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Characterization of Clinical, Hematological, and Biochemical Findings in Dogs with *Vipera aspis* Envenomation

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Abstract

Viper envenomation in dogs represents a significant medical emergency in regions where vipers are endemic. Despite its clinical relevance, detailed data on the haematological and biochemical alterations in canine viper envenomation remain limited. This study aimed to evaluate the clinical presentation and haematological, biochemical and coagulative changes occurring in dogs following bites from the *Vipera aspis* species, and to assess their diagnostic and prognostic significance. Twelve dogs with suspected Vipera aspis envenomation were encompassed in the study. Clinical data were gathered and blood samples were collected at hospital admission (T1), 24 h (T2) and 48 h later (T3). Complete blood counts, biochemical profiles and coagulation parameters were analysed using standard automated systems. Common clinical signs included local pain and swelling, depression, fever, haematuria and melena. Haematological evaluation revealed progressive anaemia, leucocytosis and thrombocytopenia. Biochemical findings showed elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and creatine kinas (CK), indicating hepatic and muscular injury; however, no consistent evidence of renal failure was found. Coagulation analysis revealed a significant shortening of activated partial thromboplastin time (aPTT) and prothrombin time (PT) over time, alongside marked increases in fibrinogen and antithrombin III. This indicates an inflammatory rather than consumptive coagulopathy. Viper envenomation in dogs induces complex haematological and biochemical alterations, reflecting both direct venom toxicity and systemic inflammatory responses. Early recognition, supportive care and continuous laboratory monitoring are essential for improving prognosis.

Keywords: dog envenomation; snakebite; veterinary toxicology

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1. Introduction

Viper envenomation is a significant medical emergency in veterinary medicine, particularly in regions where vipers are endemic. This is due to the complex pathophysiological effects of envenomation and variable clinical outcomes associated with the condition. Of the estimated 3500 species of snake worldwide, only around 300 are venomous, belonging to five families: Elapidae, Colubridae, Hydrophidae, and Viperidae. In Europe, only the Viperidae family is present, except in some countries where vipers are absent, such as Ireland. In Italy, four species occur—*Vipera aspis*, *Vipera berus*, *Vipera ammodytes*, and *Vipera*

ursinii—with Sardinia being the only region where they are absent [1]. Viper bites represent one of the most frequently reported types of envenomation in dogs, often resulting in severe local and systemic effects. The clinical presentation can vary significantly depending on the viper species, the amount of venom injected, the size of the bitten animal, the bite location, and the time elapsed between the bite and treatment [2].

Viper venom contains a mixture of proteases, phospholipases, and other bioactive components that can induce local tissue damage, systemic inflammation, haemolysis, and coagulopathies. Although several studies have described the epidemiological and clinical manifestations of viper bites in dogs, the mechanisms underlying haematological and biochemical alterations remain incompletely understood [3–11].

In veterinary practice, canine viper envenomation is characterised by a rapid onset of swelling at the bite site, haemorrhagic tendencies and alterations in haematological and biochemical parameters. Neurotoxic manifestations may also occur following envenomation by several viper species. Common laboratory abnormalities include thrombocytopenia, leucocytosis, elevated liver and muscle enzymes, and alterations in renal function markers, reflecting both the direct effects of venom and secondary systemic responses [12]. It is essential to understand the pathophysiological mechanisms underlying these clinical and laboratory changes to optimise diagnosis, prognostic evaluation and therapeutic management. Despite its recognised clinical relevance, detailed data on the biochemical and haematological consequences of *Vipera aspis* envenomation in dogs remain limited, particularly in cases observed in the field. In contrast, the effects of *Vipera berus* envenomation are better documented [11–17].

This study aimed to evaluate the clinical, haematological and biochemical alterations observed in dogs following *Vipera aspis* bites, shedding light on their diagnostic value and significance.

2. Materials and Methods

This prospective study was carried out in accordance with European veterinary good practice [18]. A written consent form was signed by each owner to include their animal in the study, and the form was completed properly and in full.

2.1. Study Group

The study looked at twelve dogs that had been bitten by the Italian viper (*Vipera aspis*), the most widespread venomous snake in Italy. The inclusion criteria required a well-founded suspicion of *Vipera aspis* envenomation at the time of presentation, based either on the owner's account—such as direct observation of the bite or the presence of a viper near the dog—or on clinical manifestations consistent with snakebite. The time between being bitten by a viper and receiving medical care varied, ranging from less than 7 to 28 h afterwards.

