi(h_2)) \neq 0$.*
(iii) *Assume that $R_0 < 1$. There exists some $\alpha_3 > \alpha^{**}$ such that, if $\alpha > \alpha_3$, then the vascular injury equilibrium Q_1^* is unstable. If $\Delta_4(V_1^*(\alpha^{**})) > 0$, then there exists some $h_3 > 0$ such that $\Delta_4(V_1^*(h_3)) = 0$, and Model (1.2) has a Hopf bifurcation at the vascular injury equilibrium Q_1^* when $\Delta_4(V_1^*(h_3)) = 0$ and $\Theta(\varpi(h_3)) \neq 0$.*

Remark 5.9. (i) Assume that $R_0 > 1$ and $\alpha = 0$. It is not difficult to see that $D_3(V_1^*(0)) > 0$ and $D_4(V_1^*(0)) > 0$. By the proof in Theorem 5.3, we can obtain that if $\Upsilon_1^* \geq 0$, then all roots of the characteristic equation (5.3) at Q_1^* have negative real parts. Thus, $\Delta_3(V_1^*(0)) > 0$, $\Delta_4(V_1^*(0)) > 0$ and $\Delta_5(V_1^*(0)) > 0$. It then follows from Lemma 5.6 that $D_4(V_1^*(\alpha)) = 0$ has at least one positive root on $(0, +\infty)$.
(ii) Similarly, if $R_0 < 1$ and $\Upsilon^*(V_1^*(\alpha^{**})) > 0$, then $D_4(V_1^*(\alpha)) = 0$ has at least one positive root on $(\alpha^{**}, +\infty)$.

By Remark 5.9 and Theorems 5.3 and 5.8, we have the following corollary.

Corollary 5.10. *The following statements are valid.*
(i) *If $R_0 > 1$ and $\Upsilon_1^* \geq 0$, then there exists some $\hat{h}_1 > 0$ such that $\Delta_4(V_1^*(\hat{h}_1)) = 0$, and Model (1.2) has a Hopf bifurcation at the vascular injury equilibrium Q_1^* when $\Delta_4(V_1^*(\hat{h}_1)) = 0$ and $\Theta(\varpi(\widehat{h_1})) \neq 0$.*
(ii) *If $R_0 < 1$ and $\Upsilon^*(V_1^*(\alpha^{**})) > 0$, then there exists some $\hat{h}_3 > 0$ such that $\Delta_4(V_1^*(\hat{h}_3)) = 0$, and Model (1.2) has a Hopf bifurcation at the vascular injury equilibrium Q_1^* when $\Delta_4(V_1^*(\hat{h}_3)) = 0$ and $\Theta(\varpi(\hat{h}_3)) \neq 0$.*

5.2 Global Stability of the Vascular Injury Equilibrium

In this subsection, we will consider the global stability of the vascular injury equilibrium Q_1^* by constructing some appropriate Lyapunov functions. We define the following set

$$\Omega_1^+ := \big\{(E_N, E_I, V, C, P) \in \Omega_1 : \ E_I > 0, \ V > 0, \ C > 0, \ P > 0\big\}.$$

First let us define some parameters

$$\begin{aligned}
&\Upsilon = d_N - r + \frac{r}{K}E_{N_1}^* - \frac{\alpha V_1^*}{1+V_1^*}, \qquad \theta^* = \frac{\big(\Upsilon + d_I + \frac{r}{K}M_1\big)^2}{2d_I\big(\frac{r}{K}M_1 + \Upsilon\big)},\\
&b_{11} = \theta^* M_1\frac{r}{K} + \Upsilon + \max\Big\{2\sqrt{\frac{r}{K}\Upsilon\theta^* M_1}, \ \frac{\Upsilon\theta^* M_1}{E_{N_1}^*} + \frac{r}{K}m_1\Big\},\\
&\widehat{b}_{11} = \theta^* M_1\frac{r}{K} + \Upsilon + \max\Big\{2\sqrt{\frac{r}{K}\Upsilon\theta^* M_1}, \ \Upsilon\theta^* + \frac{r}{K}E_{N_1}^*\Big\},\\
&b_{12} = \frac{1}{2}\Big(\Upsilon + d_I + \frac{r}{K}E_{N_1}^*\Big), \qquad \widehat{b}_{12} = \frac{1}{2}\Big(\Upsilon + d_I + \frac{r}{K}M_1\Big),\\
&b_{13} = \frac{\alpha(\theta^* M_1 + E_{N_1}^*)}{2(1+V_1^*)}, \qquad \widehat{b}_{13} = \frac{\alpha M_1(\theta^*+1)}{2(1+V_1^*)^2},\\
&b_{22} = d_I, \qquad b_{23} = \frac{1}{2}\Big(\frac{\alpha E_{N_1}^*}{1+V_1^*} + \frac{d_I d_v}{\gamma_1}\Big), \qquad \widehat{b}_{23} = \frac{1}{2}\Big(\frac{\alpha M_1}{(1+V_1^*)^2} + \frac{d_I d_v}{\gamma_1}\Big),\\
&\widetilde{b}_{23} = \frac{1}{2}\Big(\frac{\alpha E_{N_1}^*}{(1+V_1^*)^2} + \frac{d_I d_v}{\gamma_1}\Big), \qquad \bar{b}_{23} = \frac{1}{2}\Big(\frac{\alpha M_1}{1+V_1^*} + \frac{d_I d_v}{\gamma_1}\Big), \qquad b_{33} = \frac{d_I d_v^2}{\gamma_1^2}.
\end{aligned}$$

