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REVIEW ARTICLE

Immunopathophysiology, biochemistry, and clinical implications of *Daboia siamensis* venom: A possible challenge to macrophages' immunomodulation

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Abstract

Daboia siamensis (Eastern Russell's viper) envenomation remains a major public health problem in Southeast Asia and is frequently associated with severe systemic complications, particularly coagulopathy and acute kidney injury (AKI). A complex mixture of biologically active toxins, including snake venom metalloproteinases (SVMPs), serine proteases (SVSPs), phospholipase A_2 (PLA_2), and other enzymes, synergistically disrupts vascular integrity, hemostasis, and organ microcirculation. Beyond the direct toxic effects of venom, secondary immune-mediated processes amplify tissue injury through endothelial activation, inflammatory mediators, and oxidative stress that contribute to microvascular dysfunction and ischemic injury, a major pathophysiology of AKI even after correction of systemic coagulation abnormalities. Although antivenom therapy remains the most effective treatment when administered early, its ability to prevent established organ damage is limited once tissue injury has occurred. Hence, immunomodulatory strategies targeting macrophage activation may be beneficial. This review integrates current knowledge on venom composition, immunopathophysiological mechanisms, and clinical manifestations of *D. siamensis* venom, with particular emphasis on factors contributing to renal injury. Improved understanding of the interconnected processes between venom and immune responses may support the development of adjunctive strategies to reduce organ complications and improve outcomes following Russell's viper envenomation.

Key words: *Daboia siamensis* envenoming, immune-mediated amplification, endothelial injury, microvascular dysfunction, acute kidney injury

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Introduction

Snakebite envenomation is classified by the World Health Organization as a neglected tropical disease that continues to impose a substantial health burden, particularly in low- and middle-income countries in tropical and subtropical regions.[1] Rural populations engaged in agricultural activities are disproportionately affected, where frequent human–snake encounters and limited access to timely medical care contribute to high morbidity and mortality.[2,3,4]

D. siamensis (**Figure 1**), the most medically important venomous snake in Southeast Asia, belongs to the family Viperidae and subfamily Viperinae and is a distinct species within the *D. russelii* species complex.[5,6,7] The species is widely distributed across Thailand and neighboring countries, and its bites account for a major proportion of snakebite-related hospital admissions, particularly in rural communities.[8] Its envenomation is characteristically associated with venom-induced consumption coagulopathy (VICC), AKI, and hemorrhagic complications, which together contribute to high fatality rates and long-term morbidity.[8,9]

Figure 1. Adult *D. siamensis* with dorsal ocellated pattern.
Photo credit: Tom Charlton / Eco Animal Encounters (used with permission)

The *D. siamensis* venom is a complex mixture of enzymatic and non-enzymatic components, including SVMPs, PLA_2, and SVSPs, with additional contributions from L-amino acid oxidase (LAAO), disintegrins, C-type lectin-like proteins (CTLs), and other bioactive compounds.[7,10,11] These toxins synergistically produce overlapping effects on coagulation, endothelial stability, and tissue injury, while the host immunity amplifies these effects.[12] Although antivenom effectively neutralizes circulating venom components and corrects coagulopathy, it often fails to prevent established organ injury, especially in delayed treatment.[9,13] This review clarifies the biochemical composition, pathophysiological mechanisms, and clinical manifestations of *D. siamensis* venom.

Biochemical composition of *D. siamensis* venom and macrophage responses

The major toxin families identified in *D. siamensis* venom, the principal molecular targets, and pathophysiological effects are listed in **Table 1**.

Table 1 summarizes the dominant toxin families identified in *D. siamensis* venom, their primary molecular targets, and their key contributions to systemic pathophysiology. The listed toxin groups act synergistically to disrupt vascular integrity, hemostasis, and organ microcirculation, thereby driving clinical manifestations such as coagulopathy, hemorrhage, and AKI.

Table 1. Major venom toxin families of *D. siamensis* and their principal pathophysiological effects.

Toxin family	Major components	Primary molecular targets	Principal pathophysiological effects
Snake venom metalloproteinases (SVMPs)	Predominantly P-III class	Vascular basement membrane, extracellular matrix	Endothelial disruption, hemorrhage, microvascular injury, and contribution to AKI
Snake venom serine proteases (SVSPs)	Thrombin-like enzymes	Coagulation factors (e.g., fibrinogen)	VICC, incoagulable blood, bleeding tendency
Phospholipase A_2 (PLA_2)	Asp49 and Lys49 isoforms	Cell membranes, muscle fibers	Myotoxicity, inflammation, hemolysis, and aggravation of renal injury
L-amino acid oxidase (LAAO)	Flavoenzyme proteins	Cellular redox systems	Oxidative stress, cytotoxicity, and amplification of inflammatory responses
Other components (C-type lectin-like, disintegrins)	C-type lectin-like proteins, disintegrins	Platelet receptors, coagulation pathways	Platelet dysfunction, modulation of hemostasis