These included lethargy and/or localised swelling at the presumed site of envenomation. Dogs were excluded if they were receiving glucocorticoid treatment for conditions other than viper bites, or if they had a history of known liver disease. For each dog, a detailed case history was collected, including signalment (breed, age, sex and body weight) and the time elapsed between the bite and clinical presentation. Clinical variables such as mental status, body temperature, and cardiovascular parameters (including mucous membrane colour, capillary refill time, and heart rate/rhythm) were documented, as were bite location and the extent of local swelling.

Blood samples were collected at the following time points: upon hospital admission (T1), before the initiation of any therapeutic procedures; and subsequently at 24 (T2) and after 48 (T3) hours following the onset of clinical manifestations.

Venous blood samples were collected from either the jugular or cephalic vein and allocated into three separate collection tubes.

The first tube, containing K_3EDTA as an anticoagulant, was designated for haematological analysis to determine the complete blood count (CBC). These measurements were obtained with a haematology analyser that is founded on focused flow impedance and flow cytometry principles (ADVIA 2120, Siemens Healthineers—Lab Diagnostics, Tarrytown, NY, USA).

Blood smears were then prepared using an automated slide stainer (ADVIA S60, Siemens Healthineers—Lab Diagnostics, Tarrytown, NY, USA) and subjected to modified Wright staining (methylene blue and eosin) for microscopic examination, thereby completing the haematological evaluation.

The second tube, which contained no additives, was used for serum biochemical profiling. The following parameters were measured: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), urea (UREA), creatinine (CREA), bilirubin (BIL), total protein (TP) and creatine phosphokinase (CPK). Analyses were performed using a chemistry analyser (DADE RXL MAX, Siemens Healthineers—Lab Diagnostics, Tarrytown, NY, USA).

The third tube, which contained sodium citrate, was used for coagulation studies, including determining Partial Thromboplastin Time (PTT), Activated Partial Thromboplastin Time (aPTT), Prothrombin Time (PT), Fibrin Degradation Products (FDPs), D-Dimer (D-DIM), Fibrinogen (FIB) and Antithrombin III (AntiTromb III).

2.2. Statistical Analysis

Statistical analyses were performed using SPSS software (version 17.0, SPSS Inc., Chicago, IL, USA). The normality of the data distribution was assessed using the Shapiro–Wilk test. Categorical variables, such as laboratory and clinical signs, were expressed as absolute frequencies and percentages. Laboratory variables were also expressed as quantitative descriptive variables. Data were presented as mean $\pm$ standard deviation (SD) if they were normally distributed. One-way ANOVA was used to assess differences in clinical, haematological, and biochemical variables at different time points after the snakebite (<24 h, T1; >24–48 h, T2; >48 h, T3). No basal values were available as all examinations were performed after the snakebite. A p-value ≤ 0.05 was set as statistically significant.

3. Results

Of the 12 dogs examined, seven were male and five were female. They belonged to different breeds (six crossbreeds, two Jack Russells, one German Shepherd, one Pinscher and one Dachshund). The mean age was 5 years (range 2–7 years), with a mean body weight of 10.2 kg (range 3–25 kg). All dogs were referred between April and November. At the time of admission, the following clinical signs were observed: pain and swelling at the bite site (12/12; 100%), depression of mental status (8/12; 66%), fever (8/12; 66%), haematuria (8/12; 66%), melena (6/12; 50%), and subcutaneous and mucosal petechial and ecchymosis (5/12; 41.7%). Most dogs (9/12; 75%) were bitten on the front or hind limbs, while bites on other parts of the body, such as the head or nose, were less frequent. On average, it took 11 $\pm$ 6 h from being bitten by a viper to receiving medical care.

Haematological alterations recorded upon admission included anaemia (5/12; 41.6%), leucocytosis (9/12; 75%) and thrombocytopenia (4/12; 33.4%). Biochemical test alterations included increased BUN and CREA (3/12; 25%), and increased ALT, AST, ALP and CPK (9/12; 75%). An increase in aPTT and fibrinogen was also recorded in five dogs (41.6%). All dogs were given glucocorticoid treatment (methylprednisolone or prednisone, respectively

in 5/12 and 7/12; 41.7% and 58.3%), in conjunction with antimicrobials (i.e., cefazolin in 3/12; 25% and enrofloxacin in 9/12; 75%), fluid therapy and opioids (tramadol in 8/12; 66% or methadone in 4/12; 33.4%). Of the seven dogs admitted, five were discharged after 3 ± 1 days, while seven (58.4%) died within 48 h due to serious clinical conditions (i.e., extensive necrosis, bleeding, shock).

