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The Role of Procalcitonin in Predicting Necessity of Antivenom Administration and Clinical Severity in Snake Bites

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One of the most important steps for preventing deaths due to snake bites is to administer snake antivenom to the eligible patients in a swift manner. In our study, we aimed to investigate whether procalcitonin is useful for predicting the clinical severity and the necessity of antivenom therapy at the early stages in patients presenting with snake bite. A total of 78 patients over the age of 18 who applied to the emergency department within the first 24 hours were included in this retrospective cross-sectional study. Age and sex of patients, severity of snake bites, total antivenom vials administered, observation periods and outcomes were recorded. Patients were graded according to their clinical severity after the snake bite. Procalcitonin, complete blood count and biochemical parameters of the patients were recorded. According to their clinical severity, the patients' grades were as follows: 21 (26.9%) patients were grade 0; 21 patients (26.9%) were grade 1; 16 patients (20.5%) were grade 2; and 20 patients (25.6%) were grade 3. Snake antivenom was administered to 57 (73.1%) patients. There was a statistically significant difference between procalcitonin levels of patients in respect to their grade ($P < 0.001$). Sensitivity and specificity of procalcitonin levels of 13.45 and above were 100% and 100% respectively, both for the need of antivenom administration and for the blister formation in the patients. According to our study, we believe that elevated procalcitonin levels should alert the clinicians for possible blister formation, higher clinical severity, and increased requirement for antivenom administration.

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Introduction

The World Health Organization (WHO) estimates that there are a total of 5.4 million snake bites annually worldwide of which approximately 2.7 million are venomous, and approximately 5% of these venomous snake bites result in death (137,880 deaths per year) (WHO 2019). Snake bites in Turkey commonly occur in hot regions such as the Southeastern, Eastern Anatolia regions and Mediterranean region where our hospital is located (Aslan et al. 2019). Out of more than 40 snake species living in our country, 28 species are non-venomous while 13 species are venomous, and the most common group among poisonous species is the Viperidae (viper) family (Bilir 2020).

Snake venom may be loosely defined as "antigen soup" as it contains a plethora of complex enzymes and toxic proteins such as metalloproteinases, collagenase, phospholipase and hyaluronidase, which can cause myonecrosis and dermatonecrosis (Gutierrez et al. 2007). Tumor necrosis factor (TNF)-α, a cytokine increased by the inter-

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action and stimulation of these proteins, is one of the most potent inducers that plays a role in myonecrosis and inflammation caused by snakebite and in the procalcitonin (PCT) release (Szold et al. 2001; Lu et al. 2005; Kara 2011; Acikalin and Gokel 2011).

While production and secretion of PCT is regulated by C cells of the thyroid gland in normal metabolic conditions, increased release of this peptide precursor in the presence of bacterial infections is caused by neuroendocrine cells in the lung, liver, skin, intestines and pancreas (Meisner 2000; Gendrel and Bohuon 2000). This production of PCT is stimulated by bacterial endotoxins, exotoxins and some cytokines. In experimental conditions, bacterial endotoxins and TNF-α are shown to be most potent inducers of PCT (Ortatatli et al. 1999; Maruna et al. 2000).

Careful monitoring, supportive treatment and administering antivenom treatment to the eligible patients in a swift manner can reduce morbidity and mortality significantly in patients presenting with snake bites (Altun et al. 2016). In our study, we aimed to investigate whether PCT is a useful parameter for predicting clinical severity of snake bites and necessity of antivenom therapy at the early stages.

Methods

Patient selection

Our study was a cross-sectional study and conducted retrospectively after obtaining ethical consent from our hospital's ethics committee (Adana City Training and Research Hospital Clinical Research Ethics Committee, meeting date: June 2, 2021, meeting number: 82, decision number: 1427). Using the ICD-10 diagnostic coding system, T63 and subgroup codes (Toxic effect of contact with animals) and X20 (Contact with venomous snakes and lizards) codes were scanned within the hospital's information management system. The data of patients applied to our emergency medicine clinic between January 01, 2019 and December 31, 2020 were scanned. Information of 288 patients were obtained. Exclusion criteria were as follows: Patients aged < 18 years, patients with insufficient data, patients who applied to the emergency department after more than 24 hours from the snake bite, patients who have made an incision at the bite site, patients whose lesions have sign of fluctuation due to the presence of infection, patients with drug use that may cause bleeding diathesis, patients who have additional diseases that cause bleeding disorder, patients diagnosed with rheumatologic and oncologic disorders and were either immunocompromised or received neoplastic drug therapy, patients with heart failure and chronic kidney disease/failure, patients who refused the treatment and patients who were referred to another emergency center, or bitten or stung by an animal other than a snake. A total of 79 patients under the age of 18 years were excluded from the study. Out of the remaining 209 files which were examined individually, 131 patients who met the exclusion criteria were excluded from the study. Eventually, a total of 78 patients were included in the study (Fig. 1). The