We define some real symmetric matrices as follows

$$\begin{aligned}
P_1 &= \begin{pmatrix} b_{11} & 0 & -b_{13}\\ 0 & b_{22} & -b_{23}\\ -b_{13} & -b_{23} & b_{33}\end{pmatrix}, \qquad P_2 = \begin{pmatrix} \widehat{b}_{11} & 0 & -\widehat{b}_{13}\\ 0 & b_{22} & -\widehat{b}_{23}\\ -\widehat{b}_{13} & -\widehat{b}_{23} & b_{33}\end{pmatrix},\\
P_3 &= \begin{pmatrix} b_{11} & -b_{12} & -b_{13}\\ -b_{12} & b_{22} & 0\\ -b_{13} & 0 & b_{33}\end{pmatrix}, \qquad P_4 = \begin{pmatrix} b_{11} & -b_{12} & 0\\ -b_{12} & b_{22} & -\widetilde{b}_{23}\\ 0 & -\widetilde{b}_{23} & b_{33}\end{pmatrix},\\
P_5 &= \begin{pmatrix} \widehat{b}_{11} & -\widehat{b}_{12} & 0\\ -\widehat{b}_{12} & b_{22} & -\bar{b}_{23}\\ 0 & -\bar{b}_{23} & b_{33}\end{pmatrix}, \qquad P_6 = \begin{pmatrix} \widehat{b}_{11} & -\widehat{b}_{12} & -\widehat{b}_{13}\\ -\widehat{b}_{12} & b_{22} & 0\\ -\widehat{b}_{13} & 0 & b_{33}\end{pmatrix}.
\end{aligned}$$

Theorem 5.11. *If $R_0 > 1$, $\Upsilon > 0$ and the matrices P_i $(i = 1, 2, \cdots, 6)$ are semi-positive definite, then the vascular injury equilibrium Q_1^* is globally asymptotically stable in Ω_1^+.*

Proof. It is not difficult to prove that Ω_1^+ is positively invariant and attractive with respect to Model (1.2). Let $g(x) = x - 1 - \ln x$ $(x > 0)$. We define the following Lyapunov function on Ω_1^+,

$$U(t) = \theta^* M_1 U_1(t) + U_2(t) + U_3(t),$$

where

$$U_1(t) = E_{N_1}^* g\Big(\frac{E_N(t)}{E_{N_1}^*}\Big) + E_{I_1}^* g\Big(\frac{E_I(t)}{E_{I_1}^*}\Big) + \frac{d_I\eta V_1^*}{\gamma_1\eta + \gamma_2 d_v} g\Big(\frac{V(t)}{V_1^*}\Big)$$

$$+\frac{d_I d_v C_1^*}{\gamma_1\eta+\gamma_2 d_v} g\Big(\frac{C(t)}{C_1^*}\Big)+\frac{d_I d_v d_c P_1^*}{\delta(\gamma_1\eta+\gamma_2 d_v)} g\Big(\frac{P(t)}{P_1^*}\Big),$$

$$U_2(t)=\frac{1}{2}[(E_N(t)-E_{N_1}^*)+(E_I(t)-E_{I_1}^*)]^2,$$

$$U_3(t)=\frac{d_I d_v}{2\gamma_1^2}(V(t)-V_1^*)^2.$$

It is clear that $U(t)$ is continuous on Ω_1^+ and positive definite with respect to Q_1^* and satisfies condition (ii) of Theorem 1.2 in [34] on $\partial\Omega_1^+=\overline{\Omega_1^+}\setminus\Omega_1^+$.

We rewrite the first equation of Model (1.2) as follows

$$\begin{aligned}
\dot{E}_N(t)=&-(d_N-r)(E_N(t)-E_{N_1}^*)+\frac{r}{K}[(E_{N_1}^*)^2-(E_N(t))^2]\\
&+\frac{\alpha E_N(t)V(t)}{1+V(t)}-\frac{\alpha E_{N_1}^* V_1^*}{1+V_1^*}+\beta E_{N_1}^* P_1^*-\beta E_N(t)P(t)\\
=&-\Big[d_N-r+\frac{r}{K}(E_{N_1}^*+E_N(t))-\frac{\alpha V_1^*}{1+V_1^*}\Big](E_N(t)-E_{N_1}^*)\\
&+\frac{\alpha E_N(t)(V(t)-V_1^*)}{(1+V(t))(1+V_1^*)}+\beta E_{N_1}^* P_1^*-\beta E_N(t)P(t)\\
=&-\Big[\Upsilon+\frac{r}{K}E_N(t)\Big](E_N(t)-E_{N_1}^*)+\frac{\alpha E_N(t)(V(t)-V_1^*)}{(1+V(t))(1+V_1^*)}\\
&+\beta E_{N_1}^* P_1^*-\beta E_N(t)P(t).
\end{aligned}\tag{5.10}$$

From (2.5) and (2.6), we have

$$\begin{aligned}
&\beta E_{N_1}^* P_1^*=d_I E_{I_1}^*,\qquad \beta E_{N_1}^*=\frac{d_I d_v d_c d_p}{\delta(\gamma_1\eta+\gamma_2 d_v)},\\
&V_1^*=\frac{\gamma_1}{d_v}E_{I_1}^*,\qquad C_1^*=\Big(\frac{\gamma_1\eta+\gamma_2 d_v}{\gamma_1 d_c}\Big)\frac{\gamma_1}{d_v}E_{I_1}^*.
\end{aligned}\tag{5.11}$$