A comparison of haematological variables at different time points following snakebite revealed a significant diminution in red blood cells (RBCs) count at T2 and T3 compared with baseline values (T1) ($p = 0.01$ and $p = 0.02$, respectively), which is consistent with the development of anaemia. The number of bands and neutrophils increased significantly at T2 and T3 relative to T1 ($p = 0.02$ and $p = 0.02$, respectively), indicating bone marrow activation and the release of immature neutrophils in response to inflammation or infection. A pronounced increase in monocyte count was also observed at T2 and T3 compared with T1 ($p = 0.005$ and $p = 0.002$, respectively). Platelet count (PLT) showed a significant decline at T2 compared to T1 ($p = 0.03$) (Table 1).

Table 1. Haematological parameters expressed as mean and standard deviation (SD) recorded at T1, T2 and T3.

Hematological Variables	T1	T2	T3	Reference Range [19]
RBCs (10^6/mcL)	3.40 ± 3.6 ^{ab}	2.05 ± 1.9 ^{a}	1.36 ± 2.2 ^{b}	5.5–8.5
Hgb (g/dL)	7.79 ± 8.3	4.61 ± 4.9	3.27 ± 5.3	12.0–18.0
PCV (%)	44.08 ± 6.2	22.65 ± 7	29.66 ± 3.8	37.0–55.0
WBCs (10^3/mcL)	24,160 ± 2908.12	22,456.67 ± 6665	29,183.33 ± 4179	6.0–17.0
NEU BAND (10^3/mcL)	690 ± 60.4 ^{ab}	720.6.5 ± 143.28 ^{a}	1368 ± 595.3 ^{b}	0–300
NEU SEG (10^3/mcL)	21,264.16 ± 2936	18,874.5 ± 6172	18,874.5 ± 5135	3800–8800
MONO (10^3/mcL)	1004.7 ± 350 ^{AB}	790.33 ± 379 ^{A}	2038.66 ± 791 ^{B}	200–740
PLT (10^3/mcL)	231.6 ± 83.4 ^{a}	108.16 ± 88.86 ^{a}	201.66 ± 90.56	160–430
MPV (fL)	13.02 ± 3.27	14.93 ± 4.1	12.3 ± 1.7	7.5–11.5
MPC (g/dL)	19.18 ± 2.8	20.18 ± 2.7	21.93 ± 1.9	<25.3

T1 (within 24 h of snakebite); T2 (within 24–48 h of snakebite); T3 (>48 h of the snakebite); RBCs (red blood cells); Hgb (hemoglobin); PCV (packed cell volume); WBCs (white blood cells); NEU BAND = banded neutrophils; SEG = segmented neutrophils; MONO = monocytes; PLT = platelet count; MPV = mean platelet volume; MPC = mean platelet component concentration. Lowercase letters in the superscripts indicate statistical significance between rows ($p < 0.05$). Capital letters in the superscripts indicate statistical significance between rows ($p < 0.01$).

No statistically significant changes in serum biochemical parameters were detected at the different time points following envenomation (see Table 2).

Table 2. Biochemical parameters are expressed as mean and SD, and were recorded at T1, T2 and T3.

Biochemical Variables	T1	T2	T3	Reference Range [20]
CPK (IU/L)	1193.25 ± 412.85	7768.57 ± 1968.29	5159.65 ± 4342.81	53.0–539.0
AST (IU/L)	480.5 ± 345.29	1552.45 ± 1535.66	1006. 53 ± 367.85	15–56
ALT (IU/L)	247 ± 149.7	241.74 ± 137.78	247.75 ± 141.35	21–73
ALP (IU/L)	324.25 ± 106.42	338.08 ± 149.34	305.86 ± 110.81	20–156
GGT (IU/L)	16.5 ± 9.98	22.19 ± 16.10	25.02 ± 12.35	1.2–6.4
BIL (mg/dL)	0.33 ± 0.11	1.47 ± 2.53	1.93 ± 2.45	0.0–0.3
UREA (mg/dL)	104.25 ± 98.83	136.36 ± 151.6	145.73 ± 151.04	21.4–59.9

Table 2. *Cont.*

Biochemical Variables	T1	T2	T3	Reference Range [20]
CREA (mg/dL)	1.7 ± 0.78	2.41 ± 2.9	3.04 ± 3.51	0.5–1.5
TP (g/dL)	5.15 ± 2.17	6.33 ± 3.8	2.53 ± 3.36	6.0–8.0

T1 (within 24 h of snakebite); T2 (within 24–48 h of snakebite); T3 (>48 h of the snakebite); CPK = creatine phosphokinase; AST = aspartate aminotransferase; ALT = alanine aminotransferase; GGT= gamma-glutamyl transferase; ALP = alkaline phosphatase; UREA = urea; CREA = creatinine; BIL = bilirubin; TP = total protein.