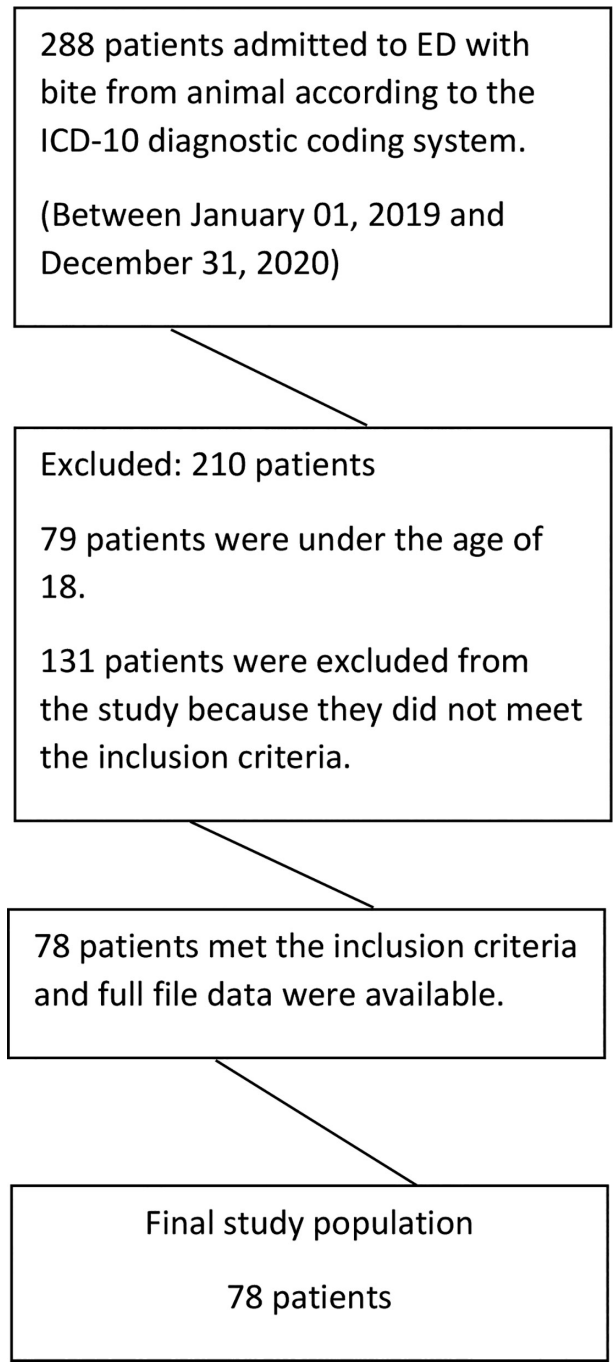

Fig. 1. Flow chart of the patients included in the study. ED, emergency department.

patients' age and sex, the severity of snake bites, the total antivenom vials administered, and the patients' observation periods and outcomes were recorded.

Snake bite severity grading score

Patients without signs of local or systemic poisoning findings 6-8 hours after the bite were accepted as grade 0 (Riley et al. 2011; Bilir 2020). A total of 21 (26.9%) patients who met this criterion were included in the grade 0 group. Patients with mild tissue swelling or pain, normal

laboratory findings, and no systemic findings were accepted as grade 1 (Riley et al. 2011; Bilir 2020). A total of 21 (26.9%) patients who met this criterion were included. Patients with progressive swelling, ecchymosis with pain, mild systemic symptoms, and mild laboratory changes such as minimal thrombocytopenia were accepted as grade 2 (Riley et al. 2011; Bilir 2020). A total of 16 (20.5%) patients who met this criterion were included. Patients with progressive swelling, severe pain in the bitten area accompanied with ecchymosis, hemorrhagic vesicles, necrosis or compartment syndrome; severe systemic symptoms, rhabdomyolysis, acute renal injury, and severe thrombocytopenia and/or coagulopathy were accepted as grade 3 (Riley et al 2011; Bilir 2020). A total of 20 (25.6%) patients who met these criteria were included. Worsening of local edema, manifestation of systemic findings and deterioration of laboratory parameters were considered as grade progression in the follow-ups.