From (5.10) and (5.11), we have, for $t\geq 0$,

$$\begin{aligned}
\dot{U}_1(t)=&\Big(1-\frac{E_{N_1}^*}{E_N(t)}\Big)\dot{E}_N(t)+\Big(1-\frac{E_{I_1}^*}{E_I(t)}\Big)\dot{E}_I(t)+\frac{d_I\eta}{\gamma_1\eta+\gamma_2 d_v}\Big(1-\frac{V_1^*}{V(t)}\Big)\dot{V}(t)\\
&+\frac{d_I d_v}{\gamma_1\eta+\gamma_2 d_v}\Big(1-\frac{C_1^*}{C(t)}\Big)\dot{C}(t)+\frac{d_I d_v d_c}{\delta(\gamma_1\eta+\gamma_2 d_v)}\Big(1-\frac{P_1^*}{P(t)}\Big)\dot{P}(t)\\
=&-\Big[\frac{\Upsilon}{E_N(t)}+\frac{r}{K}\Big](E_N(t)-E_{N_1}^*)^2+\frac{\alpha(E_N(t)-E_{N_1}^*)(V(t)-V_1^*)}{(1+V(t))(1+V_1^*)}\\
&+\beta E_{N_1}^* P_1^*+\beta E_{N_1}^* P(t)-\beta E_{N_1}^* P_1^*\frac{E_{N_1}^*}{E_N(t)}+d_I E_{I_1}^*-\beta E_N(t)P(t)\frac{E_{I_1}^*}{E_I(t)}\\
&+\frac{\eta d_I d_v}{\gamma_1\eta+\gamma_2 d_v}V_1^*-\frac{d_I\eta\gamma_1 E_{I_1}^*}{\gamma_1\eta+\gamma_2 d_v}\frac{E_I(t)V_1^*}{E_{I_1}^* V(t)}+\frac{d_I d_v d_c}{\gamma_1\eta+\gamma_2 d_v}C_1^*\\
&-\frac{d_I d_v\gamma_2 E_{I_1}^*}{\gamma_1\eta+\gamma_2 d_v}\frac{E_I(t)C_1^*}{E_{I_1}^* C(t)}-\frac{d_I d_v\eta V_1^*}{\gamma_1\eta+\gamma_2 d_v}\frac{V(t)C_1^*}{V_1^* C(t)}+\frac{d_I d_v d_c d_p}{\delta(\gamma_1\eta+\gamma_2 d_v)}P_1^*\\
&-\frac{d_I d_v d_c d_p}{\delta(\gamma_1\eta+\gamma_2 d_v)}P(t)-\frac{d_I d_v d_c C_1^*}{\gamma_1\eta+\gamma_2 d_v}\frac{C(t)P_1^*}{C_1^* P(t)}\\
=&-\Big(\frac{\Upsilon}{E_N(t)}+\frac{r}{K}\Big)(E_N(t)-E_{N_1}^*)^2
\end{aligned}$$

$$+\frac{\alpha(E_N(t)-E_{N_1}^*)(V(t)-V_1^*)}{(1+V(t))(1+V_1^*)}+\Phi_1(t)+\Phi_2(t), \tag{5.12}$$

where

$$\Phi_1(t)=\frac{\gamma_1\eta}{\gamma_1\eta+\gamma_2 d_v}d_I E_{I_1}^*\Big(5-\frac{E_{N_1}^*}{E_N(t)}-\frac{E_{I_1}^*E_N(t)P(t)}{E_I(t)E_{N_1}^*P_1^*}-\frac{E_I(t)V_1^*}{E_{I_1}^*V(t)}-\frac{V(t)C_1^*}{V_1^*C(t)}-\frac{C(t)P_1^*}{C_1^*P(t)}\Big),$$

$$\Phi_2(t)=\frac{\gamma_2 d_v}{\gamma_1\eta+\gamma_2 d_v}d_I E_{I_1}^*\Big(4-\frac{E_{N_1}^*}{E_N(t)}-\frac{E_{I_1}^*E_N(t)P(t)}{E_I(t)E_{N_1}^*P_1^*}-\frac{E_I(t)C_1^*}{E_{I_1}^*C(t)}-\frac{C(t)P_1^*}{C_1^*P(t)}\Big),$$

$$\begin{aligned}\dot U_2(t)=&[(E_N(t)-E_{N_1}^*)+(E_I(t)-E_{I_1}^*)](\dot E_N(t)+\dot E_I(t))\\ =&[(E_N(t)-E_{N_1}^*)+(E_I(t)-E_{I_1}^*)]\\ &\times\Big\{-\big[\Upsilon+\frac{r}{K}E_N(t)\big](E_N(t)-E_{N_1}^*)+\frac{\alpha E_N(t)(V(t)-V_1^*)}{(1+V(t))(1+V_1^*)}-d_I(E_I(t)-E_{I_1}^*)\Big\}\\ =&-\big(\Upsilon+\frac{r}{K}E_N(t)\big)(E_N(t)-E_{N_1}^*)^2-d_I(E_I(t)-E_{I_1}^*)^2\\ &-\big(\Upsilon+d_I+\frac{r}{K}E_N(t)\big)(E_N(t)-E_{N_1}^*)(E_I(t)-E_{I_1}^*)\\ &+\frac{\alpha E_N(t)}{(1+V(t))(1+V_1^*)}[(E_N(t)-E_{N_1}^*)(V(t)-V_1^*)+(E_I(t)-E_{I_1}^*)(V(t)-V_1^*)],\end{aligned} \tag{5.13}$$

$$\begin{aligned}\dot U_3(t)=&\frac{d_I d_v}{\gamma_1^2}(V(t)-V_1^*)[\gamma_1(E_I(t)-E_{I_1}^*)-d_v(V(t)-V_1^*)]\\ =&-\frac{d_I d_v^2}{\gamma_1^2}(V(t)-V_1^*)^2+\frac{d_I d_v}{\gamma_1}(E_I(t)-E_{I_1}^*)(V(t)-V_1^*).\end{aligned} \tag{5.14}$$