Evaluation of coagulation parameters revealed a significant reduction in activated partial thromboplastin time (aPTT) at T2 and T3 compared to T1 ($p = 0.002$ and $p = 0.001$, respectively), as well as a decrease in prothrombin time (PT) ($p = 0.006$ and $p = 0.02$, respectively). Conversely, fibrinogen concentrations were markedly elevated at T2 and T3 (both $p \leq 0.001$) and were accompanied by a significant increase in antithrombin III activity ($p = 0.02$ and $p = 0.02$, respectively) (see Table 3).

Table 3. Coagulation parameters expressed as mean and standard deviation (SD) at T1, T2 and T3.

Coagulative Parameters	T1	T2	T3	Reference Range [20]
aPTT (s)	74.1 ± 39.65 ^{AB}	23.7 ± 13.66 ^{A}	27.8 ± 11.34 ^{B}	11.0–17.5
PT (s)	48.85 ± 47.60 ^{AB}	12.6 ± 5.98 ^{A}	21.73 ± 2.74 ^{B}	11.0–15.5
FDPs (mcg/mL)	2.6 ± 0.29	2.62 ± 0.43	2.64 ± 0.51	<10
D-DIM (ng/mL)	1.96 ± 0.30	0.62 ± 0.21	0.32 ± 0.13	0–400
FIB (mg/dL)	89.6 ± 17.98 ^{AB}	843 ± 52.39 ^{A}	845.2 ± 54.04 ^{B}	113–385
AntiThromb III (%)	92.2 ± 11.38 ^{a}	116.4 ± 9.34 ^{A}	115.4 ± 5.7 ^{A}	65–145

T1 (within 24 h of snakebite), T2 (within 24–48 h of snakebite), T3 (>48 h of the snakebite), PTT (Partial Thromboplastin Time), aPTT (Activated Partial Thromboplastin Time), PT (Prothrombin Time), FDPs (Fibrin Degradation Products): D-Dimer; Fibrinogen; and Antithrombin III. Lowercase letters in the superscripts indicate a statistical significance between rows ($p < 0.05$). Capital letters in the superscripts indicate a statistical significance between rows ($p < 0.01$).

Other reported abnormalities included toxic changes to neutrophils, reticulocytes, spherocytes, sphero-echinocytes and rouleaux. Polychromasia and hypochromia were also observed, as were Howell-Jolly bodies and codocytes. These changes were evident in blood smears taken at various times after the snakebite (see Table 4 and Figures 1–4).

Table 4. Abnormalities in blood smears recorded at T1, T2 and T3.

Blood Smears Abnormalities	T1	T2	T3
Toxic change in neutrophils	2/12 (25%)	6/12 (50%)	6/12 (50%)
NRBCs	6/12 (50%)	3/12 (30%)	5/12 (41.6%)
Spherocytes	6/12 (50%)	6/12(50%)	6/12 (50%)
Spheroechinocytes	6/12 (50%)	9/12 (75%)	9/12 (75%)
Rouleaux	5/12 (41.6%)	6/12 (50%)	4/12 (33.4%)
Spherocytes	6/12 (50%)	6/12 (50%)	6/12 (50%)
Polychromasia	4/12 (33.4%)	5/12 (41.6%)	6/12 (50%)
Hypochromasia	0/12 (0%)	9/12 (75%)	6/12 (50%)
HJ bodies	3/12 (30%)	4/12 (33.4%)	3/12 (30%)
Codocytes	0/12 (0%)	4/12 (33.4%)	4/12 (33.4%)

T1 (within 24 h of the snakebite); T2 (within 24–48 h of the snakebite); T3 (>48 h of the snakebite); NRBCs = nucleated red blood cells; HJ bodies = Howell–Jolly bodies.

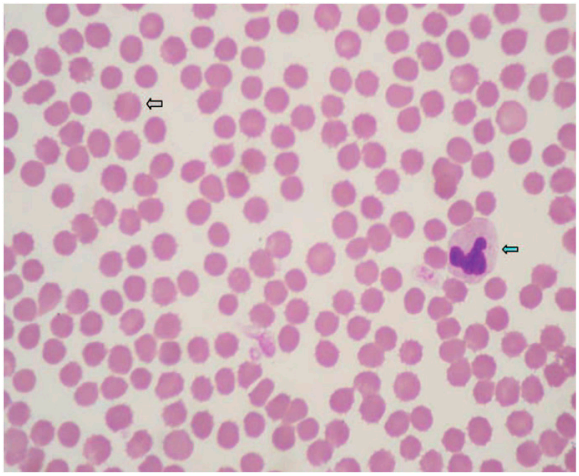

Figure 1. Blood smear of one of the dogs (ID1) included in the study. Venom within 24 h of the event. Sphero-echinocytes (erythrocytes lacking central pallor with a jagged outline and regular spicules along their entire circumference) (grey arrow). A neutrophil with a visible Döhle body inside (blue arrow). There is an almost total absence of platelets. Wright, 100× (immersion).