Characteristics of the antivenom used

The antivenom used in the treatment was polyvalent snake antivenom. Each 10 ml of antivenom contains at least 500 LD50 Macrovipera lebetina, 500 LD50 Montivipera xanthina and 1000 LD50 Vipera ammodytes equine antitoxic immunoglobin fragments that neutralize snake venom. The total amount of protein is ≤ 100 mg/ml, M-Cresol ≤ 3.5 mg/ml and NaCl 85-95 mg/ml.

Management of patients

All patients who applied to the emergency department due to snake bite were first evaluated in terms of their airway, respiration and circulation status at the time of admission. Intravenous access was established in all patients and blood samples for laboratory tests were taken simultaneously. The limb with the snake bite was immobilized. The patients were admitted to the emergency/intensive care unit for close follow-up and they were constantly monitored and observed for systemic and local findings. Appropriate fluid therapy was initiated, wound care was performed and tetanus prophylaxis was applied if necessary. Antivenom therapy was administered to patients whose clinical stage were 1, 2 or 3.

Laboratory analysis

The patients' complete blood count and biochemical parameters were measured from the samples taken from veins of antecubital region at the first admission. White blood cell count (WBC), hemoglobin, hematocrit levels, platelets, monocyte count, neutrophil count, blood urea nitrogen (BUN), creatinine, C-reactive protein (CRP), prothombin time (PTZ), INR, activated partial thromboplastin time (aPTT) and PCT levels were measured. Complete blood count measurements were performed using the Sysmex XN 10 automated measuring device (Automated Hematology Analyzer XN series, Sysmex Corporation, Kobe, Japan). Measurement of biochemical parameters were performed using the automatic measuring device Beucher Coulter AU5800 (Beckman Coulter GmbH, Krefeld, Germany). PCT measurement was performed using the Access PCT method with the chemiluminescence immunoassay (CLIA) principle, using the UniCel DXI automated measuring device (Beckman Coulter Inc., Brea, CA, USA).

Statistical evaluation

SPSS (Statistical Package for the Social Sciences) 23.0 package program was used for statistical analysis of the data. Categorical measurements were summarized as numbers and percentages, and continuous measurements were summarized as mean and standard deviation (median and minimum-maximum where appropriate). Shapiro-Wilk test was used to determine whether the parameters in the study showed a normal distribution. Independent t-test was used for paired group analysis and one-way ANOVA test was used in presence of more than two groups with normally distributed parameters. Mann-Whitney U test was used for paired groups and Kruskal-Wallis test was used in presence of more than two groups for parameters without normal distribution. In order to determine the source of the difference between the groups, Post Hoc Tests were used for parameters with normal distribution, Bonferroni tests, and Tamhane's T2 tests were used for parameters that did not show normal distribution. Based on the presence of vesicles in the patients included in the study, sensitivity and specificity values were calculated for the PCT levels and cut-off value was determined by the area under the receiver operatorating characteristic (ROC) curve. The level of statistical significance is accepted as $P < 0.05$ in all tests.

Results

A total of 78 cases were included in the study. The mean age was 37 years, and 56 (71.8%) of the patients were male. More than half of (73.1%, n = 57) patients were administered snake antivenom, and thirty-three (42.3%) patients had vesicle formation. Mean observation period was 34 ± 26.13 hours. Demographic data of the patients, their biochemical parameters, complete blood count values and their distribution according to vital signs are presented in Table 1.

There was no statistically significant difference between sex, age, temperature, pulse rates, oxygen saturation, systolic blood pressure, diastolic blood pressure values of patients and the presence of vesicles, PCT elevation and grading scores of the patients ($P > 0.05$). Comparison of patients' demographic data, complete blood count parameters and vital signs with presence of vesicles and PCT elevation are presented in Table 2.

Presence of vesicles ($P < 0.001$), frequency of patients with severity scores higher than grade 1 ($P = 0.001$), observation periods ($P = 0.025$), and rate of antivenom administration were found to be higher in patients with high PCT values compared to patients with low PCT values (Table 2).