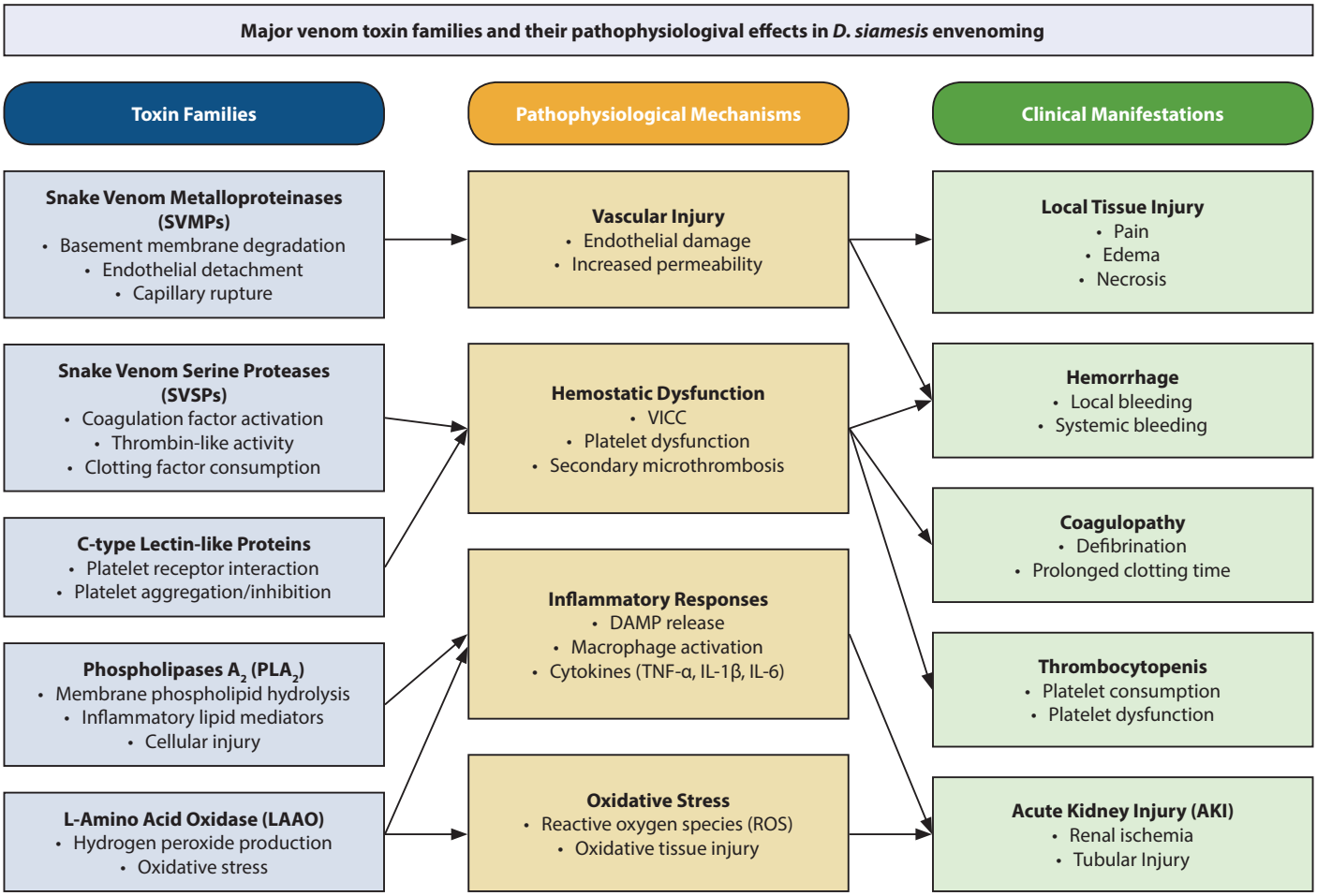

Figure 2. Major toxin families of *D. siamensis* venom and their pathophysiological effects.

The venom of *D. siamensis* contains a complex mixture of enzymatic and non-enzymatic toxins that act on multiple physiological targets in the host. Major toxin families, including SVMPs, SVSPs, and PLA_2, disrupt vascular integrity, coagulation pathways, and cellular membranes, leading to hemorrhage, inflammation, and organ injury. An overview of the principal toxin families and their associated mechanisms is illustrated in **Figure 2**.

The major toxin groups in *D. siamensis* venom, including SVMPs, SVSPs, PLA_2, LAAO, and other minor components such as CTLs, act on multiple molecular targets in the host. These toxins disrupt vascular integrity, coagulation pathways, and cellular membranes, leading to endothelial injury, hemorrhage, inflammation, oxidative stress, and platelet dysfunction. The combined actions of these toxins contribute to systemic manifestations of envenomation, including coagulopathy, thrombocytopenia, tissue injury, and AKI.

a. Snake venom metalloproteinases (SVMPs), major tissue damage, and macrophages

SVMPs are one of the major proportions of the total protein content of *D. siamensis* venom and are key mediators of hemorrhage and microvascular injury.[7] These zinc-dependent enzymes are classified into P-I and P-III classes based on their domain structure, with P-III SVMPs predominating in *D. siamensis* venom.[5] The multidomain structure of P-III SVMPs enables effective interactions with components of the vascular basement membrane, including type IV collagen and laminin, leading to degradation of the extracellular matrix and loss of endothelial integrity.[10]

The pronounced vascular effects of P-III SVMPs are strongly associated with systemic bleeding, tissue edema, and microvascular dysfunction.[12] In the kidney, disruption of the glomerular and peritubular microvasculature is considered a major contributor to renal ischemia and subsequent AKI following envenoming.[14,15] SVMPs induce severe local inflammatory responses and tissue necrosis that not only damage tissue directly but also "prime" and recruit macrophages to amplify the injury.[12]

As such, SVMPs are also primarily associated with structural damage to the vascular basement membrane, leading to endothelial disruption, hemorrhage, and microvascular injury. These vascular effects are particularly important in organs with dense microcirculation, such as the kidney, where impaired perfusion can contribute to AKI.[14] In parallel, SVSPs mainly affect the hemostatic system by activating and depleting coagulation factors, resulting in VICC and a high risk of bleeding.[9] Although SVSPs do not directly damage blood vessels, their effects on coagulation amplify the consequences of SVMP-mediated vascular injury.[13] Because of macrophage activation through the damage-associated molecular patterns (DAMPs) caused by SVSPs, inhibition of macrophage function might attenuate tissue damage and renal complications of *D. siamensis* envenomation.[16]

b. Phospholipase A_2 (PLA_2) enzymes, myotoxicity, and macrophages

PLA_2 enzymes constitute another important toxin family in *D. siamensis* venom. Both catalytically active Asp49 and catalytically inactive Lys49 PLA_2 isoforms have been identified, with distinct but overlapping biological effects.[11] These toxins hydrolyze membrane phospholipids or disrupt membrane integrity, resulting in local tissue damage, inflammation, and myotoxicity.[17] Systemically, PLA_2-induced muscle damage and hemolysis may release myoglobin and hemoglobin, which can exacerbate renal tubular injury and renal dysfunction.[14,15] In addition, PLA_2-mediated generation of inflammatory lipid mediators contributes to vascular permeability and amplifies tissue injury at sites distant from the bite.[17] Hence, PLA_2 enzymes contribute to both local and systemic toxicity through membrane disruption, inflammation, and myotoxicity. Secondary effects such as hemolysis and muscle breakdown may further aggravate renal injury by increasing the burden on renal tubules.[14]