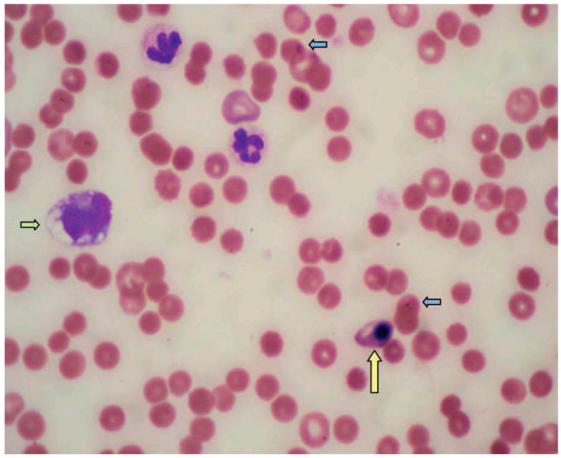

Figure 2. Blood smear of one of the dogs (ID4) included in the study. Viper venom, 24 h after the event. Spherocytes and erythrocytes with central pallor. Also present are Howell-Jolly bodies (blue arrow), one NRBC (yellow arrow), a vacuolated monocyte (green arrow), and two neutrophils with cytoplasmic foam. Rare platelets. Wright, 100× (immersion).

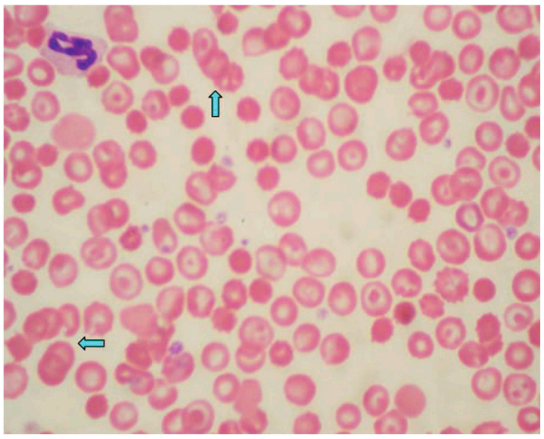

Figure 3. Blood smear of one of the dogs (ID3) included in the study. Viper venom, 24 h after the event. Rouleaux (stacking of erythrocytes) (blue arrows). Wright, 100× (immersion).

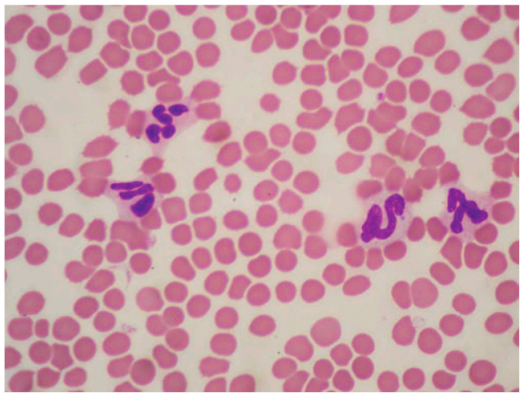

Figure 4. Blood smear of one of the dogs (ID11) included in the study. Viper venom, 48 h after the event. There is a significant decrease in sphero-echinocytes, foamy leukocytes and Döhle bodies, as well as thrombocytopenia. Wright, 100× immersion.

4. Discussion

Dogs are particularly susceptible to envenomation due to their behaviour and exposure during outdoor activities. Young and curious individuals are at a higher risk, with the mean age distribution being ≤5 years, as reported.

The clinical presentation can vary greatly, ranging from mild local effects to severe systemic manifestations. Affected dogs can develop distributive shock, showing clinical indicators such as fast heart rate, reddened mucous membranes, shortened capillary refill time, and low blood pressure, as noted in the evaluated study group.

Other anomalies may be observed due to the activity of the venom, such as enhanced leakage of fluids from blood vessels, profound disturbances in coagulation processes, modified cardiac function, neurological impairment, depressed respiratory activity, and muscle tissue necrosis. Toxins may also sometimes impair cardiac function, potentially resulting in oedema and hypovolemic shock [7,11].