Table 1. Evaluation of demographic data, biochemical parameters, complete blood count values and vital findings of the patients.

	Frequency (n)	Percentage (%)
Sex		
Male	56	71.8
Female	22	28.2
Presence of vesicles		
No	45	57.7
Yes	33	42.3
Grade		
0	21	26.9
1	21	26.9
2	16	20.5
3	20	25.6

	Mean ± SD	Median (Minimum-Maximum)
Age (years)	40.29 ± 15.99	37 (18-77)
Temperature (°C)	36.52 ± 0.29	36.5 (36-37.5)
Pulse (beat/min)	80.82 ± 14.22	80 (52-110)
SBP (mmHg)	126.02 ± 14.8	120 (90-160)
DBP (mmHg)	76.53 ± 10.29	70 (60-100)
SpO_2 (%)	98.47 ± 1.38	99 (95-100)
Procalcitonin	4.93 ± 6.13	1.23 (0.01-27.06)
CRP (mg/L)	5.15 ± 7.92	2.05 (0.03-48.7)
Platelets (10^3/µl)	207.92 ± 66.11	211 (26-371)
WBC (10^3/µl)	11.24 ± 4.75	10.25 (4.7-33.9)
Neutrophils (10^3/µl)	8.51 ± 5.17	7,0 (2,2-31,0)
Antiserum (vials)	6.05 ± 6.13	4 (0-22)
Observation time (hour)	34 ± 26.13	29 (6-96)

SBP, systolic blood pressure; DBP, diastolic blood pressure; SpO_2, blood oxygen saturation; CRP, C-reactive protein; WBC, white blood cell.

PCT elevation ($P \leq 0.001$), frequency of patients with severity scores higher than grade 1 ($P = 0.001$), observation periods ($P < 0.001$) and rate of antivenom administration were found to be higher in patients with vesicles compared to patients without vesicles (Table 2). The incidence of vesicles ($P < 0.001$) and frequency of PCT elevation ($P = 0.001$) was found to be higher in patients in the grade 2 and 3 groups than the patients in grade 0 and 1 groups (Table 2).

There was a statistically significant difference between the procalcitonin levels of patients according to their grade groups ($P < 0.001$). When the statistically significant difference between the groups is examined; PCT values were found to be higher in the patients in grade 2 and 3 groups compared to the patients in grade 0 and 1 groups (Table 3, Fig. 2). Difference was observed between patients' grade groups in regard to the amount of antivenom vials administered to the patients ($P < 0.001$) and the patients' observation time ($P < 0.001$) and this difference found to be statistically significant. Source of the difference between the groups was determined as with high grades having higher values than those with lower grade (Table 3, Fig. 2).

When CRP, platelet (PLT) count, WBC, and neutrophil values of patients were evaluated, these values were found not to be affected by PCT elevation, presence of vesicles and grade. However, PLT values were significantly lower only in patients with vesicles.

Sensitivity and specificity of PCT levels of 13.45 and above were 100% for the need of antivenom administration

Table 2. Comparison of patients' demographic data, biochemical parameters, complete blood count values and vital findings with presence of vesicles and procalcitonin values.