In addition, LAAO and other minor venom components enhance oxidative stress and inflammatory responses, thereby intensifying tissue damage.[12,14,18] Interestingly, myotoxicity is closely correlated with macrophage responses, as neutrophils and monocytes (later differentiated into macrophages) infiltrate the injured muscle within an hour, predominantly with a pro-inflammatory M1 polarization.[19] The M1 macrophages actively phagocytize the necrotic muscle debris and release pro-inflammatory cytokines, followed by an alteration in M2 polarization that possibly produces "synaptic-like" contacts with myofibers, which modulate calcium activity and directly hasten membrane repair.[20] Thus, the blocking of M1 macrophage polarization with an enhanced M2 polarization might facilitate the healing activity.

c. Snake venom serine proteases (SVSPs), direct macrophage activation

SVSPs play a central role in the coagulopathic effects characteristic of *D. siamensis* envenoming. They interact directly with components of the coagulation cascade, including fibrinogen and clotting factors, leading to rapid activation followed by consumption of coagulation factors. The resulting VICC is a defining clinical feature and is responsible for uncoagulable blood and increased bleeding risk.[9] Although SVSPs do not typically cause direct structural damage to blood vessels, their intense effects on coagulation contribute indirectly to tissue ischemia and organ dysfunction, particularly when combined with SVMP-mediated vascular injury.[3] Interestingly, SVSPs are potent direct macrophage stimulators that trigger a pro-inflammatory M1 polarization through several signaling cascades, such as the PI3K, MAPK, bradykinin, and complement system (C3 and C4 components).[16] Thus, the blockage of proinflammatory macrophages might be beneficial.

d. Other venom components

In addition to the major enzymatic toxins, *D. siamensis* venom contains several minor components that contribute to overall toxicity.[7] LAAO generates hydrogen peroxide during amino acid metabolism, promoting oxidative stress, cytotoxicity, and inflammatory responses.[18] Disintegrins interfere with platelet aggregation by targeting integrin receptors, while CTLs modulate platelet function and coagulation pathways.[7,18] Although present in lower abundance, these components act synergistically with SVMPs, PLA_2s, and SVSPs to intensify vascular damage, inflammation, and systemic toxicity. Their combined actions highlight the importance of considering venom composition as an integrated system rather than a collection of isolated toxins.[4] The DAMPs from several toxins might be responsible for a more intense macrophage stimulation than the activation by a single toxin.[12]

Pathophysiological mechanisms of envenomation and immune responses

Systemic toxicity from combined toxin families (coagulation, vascular injury, and inflammation) leads to the variability in clinical presentations,[4] especially AKI,[14] as summarized in **Figure 3**.

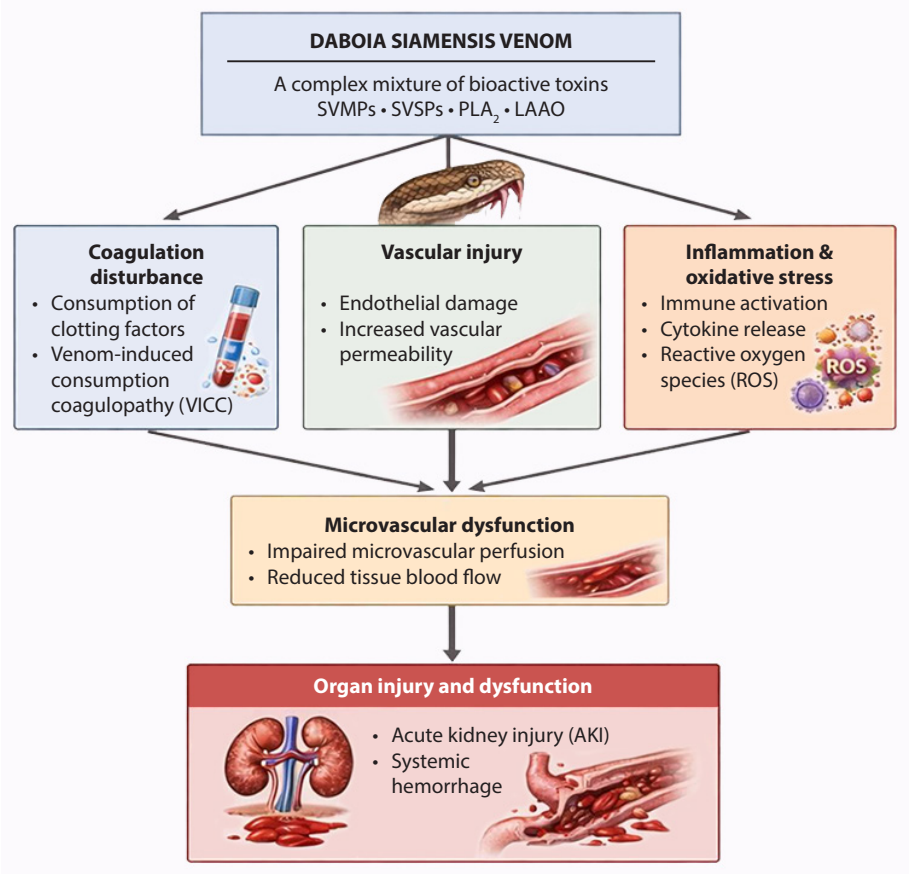

Figure 3. Conceptual schematic of the systemic effects of *D. siamensis* venom.