From (5.12)–(5.14), we have, for $t\ge 0$,

$$\begin{aligned}\dot U(t)=&-b_{11}(t)(E_N(t)-E_{N_1}^*)^2-b_{22}(E_I(t)-E_{I_1}^*)^2-b_{33}(V(t)-V_1^*)^2\\ &-2b_{12}(t)(E_N(t)-E_{N_1}^*)(E_I(t)-E_{I_1}^*)+2b_{13}(t)(E_N(t)-E_{N_1}^*)(V(t)-V_1^*)\\ &+2b_{23}(t)(E_I(t)-E_{I_1}^*)(V(t)-V_1^*)+\theta^*M_1(\Phi_1(t)+\Phi_2(t)),\end{aligned} \tag{5.15}$$

where

$$b_{11}(t)=\frac{r\theta^*M_1}{K}+\Upsilon+\frac{\theta^*M_1\Upsilon}{E_N(t)}+\frac{r}{K}E_N(t),\qquad b_{12}(t)=\frac{1}{2}\big(\Upsilon+d_I+\frac{r}{K}E_N(t)\big),$$

$$b_{13}(t)=\frac{\alpha[\theta^*M_1+E_N(t)]}{2(1+V(t))(1+V_1^*)},\qquad b_{23}(t)=\frac{1}{2}\Big[\frac{\alpha E_N(t)}{(1+V(t))(1+V_1^*)}+\frac{d_I d_v}{\gamma_1}\Big].$$

For convenience, we define $J=(|E_N(t)-E_{N_1}^*|,|E_I(t)-E_{I_1}^*|,|V(t)-V_1^*|)$. By considering the signs of crossing terms in (5.15), the following 8 cases need to be discussed.

Case (I). When $E_N(t)\le E_{N_1}^*$, $E_I(t)\le E_{I_1}^*$, $V(t)\le V_1^*$, then $b_{11}(t)\ge b_{11}$, $b_{13}(t)\le b_{13}$, $b_{23}(t)\le b_{23}$; thus we have

$$\begin{aligned}\dot U(t)\le&-JP_1J^T-2b_{12}(t)(E_N(t)-E_{N_1}^*)(E_I(t)-E_{I_1}^*)+\theta^*M_1(\Phi_1(t)+\Phi_2(t))\\ \le&-JP_1J^T+\theta^*M_1(\Phi_1(t)+\Phi_2(t)).\end{aligned}$$

Case (II). When $E_N(t)\le E_{N_1}^*$, $E_I(t)\le E_{I_1}^*$, $V(t)\ge V_1^*$, then $b_{11}(t)\ge b_{11}$; thus we have

$$\dot U(t)\le-b_{11}(E_N(t)-E_{N_1}^*)^2-b_{22}(E_I(t)-E_{I_1}^*)^2-b_{33}(V(t)-V_1^*)^2+\theta^*M_1(\Phi_1(t)+\Phi_2(t)).$$

Case (III). When $E_N(t)\ge E_{N_1}^*$, $E_I(t)\ge E_{I_1}^*$, $V(t)\le V_1^*$, then $b_{11}(t)\ge\widehat{b}_{11}$; thus we have

$$\dot U(t)\le-\widehat{b}_{11}(E_N(t)-E_{N_1}^*)^2-b_{22}(E_I(t)-E_{I_1}^*)^2-b_{33}(V(t)-V_1^*)^2+\theta^*M_1(\Phi_1(t)+\Phi_2(t)).$$

Case (IV). When $E_N(t) \geq E^*_{N_1}$, $E_I(t) \geq E^*_{I_1}$, $V(t) \geq V^*_1$, then $b_{11}(t) \geq \widehat{b}_{11}$, $b_{13}(t) \leq \widehat{b}_{13}$, $b_{23}(t) \leq \widehat{b}_{23}$; thus we have

$$\begin{aligned}\dot{U}(t) \leq & - JP_2J^T - b_{12}(t)(E_N(t) - E^*_{N_1})(E_I(t) - E^*_{I_1}) + \theta^* M_1(\Phi_1(t) + \Phi_2(t)) \\ \leq & - JP_2J^T + \theta^* M_1(\Phi_1(t) + \Phi_2(t)).\end{aligned}$$

Case (V). When $E_N(t) \leq E^*_{N_1}$, $E_I(t) \geq E^*_{I_1}$, $V(t) \leq V^*_1$, then $b_{11}(t) \geq b_{11}$, $b_{12}(t) \leq b_{12}$, $b_{13}(t) \leq b_{13}$; thus we have

$$\begin{aligned}\dot{U}(t) \leq & - JP_3J^T + 2b_{23}(t)(E_I(t) - E^*_{I_1})(V(t) - V^*_1) + \theta^* M_1(\Phi_1(t) + \Phi_2(t)) \\ \leq & - JP_3J^T + \theta^* M_1(\Phi_1(t) + \Phi_2(t)).\end{aligned}$$

Case (VI). When $E_N(t) \leq E^*_{N_1}$, $E_I(t) \geq E^*_{I_1}$, $V(t) \geq V^*_1$, then $b_{11}(t) \geq b_{11}$, $b_{12}(t) \leq b_{12}$, $b_{23}(t) \geq \widetilde{b}_{23}$; thus we have

$$\begin{aligned}\dot{U}(t) \leq & - JP_4J^T + 2b_{13}(t)(E_N(t) - E^*_{N_1})(V(t) - V^*_1) + \theta^* M_1(\Phi_1(t) + \Phi_2(t)) \\ \leq & - JP_4J^T + \theta^* M_1(\Phi_1(t) + \Phi_2(t)).\end{aligned}$$

Case (VII). When $E_N(t) \geq E^*_{N_1}$, $E_I(t) \leq E^*_{I_1}$, $V(t) \leq V^*_1$, then $b_{11}(t) \geq \widehat{b}_{11}$, $b_{12}(t) \leq \widehat{b}_{12}$, $b_{23}(t) \leq \bar{b}_{23}$; thus we have

$$\begin{aligned}\dot{U}(t) \leq & - JP_5J^T + 2b_{13}(t)(E_N(t) - E^*_{N_1})(V(t) - V^*_1) + \theta^* M_1(\Phi_1(t) + \Phi_2(t)) \\ \leq & - JP_5J^T + \theta^* M_1(\Phi_1(t) + \Phi_2(t)).\end{aligned}$$