	Presence of vesicles			Procalcitonin		
	No	Yes	P-value	Low	High	P-value
	n (%)	n (%)		n (%)	n (%)	
Sex						
Male	29 (64.4)	27 (81.8)	0.092	49 (72.1)	7 (70.0)	0.893
Female	16 (35.6)	6 (18.2)		19 (27.9)	3 (30.0)	
Presence of Vesicles						
No				45 (66.2)	0 (0)	< 0.001
Yes				23 (33.8)	10 (100)	
Grades						
0	21 (46.7)	0 (0)	< 0.001	21 (30.9)	0 (0)	0.001
1	21 (46.7)	0 (0)		21 (30.9)	0 (0)	
2	2 (4.4)	14 (42.4)		10 (14.7)	6 (60.0)	
3	1 (2.2)	19 (57.6)		16 (23.5)	4 (40.0)	
Age (years) (u)	34 (18-77)	43 (19-70)	0.072	36,5 (18-77)	40 (19-63)	0.988
Temperature (°C) (u)	36,5 (36-37.4)	36,5 (36-37.5)	0.763	36,5 (36-37.5)	36,5 (36-36.8)	0.557
Pulse (beat/min) (t)	83.8 ± 14.1	76.7 ± 13.4	0.029	81.2 ± 14.0	78.2 ± 16.2	0.563
SBP (mmHg) (u)	120 (90-160)	120 (100-160)	0.384	120 (90-160)	120 (100-160)	0.235
DBP (mmHg) (u)	80 (60-100)	70 (60-100)	0.133	75 (60-100)	70 (60-100)	0.321
SpO_2 (%) (u)	99 (95-100)	98 (95-100)	0.004	99 (95-100)	99 (95-100)	0.423
Procalcitonin (u)	0.32 (0.0-3.06)	10.84 (3.32-27.06)	< 0.001	0.53 (0.01-13.2)	14.5 (13.45-27.06)	< 0.001
CRP (mg/L) (u)	1.9 (0.03-28.5)	2.8 (0.04-48.7)	0.102	1.95 (0.03-48.7)	5.4 (0.3-16.8)	0.256
Platelet (10^3/µl) (t)	226,64 ± 53.76	182,39 ± 73.33	0.003	212,7 ± 61.6	175,0 ± 88.0	0.092
WBC (10^3/µl) (u)	10.1 (4.7-33.9)	10.3 (6.2-22.5)	0.312	10.2 (4.7-33.9)	11.5 (7.1-22.5)	0.327
Neutrophiles (10^3/µl) (u)	6.6 (2.2-31)	8.3 (3-20.2)	0.081	6.95 (2.2-31)	7.1 (5.2-20.2)	0.207
Antiserum (vials) (u)	1,0 (0-18)	10 (6-22)	< 0.001	3 (0-22)	8 (6-14)	0.025
Observation time (hour)	12 (6-72)	52 (38-96)	< 0.001	21 (6-88)	48 (39-96)	0.002

Data are shown as n (%), mean ± SD, or median (minimum-maximum). Chi-square test, independent Student t-test (t), or Mann-Whitney u test (u) was used for statistics.
SBP, systolic blood pressure; DBP, diastolic blood pressure; SpO_2, blood oxygen saturation; CRP, C-reactive protein; WBC, white blood cell.

(Table 4, Fig. 3A-C).

Cut-off, sensitivity and specificity of this value were determined by ROC analysis of the PCT value, which differed significantly in relation to vesicle formation in patients. Presence of vesicle formation had 100% sensitivity and specificity in patients with a PCT level of 3.19 and above (Table 5, Fig. 3D).

Table 3. Comparison of demographic data, biochemical parameters, complete blood cell count values and vital findings of the patients with snake bite severity scores.

Grades (severity scores)	0	1	2	3	P-value
Sex					
Male	13 (61.9)	15 (71.4)	12 (75.0)	16 (80.0)	0.623
Female	8 (38.1)	6 (28.6)	4 (25.0)	4 (20.0)	
Presence of Vesicles					
No	21 (100)	21 (100)	2 (12.5)	1 (5.0)	< 0.001
Yes	0 (0)	0 (0)	14 (87.5)	19 (95.0)	
Procalcitonin					
Low	21 (100.0)	21 (100)	10 (62.5)	16 (80.0)	0.001
High	0 (0)	0 (0)	6 (37.5)	4 (20.0)	
Age (years) (χ2)	36 (18-77)	35 (18-72)	46.5 (19-70)	35.5 (19-70)	0.666
Temperature (°C) (χ2)	36.5 (36-37.4)	36.6 (36-37.1)	36.55 (36-37.5)	36.5 (36-37.2)	0.946
Pulse (beat/min) (F)	84.2 ± 13.0	84.0 ± 16.4	76.5 ± 16.2	77.2 ± 9.9	0.168
SBP (mm-Hg) (χ2)	120 (110-60)	120 (90-150)	120 (100-160)	125 (110-160)	0.545
DBP (mm-Hg) (χ2)	70 (70-100)	80 (60-90)	70 (60-100)	70 (60-90)	0.248
SpO2 (%) (χ2)	99 (95-100)	100 (97-100)	98 (95-100)	98.5 (96-100)	0.076
CRP (mg/L) (χ2)	1 (0.2-28.5)	2 (0.03-14.6)	3.35 (0.04-16.8)	2.2 (0.2-48.7)	0.173
Platelet (10^3/µl) (F)	220.2 ± 55.4	232.6 ± 56.3	183.1 ± 63.1	188.8 ± 79.0	0.052
WBC (10^3/µl) (χ2)	9 (4.7-20.7)	10.7 (6.5-33.9)	10.25 (6.9-22.5)	10.3 (6.2-21.2)	0.505
Neutrophiles (10^3/µl) (χ2)	6 (2.2-19.7)	7 (2.9-31)	7.8 (4.4-20.2)	7.8 (3-20)	0.249