Abbreviations: SVMPs, snake venom metalloproteinases; SVSPs, snake venom serine proteases; PLA_2, phospholipase A_2; LAAO, L-amino acid oxidase.

The complex mixture of venom toxins disrupts coagulation, damages the vascular endothelium, and promotes inflammatory and oxidative stress responses, leading to microvascular dysfunction and subsequent organ injury. This schematic represents an integrative, hypothesis-driven framework synthesized from current experimental and clinical evidence rather than a single mechanistic pathway. Major toxin groups induce coagulation disturbance, vascular injury, and oxidative stress–associated inflammation. Venom-induced tissue damage leads to the release of DAMPs, which subsequently activate resident and infiltrating macrophages, as further illustrated in **Figure 4**. Activated macrophages amplify endothelial dysfunction by releasing pro-inflammatory cytokines and chemokines, sustaining microvascular instability and contributing to persistent organ injury, particularly AKI.

At the molecular level, venom-induced tissue injury may activate inflammatory signaling pathways. Experimental studies indicate that macrophage activation following venom exposure is associated with increased expression of pro-inflammatory mediators such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), as well as chemokines including monocyte chemoattractant protein-1 (MCP-1/CCL2).[4,16] These mediators promote leukocyte recruitment, endothelial dysfunction, and microvascular injury, thereby contributing to the development of AKI.[15]

Although macrophages are highlighted as central amplifiers of inflammation in this review, other innate immune cells may also participate in the inflammatory response following envenoming. Neutrophils are among the earliest leukocytes recruited to sites of tissue injury and release proteolytic enzymes and reactive oxygen species (ROS), which may aggravate endothelial injury and microvascular dysfunction. Activated neutrophils may also release neutrophil extracellular traps (NETs), which can contribute to inflammatory microvascular injury and immunothrombosis. Interactions between neutrophils and macrophages may further amplify inflammatory responses during venom-induced tissue injury.[4]

The pathogenesis of AKI following *D. siamensis* envenomation involves both direct toxin-mediated vascular injury and secondary immune-mediated amplification. Venom-induced tissue damage triggers DAMP release and macrophage activation, promoting pro-inflammatory cytokine production and microvascular dysfunction, thereby contributing to AKI. These interconnected mechanisms are illustrated in **Figure 4**.

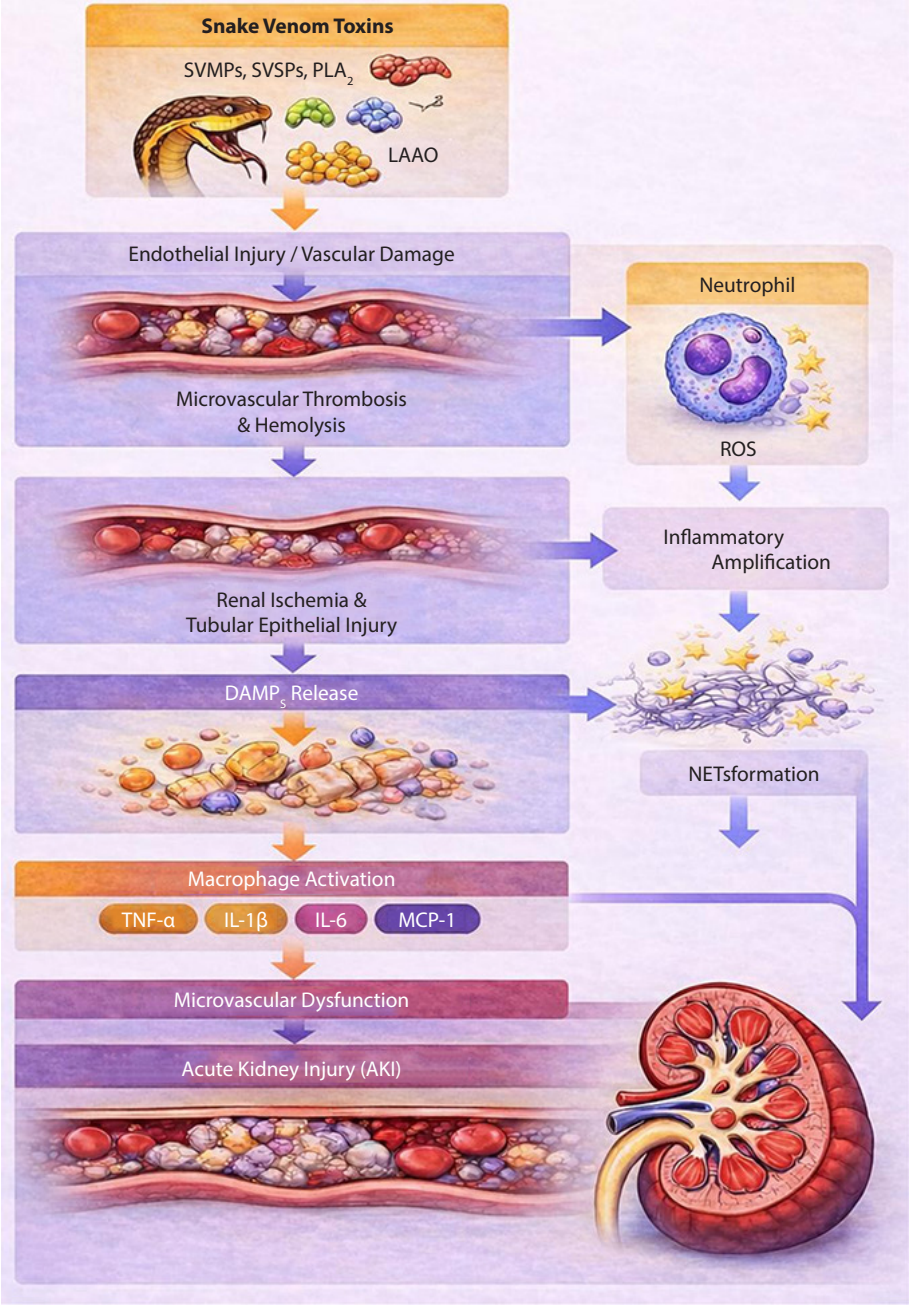

Figure 4. Proposed mechanisms of toxin-induced AKI and macrophage activation in *D. siamensis* envenomation.