Case (VIII). When $E_N(t) \geq E^*_{N_1}$, $E_I(t) \leq E^*_{I_1}$, $V(t) \geq V^*_1$, then $b_{11}(t) \geq \widehat{b}_{11}$, $b_{12}(t) \leq \widehat{b}_{12}$, $b_{13}(t) \leq \widehat{b}_{13}$; thus we have

$$\begin{aligned}\dot{U}(t) \leq & - JP_6J^T + 2b_{23}(t)(E_I(t) - E^*_{I_1})(V(t) - V^*_1) + \theta^* M_1(\Phi_1(t) + \Phi_2(t)) \\ \leq & - JP_6J^T + \theta^* M_1(\Phi_1(t) + \Phi_2(t)).\end{aligned}$$

Since the arithmetic mean is greater than or equal to the geometric mean, we have $\Phi_1(t) \leq 0$ and $\Phi_2(t) \leq 0$. In summary, if the matrixs P_i $(i = 1, 2, \cdots, 6)$ are semi-positive definite, then we have, for $t \geq 0$,

$$\dot{U}(t) \leq \theta^* M_1(\Phi_1(t) + \Phi_2(t)) \leq 0.$$

This shows that $U(t)$ is a Lyapunov function on Ω_1^+. Thus, Q^*_1 is stable (see [17]). Note that $\dot{U}(t) = 0$ implies that

$$E_N(t) = E^*_{N_1}, \quad \frac{E^*_{I_1}P(t)}{E_I(t)P^*_1} = 1, \quad \frac{E_I(t)V^*_1}{E^*_{I_1}V(t)} = 1, \quad \frac{V(t)C^*_1}{V^*_1C(t)} = 1, \quad \frac{C(t)P^*_1}{C^*_1P(t)} = 1. \tag{5.16}$$

Let M^* be the largest invariant set in $\Gamma_2 := \{(E_N, E_I, V, C, P) \in \overline{\Omega_1^+} \ : U < \infty, \ \dot{U} = 0\}$. From Model (1.2) and the invariance of M^*, we can obtain $M^* = \{Q^*_1\}$. Then, it follows from Theorem 1.2 in [34] that Q^*_1 is globally attractive. Thus, Q^*_1 is globally asymptotically stable. □

We define the following matrix:

$$P_7(\alpha) = \begin{pmatrix} \widetilde{b}_{11} & -\widehat{b}_{12} & -\widetilde{b}_{13} \\ -\widehat{b}_{12} & b_{22} & -\bar{b}_{23} \\ -\widetilde{b}_{13} & -\bar{b}_{23} & b_{33} \end{pmatrix},$$

where

$$\widetilde{b}_{11} = \theta^* M_1 \frac{r}{K} + \Upsilon + \max\Big\{2\sqrt{\frac{r}{K}\Upsilon\theta^* M_1}, \Upsilon\theta^* + \frac{r}{K}m_1\Big\}, \qquad \widetilde{b}_{13} = \frac{\alpha M_1(\theta^*+1)}{2(1+V_1^*)}.$$

Remark 5.12. Assume that $R_0 > 1$ and $\Upsilon_1 := d_N - r + \frac{r}{K}E^*_{N_1} > 0$. Note that R_0 and Υ_1 are independent of α. By Lemma 5.6, we have that Υ is monotonically decreasing with respect to α on $[0, +\infty)$. Thus, there exits some $\alpha_0^* > 0$ such that $\Upsilon > 0$ if $0 \le \alpha < \alpha_0^*$, $\Upsilon \le 0$ if $\alpha \ge \alpha_0^*$.
(i) Assume that $0 \le \alpha < \alpha_0^*$. It is easy to see that if the matrix $P_7(\alpha)$ is semi-positive definite, then the matrices P_i $(i = 1, 2, \cdots, 6)$ are all semi-positive definite.
(ii) Assume that $0 \le \alpha < \alpha_0^*$. Note that the sufficient necessary condition for $P_7(\alpha)$ to be semi-positive definite is

$$\Pi_1(\alpha) := \widetilde{b}_{11}(b_{22}b_{33} - \bar{b}_{23}^2) - b_{22}\widetilde{b}_{13}^2 - b_{33}\widehat{b}_{12}^2 - 2\widehat{b}_{12}\widetilde{b}_{13}\bar{b}_{23} \ge 0.$$

If $\alpha = 0$, then we have

$$\begin{aligned}
\Pi_1(0) =& \widetilde{b}_{11}\Big(\frac{d_I^2 d_v^2}{\gamma_1^2} - \frac{d_I^2 d_v^2}{4\gamma_1^2}\Big) - \frac{d_I d_v^2}{4\gamma_1^2}\big(\Upsilon_1 + d_I + \frac{r}{K}M_1\big)^2 \\
>& \frac{d_I d_v^2}{4\gamma_1^2}\Big\{3\theta^*\big(M_1\frac{r}{K} + \Upsilon_1\big)d_I - \big(\Upsilon_1 + d_I + \frac{r}{K}M_1\big)^2\Big\} \\
=& \frac{3d_I^2 d_v^2}{4\gamma_1^2}\big(M_1\frac{r}{K} + \Upsilon_1\big)\Big\{\theta^* - \frac{\big(\Upsilon_1 + d_I + \frac{r}{K}M_1\big)^2}{3d_I\big(M_1\frac{r}{K} + \Upsilon_1\big)}\Big\} \\
=& \frac{d_I^2 d_v^2}{4\gamma_1^2}\big(M_1\frac{r}{K} + \Upsilon_1\big)\theta^* > 0.
\end{aligned}$$

This shows that the matrix $P_7(0)$ is positive definite. Clearly, $\Pi_1(\alpha)$ is continuous with respect to $\alpha \in [0, \alpha_0^*)$. Thus, there exits some $\alpha_1^* \in (0, \alpha_0^*)$ such that $\Pi_1(\alpha) \ge 0$ if $0 \le \alpha \le \alpha_1^*$. Then, there exists $\alpha_2^* \in [\alpha_1^*, \alpha_0^*)$ such that, the matrices P_i $(i = 1, 2, \cdots, 6)$ are semi-positive definite if $0 \le \alpha \le \alpha_2^*$.