Data are shown as n (%), mean ± SD, or median (minimum-maximum). Chi-square test, one-way ANOVA test (F), Kruskal-Wallis test (χ2), or Bonferroni & Tamhane's T2 test from Post Hoc tests was used for statistics.
SBP, Systolic blood pressure; DBP, Diastolic blood pressure; SpO_2, Blood oxygen saturation; CRP, C-reactive protein; WBC, White blood cell.

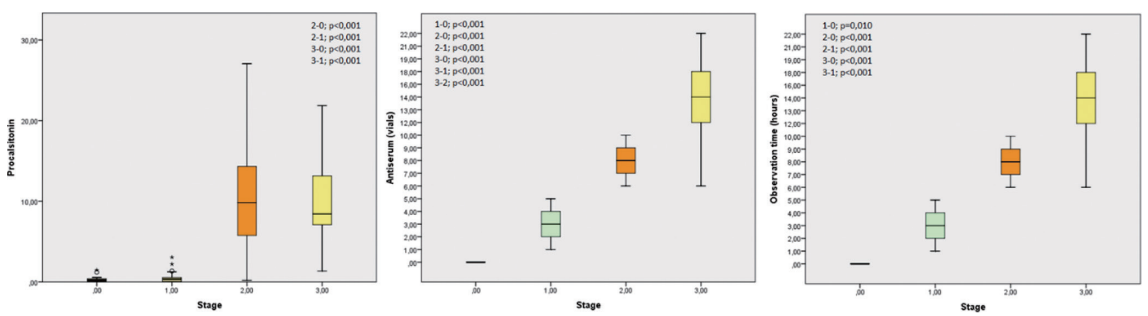

Fig. 2. Post hoc analysis of procalcitonin, the amount of given antivenom vials and observation time by the groups of the grades.

Table 4. Sensitivity and specificity analysis of procalcitonin levels regarding prediction of antivenom administration.

Procalcitonin	Sensitivity (95% CI)	Specificity (95% CI)	+PV (95% CI)	−PV (95% CI)	AUC (95% CI)
> 13.45	100.00 (89.4-100.0)	100.00 (92.1-100.0)	100.0 (100-100)	100.0 (100-100)	1.000 (0.954-1.000)
> 12.35	56.25 (29.9-80.2)	85.0 (62.1-96.8)	75.0 (49.2-90.3)	70.8 (57.5-81.3)	0.608 (0.431-0.766)
> 3.06	37.5 (15.2-64.6)	85 (62.1-96.8)	66.7 (37.1-87.1)	63 (52.7-72.2)	0.514 (0.342-0.684)

CI, confidence interval; +PV, positive predictive value; −PV: negative predictive value; AUC, area under the curve.