Treatment strategies typically include a combination of specific therapies, such as antivenom administration, alongside supportive care including fluid therapy, antibiotics and glucocorticoids. Glucocorticoids exert anti-inflammatory actions by limiting capillary widening and suppressing the release of vasoactive amines [21]. However, the use of glucocorticoids remains controversial due to conflicting evidence regarding their efficacy in modulating inflammatory responses and improving outcomes [22–25]. Due to their habit of walking and smelling with their noses near the ground, dogs are most commonly bitten in the head, nose and extremities [8,22]. Of the dogs included in the study, a large group (75%) were bitten in the front or hind limbs, and the majority (58.4%) died within 48 h. These differences may reflect variations in environmental exposure, behavioral responses, or circumstances surrounding the envenomation in our study population. In research conducted by Segev and colleagues involving 327 dogs bitten by *Daboia palaestinae*, fatalities were more likely when the bites occurred on the limb extremities [10]. Various studies have suggested that phospholipase A2 (PLA2) enzymes in snake venom play a key role in early morbidity and mortality following a snakebite [26,27]. PLA2 exerts its effects through the degradation of cell membranes, resulting in tissue destruction (necrosis and myonecrosis) and disruption of homeostatic mechanisms critical for the regulation of coagulation and oxygen transport [28–31].

These processes can determine the onset of extensive local and systemic damage, also contributing to life-threatening outcomes, such as cardiorespiratory arrest and paralysis. The severity of these effects varies depending on the specific PLA2 subtype and its concen-

tration. The use of an inhibitor of secretory PLA2, such as varespladib, has been suggested as a potential treatment for severe snake envenomation in dogs [32].

The financial implications of treatment can play a significant role in clinical decision-making [33–35]. In our experience, these costs often affect an owner's willingness or ability to pursue continued care, particularly when prolonged hospitalization, antivenom administration, or advanced supportive therapies are required. Economic considerations frequently become intertwined with discussions regarding prognosis and anticipated duration of critical care, and in some cases may contribute to decisions about euthanasia when the outlook is uncertain or guarded. Beyond individual cases in dogs, viper bites also impose broader economic consequences, associated with the financial burden of envenomation in humans, horses, and livestock. Incorporating economic factors, including medical expenses, loss of animal productivity, and the financial repercussions of morbidity or mortality, provides a more comprehensive understanding of envenomation severity [26,27,32].

Additionally, viper venom includes enzymes that promote the release of internal cytokines and other inflammatory agents. The frequency of secondary infections after Vipera berus bites in Swedish dogs has not been established, nor is it clear whether antibiotic treatment (such as cefazolin or ceftriaxone) provides any advantage [1]. Although viperid snakes carry substantial oral and fang contamination with numerous potentially pathogenic bacteria, reports indicate that human envenomation rarely leads to bacterial infections [36].

Our study also indicated that none of the dogs exhibited any clinical signs of infection, despite being treated with antibiotics. Secondary bacterial infections can significantly contribute to complications, particularly when extensive tissue necrosis occurs, potentially leading to severe soft tissue and systemic effects [37]. None of the dogs in the present study were treated with antivenom serum (immunoglobulin-based). Given that antivenom can still provide clinical benefit when administered late in animals with systemic signs, it is notable that the majority of our cohort presented 8–12 h after the bite—well beyond the optimal window for antivenom efficacy [38–41]—by which time systemic signs had already developed. This delay likely influenced the clinical management and outcomes observed in our population, and highlights the challenges associated with delayed presentation in this setting [42]. Treatment with antiserum is the only way to inactivate the enzymes in the venom by binding them to the antiserum's antibodies [38]. Antiserum should be considered for severely affected dogs for whom supportive therapy is ineffective [22,24,43,44].

Haematological alterations recorded upon admission included anaemia, leucocytosis and thrombocytopenia. The decrease in platelet counts observed at T_2, together with the concomitant rise in MPV, aligns with the thrombocytopenic effects typically described in viperid envenomation for the effects resulting from proteolytic enzymes and PLA2 capable of inducing platelet activation, aggregation, and consumption, as well as contributing to vascular endothelial damage, resulting in accelerated platelet removal from circulation [45,46]. The increase in MPV, although not significant, is consistent with two complementary processes such as platelet activation and a compensatory bone-marrow response (larger platelets are released following acute peripheral consumption, suggesting that consumption-mediated platelet loss predominates early, while regenerative mechanisms are already underway.