Abbreviations: SVMPs, snake venom metalloproteinases; SVSPs, snake venom serine proteases; PLA_2, phospholipase A_2; LAAO, L-amino acid oxidase; ROS, reactive oxygen species; DAMPs, damage-associated molecular patterns; TNF-α, tumor necrosis factor-alpha; IL-1β, interleukin-1 beta; IL-6, interleukin-6; MCP-1, monocyte chemoattractant protein-1; NETs, neutrophil extracellular traps; AKI, acute kidney injury.

Venom toxins, including SVMPs, SVSPs, PLA_2, and LAAO, induce vascular injury and renal microvascular dysfunction. These processes lead to renal ischemia, hemoglobinuria, myoglobinuria, and oxidative stress, resulting in tubular epithelial injury. Tissue damage promotes the release of DAMPs, which activate macrophages and stimulate the production of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, MCP-1). The resulting inflammatory amplification contributes to the development and progression of AKI.

a. Roles of macrophages in VICC and thrombocytopenia

One of the earliest systemic effects of *D. siamensis* envenoming is VICC.[3,9] This process is driven primarily by procoagulant venom components that activate the coagulation cascade, leading to rapid depletion of clotting factors, particularly fibrinogen.[9] Clinically, this results in uncoagulable blood and a high risk of spontaneous or procedure-related bleeding.[3,9] In severe cases, widespread derangement of coagulation may also contribute to impaired tissue perfusion and worsen downstream organ injury.[13]

On the other hand, *D. siamensis* venom induces the desialylation of platelet membranes (the increased endogenous neuraminidase-1 on the platelet surface) that are phagocytosed by macrophages, particularly the tissue-resident macrophages in the liver and spleen, causing thrombocytopenia.[21] The thrombocytopenia might present in the absence of significant VICC, and the neuraminidase blocker, such as oseltamivir (an antiviral medication), attenuates thrombocytopenia through the reduced macrophage functions.[22] Because several VICC-related toxins directly activate macrophages[16] and possibly cause thrombocytopenia, patients with VICC plus thrombocytopenia might have dominantly active proinflammatory macrophages, and the attenuation of macrophage function might be beneficial. More studies are interesting.

Venom toxins in *D. siamensis* envenomation produce diverse biochemical and cellular effects; however, the resulting systemic manifestations arise from complex interactions between venom-induced vascular injury and host immune responses. Endothelial disruption, coagulation disturbances, and tissue damage initiate inflammatory signaling that amplifies microvascular dysfunction and organ injury. Among innate immune mechanisms, macrophages act as key secondary amplifiers of venom-induced pathology. By recognizing DAMPs, activated macrophages promote cytokine production, leukocyte recruitment, and platelet clearance, thereby linking early vascular injury to sustained immune-driven microvascular dysfunction. These interconnected mechanisms are summarized as a conceptual immunopathophysiological framework in **Figure 5**.