By Theorem 5.11 and Remark 5.12, we have the following corollary.

Corollary 5.13. *Assume $R_0 > 1$ and $\Upsilon_1 > 0$. If $0 \le \alpha \le \alpha_2^*$, then the vascular injury equilibrium Q_1^* is globally asymptotically stable in Ω_1^+.*

6 Numerical Simulations

In this section, we give some numerical simulations to illustrate our theoretical results. We fix $s = 1$, $d_N = 1$, $r = 1$, $K = 2$, $\beta = 0.25$, $\gamma_1 = 1$, $d_v = 2$, $\gamma_2 = 1$, $\eta = 1$, $d_c = 1$, $\delta = 1$, $d_p = 1$ and change the values of α and d_I. Clearly, $\alpha^* = 0.75$.

Note that ω, ω^*, a_{22}, a_{33} and $\Pi(\alpha)$ can be viewed as 2-element functions with respect to R_0 and α. Then, with the help of Maple mathematical software, the curves of the implicit functions of $R_0 = \omega$, $R_0 = \omega^*$, $a_{22}a_{33} = \Pi(\alpha)$ are drawn (see Figure 6.1). The lower left part of the red solid line indicates the region where condition (H) holds; the lower left part of the solid blue line indicates the region where $R_0 < \omega^*$. By Theorem 3.2, the vascular injury-free equilibrium Q_0 is globally asymptotically stable if (α, R_0) falls on regions I, III and V; by Theorem 3.5, the vascular injury-free equilibrium Q_0 is globally asymptotically stable if (α, R_0) falls on regions I, II, V and VI.

If we further choose $\alpha = 2 > \alpha^*$ (the case of backward bifurcation) and $d_I = 0.65$, then by calculation, we have $R_0 \approx 0.815892 > \omega \approx 0.809835$. It has from Theorem 2.3

that, Model (1.2) has a vascular injury-free equilibrium $Q_0 \approx (1.414214, 0, 0, 0, 0)$ and two vascular injury equilibria $Q_1^* \approx (1.733333, 1.586897, 0.793449, 2.380346, 2.380348)$ and $Q_2^* \approx (1.733333, 0.973787, 0.486893, 1.46068, 1.46068)$. Note that $\omega < R_0 < 1$, it has from Theorems 3.1 and 5.2 that the vascular injury-free equilibrium Q_0 is locally asymptotically stable and the vascular injury equilibrium Q_2^* is unstable. In addition, the calculation gives $\Upsilon^*(V_1^*(\alpha)) \approx 0.848503 > \min\{d_I, d_c, d_p\} = 0.65$. Then, it has from Theorem 5.3 that the vascular injury equilibrium Q_1^* is locally asymptotically stable. Thus, Model (1.2) has bistable equilibria under this set of parameters (see Figure 6.2).

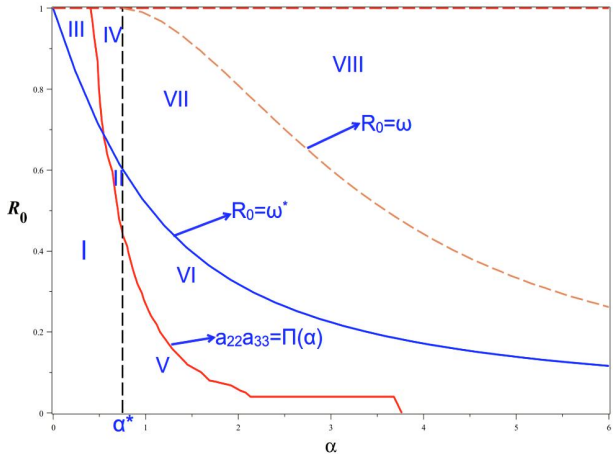


Figure 6.1. The global asymptotic stability regions of Q_0 in the α-R_0 plane. The lower left part of the red solid line indicates the region where condition (H) holds; the lower left part of the blue solid line indicates the region where $R_0 < \omega^*$. The curves $R_0 = 1$, $R_0 = \omega$ ($\alpha > \alpha^*$), $R_0 = \omega^*$, $a_{22}a_{33} = \Pi(\alpha)$ and $\alpha = \alpha^*$ dividing the first quadrant region into 8 parts. By Theorems 3.2 and 3.5, if (α, R_0) falls in the regions I, II, III, V, VI, then Q_0 is globally asymptotically stable.

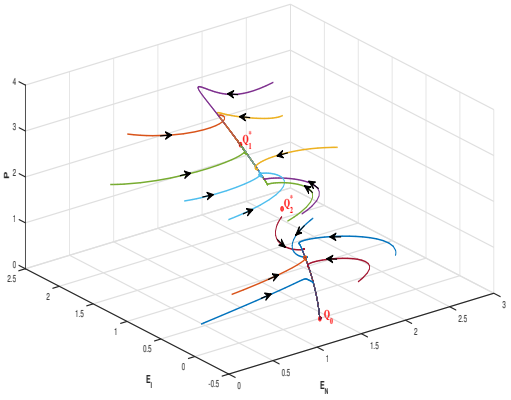


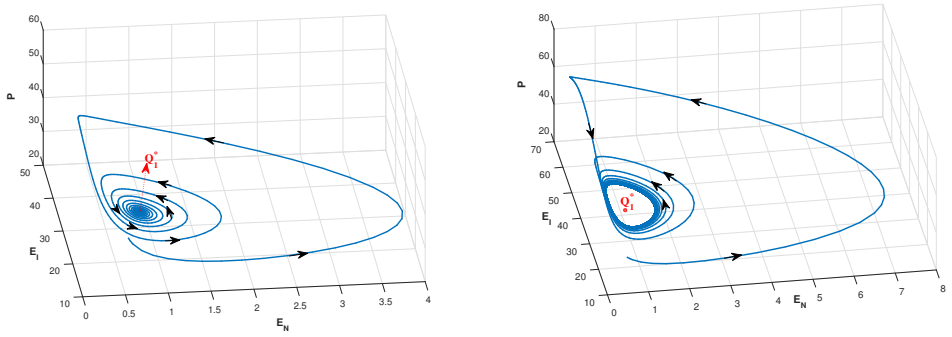
Figure 6.2. The phase trajectories of Model (1.2) with the different initial values. Here $\alpha > \alpha^*$ (the case of backward bifurcation), $\omega < R_0 < 1$, Model (1.2) has three equilibria; Q_0 and Q_1^* are locally asymptotically stable, Q_2^* is unstable.