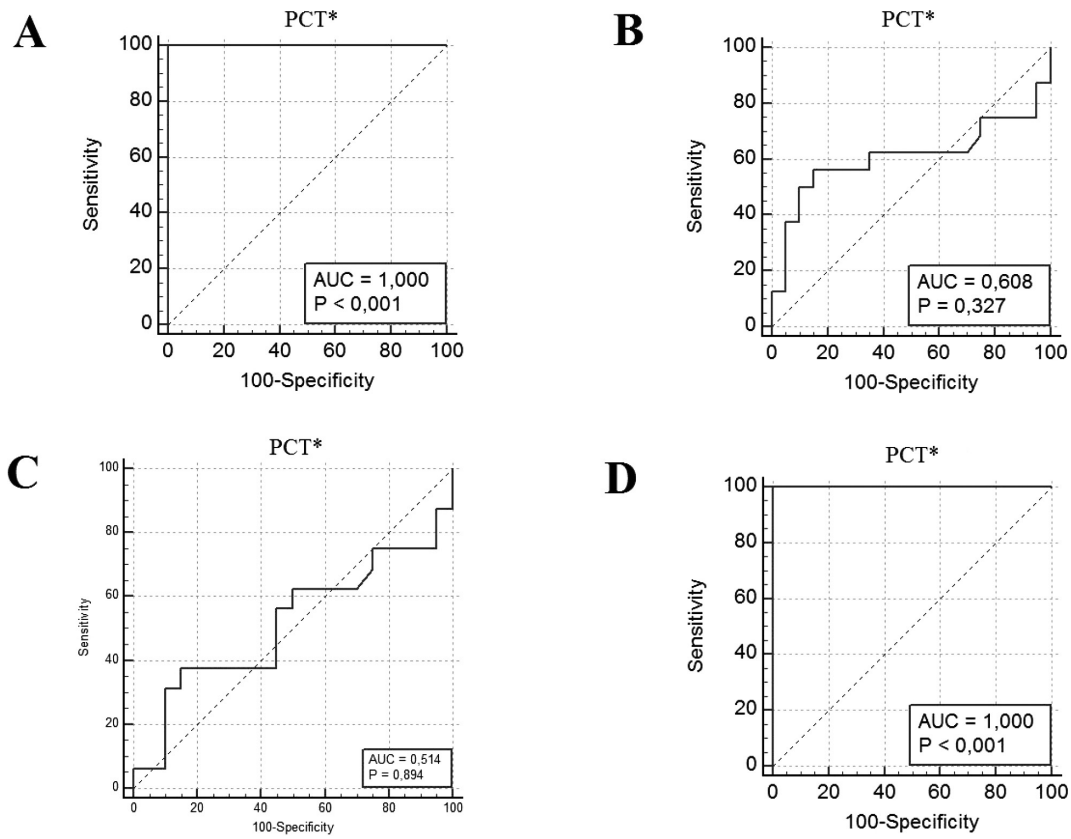

Fig. 3. ROC curve analysis of procalcitonin (PCT*).
(A, B, C) ROC curve analysis of PCT regarding prediction of antivenom administration when the cut-off value of PCT is taken as > 13.45 (A), > 12.35 (B), or > 3.06 (C). (D) ROC curve analysis of PCT in predicting vesicle when the cut-off value of PCT is taken as > 3.19.

Table 5. Sensitivity and specificity analysis of procalcitonin levels regarding prediction of vesicle formation.

Risk Factor	AUC (%95 CI)	Cut-off	P-value	Sensitivity (%)	Specificity (%)
Procalcitonin	1.000 (1.000-1.000)	3.19	0.000	100	100

AUC, area under the curve; CI, confidence interval.

Discussion

Snake bites are clinically dynamic encounters, as even seemingly insignificant bites may detoriate into severe, clinically challenging situations. Even patients with minimal signs of envenomation who do not initially require antivenom may need to be observed for 6-8 hours, sometimes up to 24 hours, for possible worsening of local symp-

toms and/or the development of any systemic or hematological toxicity.

Currently, no mediator is known to predict the necessity for antivenom administration after snake bites with absolute certainty. In our study, we investigated whether the PCT values are elevated in relation to the grades of clinical severity in patients with snake bites who were administered antivenom therapy. Out of 42 patients with grade 0 and grade 1 snake bite severity, a total of 21 patients were administered anti-venom vials due to progression in their severity scores.

Observation period of patients was 34 ± 26.13 hours on average, mean age of all patients was 37, and 56 (71.8%) of the patients were male. There was no mortality in the study groups. Our demographic data were mostly consistent with previous literatüre (Kara 2011; Gulen et al. 2020; Segmen et al. 2020). Again, in our study, we found that the grade of snake bite severity increased significantly in accordance with PCT levels especially in patients with grades 2 and 3, and PCT levels above 13.45 were predictive of the necessity of antivenom administration with 100% sensitivity and specificity. There was no statistically significant difference between different grades in terms of infection parameters which may be elevated because of the local infections caused by snake bites such as WBC, neutrophil and CRP values. In addition, we observed that PCT levels above 3.19 demonstrated presence of vesicle formations with 100% specificity and sensitivity.