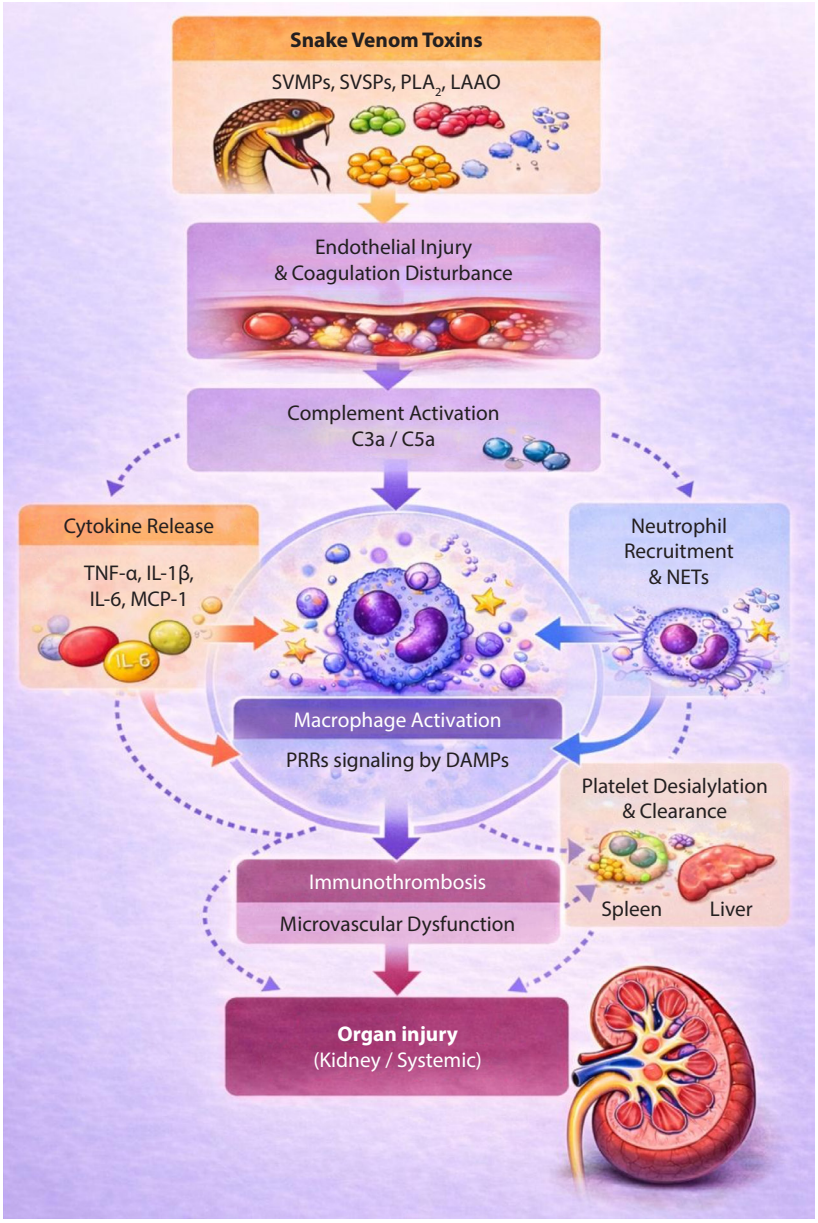

Figure 5. Conceptual immunopathophysiological framework for *D. siamensis* envenomation.

Abbreviations: SVMPs, snake venom metalloproteinases; SVSPs, snake venom serine proteases; PLA_2, phospholipase A_2; LAAO, L-amino acid oxidase; PRRs, pattern recognition receptors; DAMPs, damage-associated molecular patterns; TNF-α, tumor necrosis factor-alpha; IL-1β, interleukin-1 beta; IL-6, interleukin-6; MCP-1, monocyte chemoattractant protein-1; C3a, complement component 3a; C5a, complement component 5a; NETs, neutrophil extracellular traps.

Venom toxins, including SVMPs, SVSPs, PLA_2, and LAAO, initiate endothelial injury and coagulation disturbances. These primary events trigger complement activation (C3a and C5a) and DAMPs release, leading to macrophage activation via PRRs. Activated macrophages amplify inflammatory responses by promoting cytokine production (TNF-α, IL-1β, IL-6, and MCP-1), neutrophil recruitment, and platelet interactions. In parallel, platelet desialylation promotes macrophage-mediated platelet clearance in the spleen and liver, contributing to thrombocytopenia. The combined effects of vascular injury, immune activation, and platelet dysregulation promote immunothrombosis and microvascular dysfunction, ultimately leading to organ injury, particularly AKI.

b. Roles of macrophages in AKI

Venom-induced disruption of endothelial cells, extracellular matrix, and parenchymal tissues triggers the release of DAMPs, initiating local and systemic inflammatory signaling that intensifies tissue injury.[4,12] Although this response represents a physiological reaction to tissue damage, its rapid activation in severe envenomation enhances vascular permeability and inflammatory stress.[12,17] Coagulation disturbances are frequently accompanied by microvascular perfusion impairment, particularly in the kidney, where reduced blood flow rapidly translates into ischemic stress and contributes to AKI.[14,15]

SVMPs play a central role in this process by degrading components of the endothelial basement membrane, resulting in hemorrhage and loss of microvascular integrity.[4,12] Once established, such structural injury is poorly reversible, as antivenom primarily neutralizes circulating toxins but cannot readily repair pre-existing microvascular damage.[2,4] Consequently, early SVMP-mediated injury sets the stage for persistent perfusion abnormalities and downstream organ dysfunction, even after correction of systemic coagulation parameters.

The vascular endothelium thus serves as a critical interface linking venom toxicity and immune responses. Endothelial activation, increased adhesion molecule expression, and leukocyte recruitment promote plasma leakage and microvascular congestion, particularly in the kidney.[4,10,14] Proinflammatory cytokines and chemokines released by activated endothelial cells, resident immune cells, and infiltrating leukocytes act as secondary amplifiers that exacerbate ischemia, sustain inflammation, and accelerate tubular injury, thereby contributing to the progression of AKI.[17,23]

Oxidative stress represents an additional injury to the kidney.[14,18] As such, LAAO is a well-recognized source of ROS, generating hydrogen peroxide, which further damages host tissue and exacerbates tissue injury initiated by other venom toxins.[18] ROS also sensitize endothelial cells to produce proinflammatory cytokines and lower the threshold for endothelial activation. Indeed, mild to moderate inflammatory stimuli may lead to disproportionate vascular responses in the presence of ROS.[14,18] Proinflammatory cytokines stimulate the generation of ROS by immune and endothelial cells, while ROS further promotes cytokine release and endothelial activation, creating a self-sustaining cycle and persistent microvascular instability.[4,17] These effects provide a mechanistic explanation for continued renal dysfunction after envenomation, even after the decline of circulating venom level and improved coagulation by antivenom.[14,15] Overall, oxidative stress might serve as an amplifier that links venom toxicity to host inflammatory responses. By sustaining endothelial dysfunction and enhancing inflammatory injury, ROS-mediated mechanisms contribute to the persistence and severity of organ damage, particularly AKI.[14,18]

Then, in the kidney, endothelial activation and leukocyte accumulation within glomerular and peritubular capillaries may reduce effective perfusion and exacerbate regional hypoxia. This inflammatory microenvironment increases the renal tubular injury.[14,15] Importantly, inflammatory mediators may sustain renal injury even after circulating venom levels decline or systemic coagulation parameters improve. Persistent cytokine signaling prolongs endothelial dysfunction and tubular stress, helping to explain the clinical observation that renal impairment may progress independently of apparent improvement in coagulopathy following antivenom therapy.[14,15] Thus, cytokine and chemokine release represents a critical immunological link between initial venom toxicity and sustained vascular and renal damage.[4,14] Consequently, AKI progression cannot be explained solely by circulating venom activity or coagulation disturbances but must be understood within the broader context of microvascular and tissue-level damage. Due to the immune amplification, AKI may progress even after circulating venom levels decline or coagulopathy improves following antivenom therapy.[14]