Biochemical test alterations included increased BUN and CREA, as well as increased ALT, AST, ALP, and CPK. The biochemical changes observed here are consistent with those reported by other researchers. Aroch and Harrus [23] described comparable alterations in dogs poisoned by *Vipera xanthina palestinae*, except for notable creatine kinas (CK) and glutamate dehydrogenase values. Elevation of ALT and AST is a frequent biochemical finding in dogs following viper envenomation. This increase could be correlated with the myotoxic effects associated with the action of myotoxic components such as phospholipase

A_2 isoenzymes, metalloproteinases, and other proteolytic factors [21,47,48]. These toxins induce disruption of myonecrosis and lead to substantial leakage of AST into the bloodstream and concurrent increase in CK. Also, systemic effects of viper envenomation—such as hypotension, coagulopathies, and microvascular disturbances—can compromise hepatic perfusion, contributing to increased ALT, more specific to liver parenchyma [13,49]. The high CK values recorded at T2 suggest the onset of renal and muscle damage, which was probably caused by a local muscle injury at the snakebite site, given that there was no evidence of renal failure [11,40]. A decrease in serum creatinine values was observed in 82% of the sampled dogs between the T1 and T2 examinations. This could be associated with a reduction in glomerular filtration rate after the administered fluid therapy [50,51].

Cytological alterations included Döhle bodies, toxic granulation, spherocytes, echinocytes, sphero-echinocytes, rouleaux formation, nucleated red blood cells (NRBCs) and hypochromia.

Cytoplasmic abnormalities observed in the neutrophils, such as Döhle bodies (pale blue inclusions) and toxic granulation (larger, darker granules), suggest accelerated neutrophil production and maturation, which is typically associated with inflammation, infection, stress, or cytokine therapy [52]. Therefore, these changes indicate the body's increased response to viper venom, affecting the appearance of neutrophils as they are released from the bone marrow.

About erythrocytes, it is possible to observe the formation of spheroidal erythrocytes, also known as spherocytes. These are characterised by the loss of part of the outer membrane, a smaller diameter than normal erythrocytes, and an absence of central pallor. This anomaly is commonly seen to some degree in all haemolytic anaemias: for example, in cases of hereditary spherocytosis or autoimmune haemolytic anaemia, which are characterised by spherocytes being the only haematological variation present [53]. Considering the presence of other morphological alterations of erythrocytes in our cases, it is likely that spherocytes were formed due to the activity of phospholipases present in viper venom. Echinocytes, which are cells like erythrocytes, but characterised by a smaller size, an absence of central pallor, and numerous membrane projections arranged regularly and symmetrically, were also found alongside spherocytes. These cells appear transiently following venomous snake bites due to the action of phospholipase present in the venom. Echinocytes and spherocytes have also been found in combination as sphero-echinocytes. According to some studies, various types of venom, including bee (*Apis mellifera*), redback spider (*Latrodectus mactans*), blue-ringed octopus (*Hapalochlaena maculosa*), ten different snake venoms, phospholipase A2, and four snake venom components, cause sphero-echinocytosis of human red blood cells [54]. Therefore, the formation of sphero-echinocytes could be considered a general sign of venom activity in both humans and dogs. Studies have indicated that most venoms and toxins are unable to alter human red blood cells when molecules weighing less than 10,000 are present [54]. The absence or low number of sphero-echinocytes in these dogs could imply exposure to minimal amounts of viper venom. These erythrocyte membrane modifications cause erythrocytes to lose their ability to repel each other, resulting in the formation of persistent aggregates of cells known as rouleaux.

Rouleaux formation is typically associated with hyperglobulinaemia in dogs. Specifically, an increase in two types of globulins can result in rouleaux formation: fibrinogen (a protein released during the acute-phase response) and immunoglobulin (a complex glycoprotein produced by plasma cells that acts as an antibody and forms part of the immune system) [55]. These two types of globulins both increase in the event of inflammation or antigenic stimulation. Considering that the venom causes vascular damage, protein release and severe coagulation alterations (with the potential for destruction and consumption of factors, as well as the release of debris), the changes induced by the venom in the plasma environment may also affect the stability and aggregation of red blood cells. Direct haemolysis

caused by viper venom, combined with indirect haemolysis due to the increased fragility and tendency towards aggregation of modified erythrocytes (echinocytes, spherocytes and sphero-echinocytes), results in an elevated presence of NRBCs in the peripheral blood. NRBCs are immature red blood cells containing a nucleus that are usually found in the bone marrow, but not in the circulating blood of healthy adults [56]. The presence of NRBCs in the peripheral blood, known as polychromasia, indicates a significant underlying medical condition such as anaemia, severe hypoxia, sepsis, leukaemia, or bone marrow stress. Their presence is often associated with increased mortality and adverse outcomes [57].