In the following, we verify the existence of the Hopf bifurcation using α as the bifurcation parameter.

If we further choose $d_I = 0.3$, then $R_0 \approx 1.767767 > 1$. By Lemma 5.5, we have that, for any $\alpha \geq 0$,

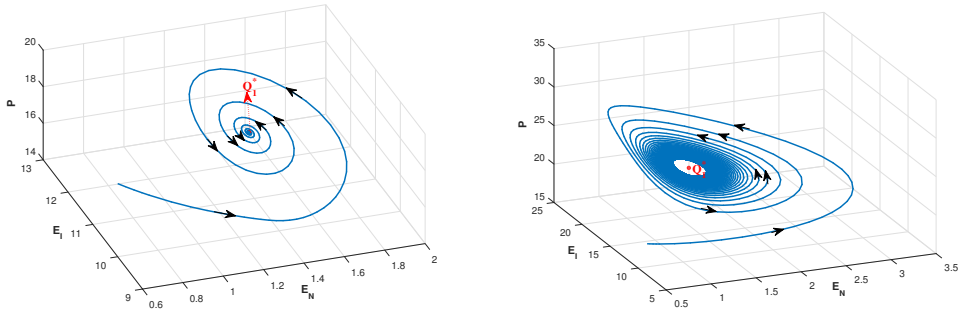
$$p(V_1^*(\alpha)) = d_I d_v \Big(\Psi_1 - \frac{\alpha V_1^*(\alpha)}{(1+V_1^*(\alpha))^2}\Big) > d_I d_v(\Psi_1 - \alpha^*) = 0.54 > 0.$$

Thus, $D_j(V_1^*(\alpha)) > 0$ $(j = 3, 4)$ for any $\alpha \geq 0$. By means of numerical calculations, we find that there exists $\varsigma_1 \approx 9.078353$ such that $\Delta_4(V_1^*(\varsigma_1)) = 0$, $\Delta_3(V_1^*(\alpha)) > 0$ and $\Delta_4(V_1^*(\alpha)) > 0$ for $0 \leq \alpha < \varsigma_1$, $\Delta_4(V_1^*(\alpha)) < 0$ for $\alpha > \varsigma_1$. Thus, when $0 \leq \alpha < \varsigma_1$, the vascular injury equilibrium Q_1^* is locally asymptotically stable (see Figure 6.3 (a)); when $\alpha = \varsigma_1$, Model (1.2) has a Hopf bifurcation ($\Theta(\varpi(\varsigma_1)) = \text{sign}\{6.101209\} = 1 \neq 0$); when $\alpha > \varsigma_1$, the vascular injury equilibrium Q_1^* is unstable (see Figure 6.3 (b)).



(a) $\alpha = 8 < \varsigma_1 \approx 9.078353$ (b) $\alpha = 10 > \varsigma_1 \approx 9.078353$

Figure 6.3. The phase trajectory of Model (1.2) with the initial value $(0.6, 16, 9, 8, 31)$. (a) Here $R_0 \approx 1.767767 > 1$, $\alpha = 8 < \varsigma_1$, $Q_1^* \approx (0.8, 21.8079, 10.9039, 32.7118, 32.711814)$ is locally asymptotically stable. (b) Here $R_0 \approx 1.767767 > 1$, $\alpha = 10 > \varsigma_1$, $Q_1^* \approx (0.8, 27.1006, 13.5503, 40.6509, 40.6509)$ is unstable.



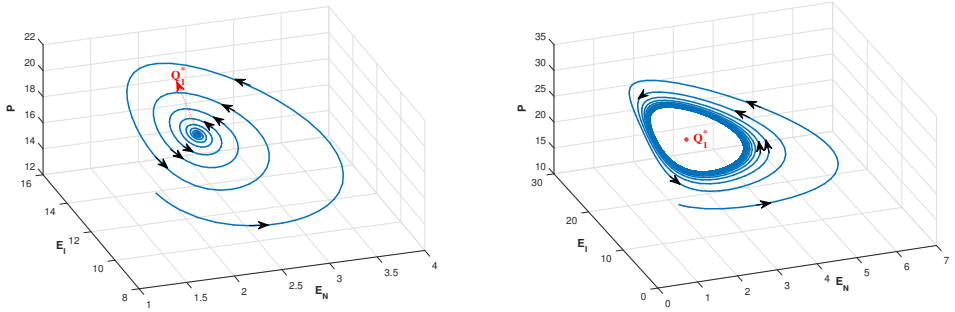
(a) $\alpha = 5 < \varsigma_2 \approx 6.578443$ (b) $\alpha = 6.6 > \varsigma_2 \approx 6.578443$

Figure 6.4. The phase trajectory of Model (1.2) with the initial value $(0.6, 10, 9, 16, 18)$. (a) Here $R_0 = 1$, $\alpha = 5 < \varsigma_2$, $Q_1^* \approx (1.41421, 11.3333, 5.66667, 17, 17)$ is locally asymptotically stable. (b) Here $R_0 = 1$, $\alpha = 6.6 > \varsigma_2$, $Q_1^* \approx (1.41421, 15.6, 7.8, 23.4, 23.4)$ is unstable.