Both direct enzymatic digestion and microvascular thrombosis or thrombotic microangiopathy from the venom induce acute tubular necrosis (ATN) and renal cortical necrosis.[24] Experimental studies in animal models of AKI suggest that macrophage responses can influence the severity of ATN. Early infiltration of pro-inflammatory M1 macrophages may exacerbate renal injury, whereas a shift toward M2 macrophage polarization has been associated with attenuation of tissue damage and promotion of renal repair.[25]

Clinical manifestations and outcomes

Clinically, envenomation by *D. siamensis* is characterized by prominent systemic toxicity, while local effects at the bite site may vary in severity.[2] The overall clinical course is largely determined by the intensity of coagulopathy, the extent of microvascular injury, and the development of organ complications, most importantly, AKI.[14] As such, VICC typically develops early after envenomation and is a hallmark of *D. siamensis* bites that typically present with uncoagulable blood and bleeding tendencies and, in severe cases, internal hemorrhage.[3,9] Even with non-overt bleeding, laboratory evidence of coagulopathy indicates the antivenom requirement.[9] Additionally, renal dysfunction, ranging from mild creatinine elevation to oliguric renal failure,[14] might present without coagulopathy due to the microvascular

Table 2. Major clinical manifestations of *D. siamensis* envenoming and their principal pathophysiological mechanisms.

Clinical manifestation	Principal pathophysiological mechanism	Evidence source	References No.
Local tissue necrosis	SVMP-mediated degradation of the extracellular matrix and the basement membrane, leading to microvascular disruption and ischemic tissue injury	Experimental / animal studies	4,12
Coagulopathy (VICC)	Activation of coagulation factors by snake venom SVSPs and prothrombin activators, leading to rapid consumption of clotting factors	Clinical + experimental	9,13
Thrombocytopenia	Platelet activation/aggregation and macrophage-mediated clearance of desialylated platelets	Clinical + experimental	21,22
Hemorrhage	SVMP-induced disruption of the capillary basement membrane, causing vascular leakage and bleeding	Experimental	12
Acute kidney injury (AKI)	Microvascular thrombosis, renal ischemia, hemolysis, and direct nephrotoxicity of venom components	Clinical + experimental	14,15

and tubular injury.[14,15] Notably, the timing of antivenom administration is a critical predictor of outcome, as early venom neutralization limits systemic effects, and delayed antivenom is unable to prevent vascular injury and organ damage.[14] The severity is influenced by venom dose, bite circumstances, and patient-specific factors, such as baseline health status and pre-existing renal reserve.[2,15] The major clinical manifestations of *D. siamensis* envenomation and their dominant pathophysiological drivers are listed in **Table 2**.

The mechanisms summarized in **Table 2** are derived from a combination of clinical observations in human envenoming, experimental animal studies, and in vitro investigations of venom toxins. Evidence sources are indicated to clarify whether the proposed mechanisms are primarily supported by clinical data or by experimental models. Abbreviations: SVMPs, snake venom metalloproteinases; SVSPs, snake venom serine proteases; VICC, venom-induced consumption coagulopathy.

a. Laboratory assessment

Initial assessment is based on patient history, examination of the bite site, and the identification of systemic manifestations or hemodynamic instability.[1] The coagulation screening, initially evaluated at the bedside through the 20-minute whole blood clotting test (20WBCT), is important decision-making information. However, the various performances of 20WBCT across clinical settings with inconsistent technique may fail to detect milder or partial coagulation abnormalities. Then, prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen concentration, and D-dimer provide a more detailed evaluation.[9] On the other hand, conventional renal biomarkers primarily reflect established functional impairment rather than ongoing tissue injury or immune-mediated processes, limiting their utility for early risk stratification following *D. siamensis* envenomation.[14,15] Although serum creatinine remains the most widely used biomarker for AKI, serum creatinine elevation occurs after a major decline in glomerular filtration rate, which may represent the late phase of envenomation.[23] Moreover, renal dysfunction can progress even when coagulation abnormalities improve after antivenom therapy, highlighting a temporal disconnect between systemic parameters and ongoing renal injury.[14] The studies using better renal injury parameters, such as cystatin C (CysC), kidney injury molecule-1 (KIM-1), and neutrophil gelatinase-associated lipocalin (NGAL), will be interesting.[26,27] Although the immune-driven processes precede overt changes in renal function and may serve as early indicators of evolving injury, the clinical importance of serum cytokines and other parameters in snake bites is still limited.[4,17]

b. Venom Antigen Detection and Immunoassays

Limitations of clinical assessment and conventional laboratory tests have driven interest in venom-specific immunodiagnostic approaches that directly detect circulating venom antigens following snakebite.[1] In *D. siamensis* envenomation, such assays offer a mechanistically relevant means of confirming systemic envenoming and supporting early, immune-guided clinical decision-making, particularly when overt clinical features are still absent.[8,11] As such, the enzyme immunoassays represent the most extensively studied platform for venom antigen detection that relies on antibody–antigen interactions to identify circulating venom components. The venom antigens can be detected in serum during the early phase of envenoming, often before the full development of coagulopathy or renal dysfunction.[28] However, their routine clinical use is limited by requirements for laboratory infrastructure, which may not be feasible in many snakebite-endemic settings.[1,11] Then, the lateral flow immunodiagnostic assays are rapid, antibody-based tools designed for point-of-care detection of circulating snake venom antigens, providing a practical alternative.[29] The assays generate visual results within minutes and do not require specialized equipment or trained laboratory personnel, but can successfully detect venom components before the onset of systemic manifestations.[28] This early diagnostic capability is particularly important in hemotoxic snakebite, where vascular and renal injury may progress rapidly despite initially mild clinical signs.[29] Evidence from Thailand further supports the feasibility of lateral-flow immunodiagnostics (qualitative or semi-quantitative) for regional snakebite management.[30] For an early confirmation

of systemic envenomation, the enzyme immunoassays can confirm a precise venom quantification.[28] When integrated with clinical assessment and conventional laboratory testing, these assays may facilitate earlier antivenom administration and support immune-guided intervention before irreversible microvascular or renal injury develops.[28,29]

Despite their diagnostic potential, several limitations remain for venom antigen detection assays. Many immunoassays are currently available only in specialized laboratories, limiting their accessibility in routine clinical settings. In addition, variations in assay design, limited standardization across laboratories, and the cost of assay development may restrict their widespread implementation.