Venom of the Viperidea family, the most common species responsible for snake bites in our country, contains many complex enzymes and toxic proteins as well as metalloproteinases (Okur et al. 2001). Metalloproteinases convert recombinant pro-TNF-α to TNF-α, and considering these enzymes also play a role in tissue damage. It is possible that TNF-α may be one of the culprits in the development of systemic and local findings in these envenomations. In the study of Gulen et al. (2020) regarding levels of TNF-α and IL-1 in snake bites, difference between TNF-α and IL-1 levels measured at the time of admission and at the 12th hour was found to be statistically significant (Kara 2011). In addition, Acikalin and Gokel (2011) demonstrated higher TNF-α levels in snake envenomation, which were elevated further as clinical severity of envenomation increased. Again, Petricevich et al. (2000) suggested that IL-1 and TNF-α may play a role in the pathophysiology of systemic changes resulting from envenomation. TNF-α is a potent PCT stimulant, and elevated TNF-α levels cause an increase in PCT values. In a study by Bammigatti et al. (2019), no statistically significant difference was found between baseline median PCT concentrations of patients with grade 2, 3 and 4 snake bite severity scores ($P = 0.15$); however, PCT levels of these patients were above normal limits. Therefore, Bammigatti et al. (2019) stated that PCT values could increase in a non-infectious manner in patients presenting with snake bites. In our study, we found that PCT levels were increased significantly as the grade of severity score increased in snake bites and this association was more pronounced in grades 2 and 3, and also PCT levels above 13.45 indicated the necessity of giving snake antivenom with 100% sensitivity and specificity. We attribute this difference between results of our study and the study of Bammigatti et al. (2019) to the frequent encounters of Viperadia snakes in our country, whose metallopreteases indirectly stimulate PCT, and to the majority of the patients included in our study having higher snakebite severity scores with necessity of snake antivenom.

Formation of vesicles is one of the important parameters regarding snake bite severity grading and whether to administer antivenom. In the study of Iliyasu et al. (2014), the rate of vesicle formation was 32.8%. Again, in the study conducted by Kumar et al. (2018) on 1,500 patients with snake bites, 201 (13.4%) of the patients had local cellulitis, necrosis or gangrene. The rate of these symptoms was 19.5% in the bites with Russell's viper type snakes in their study. In our study, vesicle formation was observed in 42.3% of the patients and snake antivenom was given to all of these patients. In addition, we observed PCT levels above 3.19 had 100% sensitivity and specificity for vesicle formation in our study. We think that the high number of both stage 2 and stage 3 patients and patients with bullae in our study is due to the fact that our hospital functions as a third level hospital due to its location and experience, and that patients with poor general condition or thought to have a worsening prognosis at the time of admission from external centers are frequently referred to our clinic. Our main purpose in the exclusion criteria is to exclude the reasons that may increase PCT levels other than snake venom and the reasons that may cause local symptoms other than snake venom. Therefore, we can state that our exclusion criteria did not affect the relationship between PCT and bullae. According to our study, we believe that procalcitonin levels above these values (3.19, and 13.45) are sensitive regarding vesicle formation and therefore are indicators of necessity of antivenom administration.

Snake bite severity scoring is crucial in observation, evaluation, treatment and discharge of patients with snake bites. Antivenom should be administered in most of the patients with grade 2 severity scores, and almost always in patients with grade 3 snake bites. In addition, deterioration of local symptoms or the emergence of systemic findings in patients with stage 0 or 1 indicate necessity of antivenom administration. Procalcitonin was found to be significantly higher in stages 2 and 3 compared to stages 1 and 2 in our study. Therefore, we believe that high PCT levels should alert the clinicians regarding to increased necessity of antivenom administration.

In conclusion, we think that high PCT levels should alert the clinicians for possible blister formation, higher clinical severity, and therefore increased requirement for antivenom administration. We believe that the results of this study can form the basis for multicentric, prospective studies with large series.

There are some important limitations in our study. Firstly, our study is conducted in a retrospective and cross-sectional manner. Another limitation is its reliance on patient information obtained from a single center. Further knowledge related to this subject can be obtained through prospective studies with a larger samples and involving more than one center. Because the PCT level of the patients was checked at the time of the patient's first admission, the time interval for PCT levels was not clear**.**

Author Contributions

Conception: F.I. and A.A., Design: F.I. and A.A., Supervision: F.I., A.A., B.S.A. and H.Y., Data collection: A.B.U., M.O.T., O.Y. and N.Y., Analysis: A.A., F.I., E.S., H.E.S., H.Y., B.S.A. and O.Y., Literature review: F.I., E.S. and A.A., Writer: F.I., E.S. and A.A., Critical review: F.I. and A.A.

Conflict of Interest

The authors declare no conflict of interest.

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