Hypochromia is a medical term used to describe red blood cells that appear paler than normal, indicating that they contain an insufficient amount of haemoglobin. This condition is often a sign of anaemia, the most common cause of which is iron deficiency. Under a microscope, hypochromic cells appear pale due to the reduced amount of haemoglobin, which carries oxygen, increasing central pallor [58]. Hypochromia is related to haemolytic anaemia caused by viper venom, which increases the production of erythrocytes. However, this increase is not balanced by an adequate iron intake, leading to the production of iron-deficient erythrocytes [59].

Finally, alterations to the coagulation cascade included elevated levels of aPTT, PT, antithrombin III, and fibrinogen.

The proteases contained in viper venom interfere with the normal activation of the coagulation cascade by degrading the molecules involved in the process. Following a viper bite, elevated aPTT and PT values are frequently found [60]. These values indicate prolonged blood clotting time, significantly increasing the risk of spontaneous haemorrhage. Viper venom can cause coagulation disorders such as disseminated intravascular coagulation (DIC), mucosal haemorrhages, and prolonged bleeding at the site of the bite. At time T1, the aPTT and PT values are higher because the enzymes in the venom act quickly. The subsequent decrease in these values after 24 and 48 h (T2 and T3, respectively) is due to treatment with dexamethasone. Fibrinogen, an acute-phase reactant, is a non-specific protein associated with inflammation. A decrease in fibrinogen levels, and therefore its consumption, is indicative of DIC [61]. However, 24 h after the viper bite (T2), fibrinogen levels were found to be increasing, indicating an inflammatory response rather than DIC. Also, the rise in fibrinogen concentration (rather than a drop) could reflect a compensatory acute-phase response consequent to envenomation inflammation, cytokine release (e.g., IL-6), and hepatic upregulation of acute-phase proteins. Although specific data in dogs are limited, this is a common mechanism in systemic inflammation [62–64].

Elevated antithrombin III levels 24 and 48 h after the viper bite (T2 and T3) indicate specific systemic inflammation. However, these increases remained within the physiological range for dogs [16,62].

Viper bites in dogs are a true medical emergency, with the severity of the clinical manifestations depending on various factors, such as the amount of venom injected, the location of the bite, the species of viper involved, and the size and health of the dog.

It is essential to promptly recognise local symptoms such as swelling, pain, and necrosis, as well as systemic signs such as lethargy, tachycardia or bleeding tendencies, to enable early therapeutic intervention.

The results demonstrate that systemic involvement is common and can progress rapidly from local tissue damage to life-threatening complications, such as coagulopathies, shock and multi-organ dysfunction. Haematological analysis consistently revealed evidence of haemoconcentration, thrombocytopenia and varying degrees of anaemia, reflecting both haemolytic and consumptive processes. Laboratory findings, particularly alterations in coagulation parameters and biochemical profiles, confirmed the systemic toxic effects of the venom. These effects include endothelial damage, activation of coagulation pathways

and secondary inflammatory responses. These changes emphasise the need for continuous monitoring and serial laboratory evaluations during the acute and recovery phases of envenomation.

This study presents potential limitations that should be considered when interpreting the findings. First, the small sample size limited the statistical power of the analysis. It may have prevented the detection of significant changes in clinical status, biochemistry parameters, or coagulation profiles associated with the time elapsed between the bite and clinical evaluation. Similarly, the limited number of cases may have hindered the identification of more pronounced differences in the most severe presentations or in those that resulted in fatality. An additional consideration is the inclusion of animals that underwent euthanasia, which may have introduced a severity-related selection bias and influenced the distribution of clinical outcomes. Additionally, the study did not evaluate the potential effects of treatments, such as corticosteroid administration, on clinical outcomes, nor did it assess the impact of the timing of antivenom administration on clinical, biochemical, or haematological changes. Overall, these limitations reduce the generalizability of the results and highlight the need for future studies with larger sample sizes and more standardised data-collection protocols. The study did not evaluate the potential effects of treatments, such as corticosteroid administration, on clinical outcomes. Additionally, the impact of the timing of antivenom administration on clinical, biochemical, and haematological changes in dogs with *Vipera aspis* envenomation was not assessed.

5. Conclusions

In conclusion, a multidisciplinary approach is required for the diagnosis and treatment of canine viper envenomation, based on clinical assessment, haematological and biochemical monitoring, and evidence-based intervention. Further studies are needed to refine treatment protocols, identify prognostic biomarkers, and evaluate the long-term consequences of envenomation. Improving veterinary awareness and access to antivenom therapy is crucial to reducing the morbidity and mortality associated with viper bites in dogs.

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