Translational relevance for early immune-guided intervention

Because renal injury and microvascular dysfunction may progress despite apparent improvement in systemic parameters following antivenom therapy in *D. siamensis*,[14] integration of venom immunodiagnostics with clinical and laboratory assessment supports a more individualized approach to snakebite management.[29] Early confirmation of venom exposure may help identify patients who would benefit most from prompt antivenom therapy or closer monitoring for immune-mediated and microvascular complications.[28,30] As these diagnostic tools continue to evolve, they offer a practical pathway toward immune-guided intervention strategies aimed at reducing the severity and persistence of organ injury following envenoming.[29,32]

a. Antivenom therapy and limitations

Antivenom therapy remains the cornerstone of treatment that is most effective when administered early in the clinical course.[2] Timely antivenom can neutralize circulating venom components, reverse VICC, and prevent systemic toxicity,[4,9] demonstrating limited effect on established damage. Because venom toxins rapidly bind to tissues and initiate irreversible injury processes, venom neutralization is less effective,[2,4,14] and coagulopathy correction does not prevent the established AKI.[8,14] Although antivenom restores coagulation function,[9] it may not uniformly neutralize other classes of toxins, for example, SVMPs (microvascular injury toxins) that are responsible for hemorrhage and AKI.[14,33] This difference helps explain why some patients develop persistent organ dysfunction, despite receiving antivenom and achieving improvement in coagulation parameters. When treatment is delayed, antivenom may still correct VICC but may not fully prevent the progression of established AKI or vascular damage.[14]

b. Adjunctive therapy

To address gaps in conventional antivenom coverage, adjunctive and next-generation strategies are increasingly being explored. Small-molecule inhibitors that target metalloproteinase activity have been proposed as early-intervention options, with the aim of limiting SVMP-driven vascular injury before irreversible damage develops.[33] In parallel, toxin-focused biologics, such as monoclonal antibodies or nanobodies, are being developed to improve specificity and neutralization of clinically important toxins that are not consistently well neutralized by traditional antivenoms.[32] Broader work on antivenom effectiveness also supports continued optimization of antibody coverage and dosing strategies for coagulopathic syndromes.[34] Unfortunately, the development of immunomodulation in snake bites is very low, despite ongoing progress in other diseases (cancers, autoimmune diseases, and sepsis).[35,36,37] Indeed, several blockage strategies targeting M1 proinflammatory macrophages have been described, including cell energy interference, microRNAs, and other specific molecules.[38,39,40] Early administration of the M1 macrophage blocker after snake bites by these existing regimens will be very interesting. Overall, these developments reflect a shift toward mechanism-guided therapy, where antivenom remains central but may be complemented by targeted agents designed to block early vascular injury and reduce the risk of AKI in severe envenomation.[14,31]

Future directions

Advances in several areas of information on toxins and pathophysiology offer a possible mechanism-based approach rather than relying solely on empirical clinical management.[5] Proteomic profiling has shown that a limited number of toxins, particularly snake venom SVMPs, SVSPs, and PLA_2 enzymes, account for most of the clinical manifestations of *D. siamensis* snakebites.[7] This proteomics-guided antivenom development supports a more focused strategy for antivenom development, in which antibody responses are optimized against limited toxins that drive severe pathology, including vascular injury and AKI.[31,32] Such an approach may improve neutralization efficiency and reduce variability in clinical response. Meanwhile, small-molecule inhibitors targeting SVMP activity show promise as early adjunctive treatments,[33] especially when combined with conventional antivenom.[34] Likewise, the emerging diagnostic tools, particularly venom detection assays, may enable more precise assessment of venom exposure and toxin burden in individual patients. Integration of such diagnostics with clinical and laboratory biomarkers could support risk stratification and guide tailored therapeutic decisions, including antivenom dosing and adjunctive treatments.[14,29] This precision-oriented framework represents a shift toward personalized management of snakebite envenomation, informed by both venom biology and patient-specific factors. Overall, applying mechanistic insights into clinical practice will depend on coordinated efforts across venom research, diagnostic innovation, and therapeutic development. For *D. siamensis* envenomation, strategies that combine optimized antivenoms, early toxin detection, and targeted adjunctive therapies hold promise for reducing the burden of severe complications, particularly AKI.[14,31]

Conclusions

D. siamensis envenomation demonstrates a complex venom mixture with severe systemic disease,[4,31] especially VICC, AKI,[9,13] endothelial injury, tissue ischemia, oxidative stress, and inflammatory damage.[14,17] Early antivenom administration remains the cornerstone of therapy[9] to neutralize circulating VICC-related components,[13,14] with a possible limited capacity against other toxins. The improved diagnosis with optimized antivenoms against several toxins and adjunctive treatment strategies might be beneficial.[31] Proteomic analysis of the venom led to the selection and development of the novel antivenom that might attenuate several clinical manifestations, not only coagulopathy.[1,31] Meanwhile, next-generation biologic agents (anti-inflammation and signaling blockage) may offer additional protection against early microvascular injury, limit disease progression, and reduce AKI incidence.[8,32] Integrating immunological insights with venom biochemistry may therefore inform more precise diagnostic and management approaches for hemotoxic snakebite in endemic regions.[4,8,29]

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Conflicts of Interest

The authors declare no conflict of interest.

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