If we further choose $d_I = 3\sqrt{2}/8$, then $R_0 = 1$. By Lemma 5.5, we have that, for any $\alpha > \alpha^* = 0.75$, $p(V_1^*(\alpha)) > d_I d_v(\Psi_1 - \alpha^*) \approx 0.704505 > 0$. Thus, $D_j(V_1^*(\alpha)) > 0$ $(j = 3, 4)$ for

any $\alpha > 0.75$. By means of numerical calculations, we find that there exists $\varsigma_2 \approx 6.578444$ such that $\Delta_4(V_1^*(\varsigma_2)) = 0$, $\Delta_3(V_1^*(\alpha)) > 0$ and $\Delta_4(V_1^*(\alpha)) > 0$ for $0.75 < \alpha < \varsigma_2$, $\Delta_4(V_1^*(\alpha)) < 0$ for $\alpha > \varsigma_2$. Thus, when $0.75 < \alpha < \varsigma_2$, the vascular injury equilibrium Q_1^* is locally asymptotically stable (see Figure 6.4 (a)); when $\alpha = \varsigma_2$, Model (1.2) has a Hopf bifurcation ($\Theta(\varpi(\varsigma_2)) = \text{sign}\{11.087761\} = 1 \neq 0$); when $\alpha > \varsigma_2$, the vascular injury equilibrium Q_1^* is unstable (see Figure 6.4 (b)).

If we further choose $d_I = 0.8$, then $R_0 \approx 0.662913 < 1$ and $\alpha^{**} \approx 2.687226$. By means of numerical calculations, we find that, for any $\alpha > \alpha^{**}$, $D_j(V_1^*(\alpha)) > 0$ ($j = 3, 4$); there exists $\varsigma_3 \approx 7.104526$ such that $\Delta_4(V_1^*(\alpha)) = 0$, $\Delta_3(V_1^*(\alpha)) > 0$ and $\Delta_4(V_1^*(\alpha)) > 0$ for $\alpha^{**} < \alpha < \varsigma_3$, $\Delta_4(V_1^*(\alpha)) < 0$ for $\alpha > \varsigma_3$. Thus, when $\alpha^{**} < \alpha < \varsigma_3$, then the vascular injury equilibrium Q_1^* is locally asymptotically stable (see Figure 6.5 (a)); when $\alpha = \varsigma_3$, Model (1.2) has a Hopf bifurcation ($\Theta(\varpi(\varsigma_3)) = \text{sign}\{22.299169\} = 1 \neq 0$); when $\alpha > \varsigma_3$, the vascular injury equilibrium Q_1^* is unstable (see Figure 6.5 (b)).



(a) $\alpha = 6 < \varsigma_2 \approx 7.104526$ (b) $\alpha = 7.5 > \varsigma_2 \approx 7.104526$

Figure 6.5. The phase trajectory of Model (1.2) with the initial value $(1.3, 9, 9, 8, 18)$. (a) Here $R_0 \approx 0.66291 < 1$, $\alpha = 6 < \varsigma_3$, $Q_1^* \approx (2.13333, 12.1429, 6.07147, 18.2144, 18.214415)$ is locally asymptotically stable. (b) Here $R_0 \approx 0.662913 < 1$, $\alpha = 7.5 > \varsigma_3$, $Q_1^* \approx (2.13333, 16.2088, 8.10441, 24.3132, 24.3132)$ is unstable.

7 Conclusions

In this paper, we propose and study a class of 5-dimensional ordinary differential equation model describing the vascular endothelial cell injury in the lesion area of KD. We establish a very important parameter α^*; when $\alpha \leq \alpha^*$, Model (1.2) has a forward bifurcation, when $\alpha > \alpha^*$, Model (1.2) has a backward bifurcation. The presence of backward bifurcation means that controlling the basic reproduction number $R_0 < 1$ is no longer sufficient to heal injury in the lesion area of KD.

By analysing the corresponding characteristic equation, our results show that if the basic reproduction number $R_0 < 1$, then the vascular injury-free equilibrium Q_0 is locally asymptotically stable. Further, by constructing suitable Lyapunov functions and combining the Lyapunov-LaSalle invariance principle, we obtain two types of sufficient conditions for the global asymptotic stability of the vascular injury-free equilibrium Q_0. This provides two theoretical control strategies for controlling vascular injury in the lesion area of KD.

By analyzing in detail the properties of any positive solution of Model (1.2), we obtain the permanence of Model (1.2). Our results show that Model (1.2) is permanent if the basic reproduction number $R_0 > 1$, and some explicit expressions of ultimate lower bounds for

the components of any positive solution of Model (1.2) are given. The permanence result shows that the vascular injury and inflammation in the KD lesion area will persist, and KD is uncontrollable.

Subsequently, we also study the local and global asymptotic stability of the vascular injury equilibria and the existence of Hopf bifurcation induced by the parameter α. We obtain some sufficient conditions for the local asymptotic stability of the vascular injury equilibrium Q_1^* and find that α can lead to the Hopf bifurcation within a certain range of parameters. In addition, our results show that the vascular injury equilibrium Q_2^* is always unstable if it exists, and the vascular injury equilibrium Q_1^* is also unstable if it exists and α is sufficiently large. Finally, we give some sufficient conditions for the global asymptotic stability of the vascular injury equilibrium Q_1^* by constructing suitable Lyapunov functions and combining the Lyapunov-LaSalle invariance principle. Our theoretical results also suggest that the control of vascular injury in the lesion area of KD is not only correlated with the basic reproduction number R_0, but also with the growth rate (α) of normal vascular endothelial cells promoted by the vascular endothelial growth factor. Therefore, in order to control the injury in the lesion area of KD, it is necessary to try to control certain parameters such that the basic reproduction number $R_0 < 1$, and furthermore it is necessary to reduce the parameter α less than α^{**}.

Conflict of Interest

The authors declare no conflict of interest.

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