Original Article

Clotting Tests Associated with Hypofibrinogenemia and Systemic Bleeding in Green Pit Viper or Russell's Viper Bite Patients

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Background: Serum fibrinogen of less than 100 mg/dL is recommended for predicting systemic bleeding risk in hematotoxic snake bite patients, but it is not widely available. Data on using venous clotting time (VCT), 20-minute whole blood clotting test (20WBCT), platelets, prothrombin time (PT), international normalized ratio (INR), and partial thromboplastin time (PTT) to predict systemic bleeding in hematotoxic snake bite patients are limited.

Objective: To determine association between clotting tests (VCT, 20WBCT, platelets, PT, PTT, and INR) and 1) serum fibrinogen of less than 100 mg/dL, and 2) systemic bleeding in patients bitten by green pit viper (GPV) or Russell's viper (RV).

Materials and Methods: This prospective cohort study included patients bitten by GPV or RV at Sawanpracharak Hospital, Nakhon Sawan, Thailand, between October 2016 and December 2017. Patient's blood specimens were collected for fibrinogen, PT, INR, PTT, platelet count, VCT, and 20WBCT at initial presentation and every six hours until 24 hours of admission, or patients' recovery. The association were determined by using Fisher's exact test.

Results: There were 30 patients, 21 were bitten by GPV, and nine were bitten by RV. One hundred sixty-one sets of blood specimens were collected. There were four cases with systemic bleeding. Factors associated with fibrinogen of less than 100 mg/dL were VCT of 20 minutes or more (p=0.01), unclotted 20WBCT (p=0.01), PT of more than 13 seconds (p=0.04), and INR of 1.2 or more (p<0.01). Factors that associated with systemic bleeding were VCT of 20 minutes or more (p<0.01), unclotted 20WBCT (p<0.01), INR of 1.2 or more (p=0.04), and fibrinogen of less than 100 mg/dL (p=0.01).

Conclusion: VCT of 20 minutes or more, unclotted 20WBCT, and INR of 1.2 or more are associated with serum fibrinogen less than 100 mg/dL and systemic bleeding in GPV and RV envenomation.

Keywords: Green pit viper, Russell's viper, Fibrinogen, 20WBCT, VCT

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Snake bite is a health problem of tropical countries[1]. In Thailand, hematotoxic snake envenomation is commonly reported[2]. Serum fibrinogen of less than 100 mg/dL is reported to be the most accurate in predicting systemic bleeding risk in hematotoxic snake envenomation, but it is not widely available[3-5]. According to current recommendation in Thailand, hematotoxic snake antivenom is indicated in patients with one of the followings, 1) clinical systemic bleeding (bleeding on site[s] other than the bitten area, except microscopic hematuria), 2) venous clotting time (VCT) of 20 minutes or more, 3) unclotted 20-minute whole blood clotting test

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(20WBCT), 4) international normalized ratio (INR) of 1.2 or more, 5) platelet of less than 50,000, and 6) compartment syndrome[6].

Data on using VCT, 20WBCT, prothrombin time (PT), INR, and partial thromboplastin time (PTT) to predict systemic bleeding in patients bitten by hematotoxic snake are limited. In the recent studies, 20WBCT is an insensitive parameter in Russell's viper (RV) envenomation patients but is highly sensitive and specific in green pit viper (GPV) envenomation patients[5,7].

The objective of the present study was to determine association between clotting tests (VCT, 20WBCT, platelets count, PT, PTT, and INR) and outcome, including fibrinogen of less than 100 mg/dL, and systemic bleeding in patients bitten by GPV or RV.

Materials and Methods

Study population

This was a prospective cohort study involving adult patients bitten by GPV or RV admitted to Sawanpracharak Hospital, Nakhon Sawan, Thailand, between October 2016 and December 2017. Nakhon Sawan is the fifth ranking province of the most hematotoxic snake bite's area[2] and test for serum fibrinogen was available. The present study was approved by the Ethical Committees of Ramathibodi and Sawanpracharak Hospital. According to a previous study, at least eight specimens with unclotted 20WBCT and eight specimens with clotted 20WBCT were needed for determining association between 20WBCT and serum fibrinogen of less than 100 mg/dL with the power of 90% (beta 10), and the alpha error of 0.05[5].

Inclusion criteria were 1) adult patients aged 15 to 80 years, 2) patients were bitten by GPV or RV with clear identification of the snake from either bringing the snakes, snake carcasses, or patient recognition and confirmation with the example photos, 3) patients were admitted to Sawanpracharak Hospital, and 4) patients were advised on the study protocol and ethical considerations by the primary physician, and informed consents were obtained. For the patient younger than 18 years, the inform consents was obtained from the parents. Patients with cirrhosis, hemophilia, or receiving an anticoagulant (including warfarin, heparin, low-molecular weight heparin, and oral anticoagulant) or an antiplatelet were excluded. The underlying diseases and current medications were identified by history taking and reviewing medical records.

Data collection

The types of snakes, identification methods, bitten time, visit time, referral time, age, gender, occupation, underlying diseases, current medications, systemic bleeding locations, treatments, indications for antivenom, amounts of given antivenom, complications, and baseline creatinine were recorded.

Blood specimens were collected at initial presentation and every six hours until 24 hours of admission, or patient recovery. A specimen of 10 ml blood was obtained in each blood drawn, and was sent for VCT, 20WBCT, PT, INR, PTT, complete blood count, and serum fibrinogen concentration. Abnormal clotting tests were defined as VCT of 20 minutes or more, unclotted 20WBCT (blood is still liquid and runs out)[8], platelets count of less than 50,000/mcL, INR of 1.2 or more, PT of 13 seconds or more, and PTT of 38 seconds or more.

The clotting tests in Sawanpracharak Hospital were complied with Laboratory Accreditation from Thailand medical technology council standard. Coagulation tests and fibrinogen concentration were reported within 30 minutes after having been sent to the laboratory. Serum fibrinogen concentration tests were performed only in Sawanpracharak Hospital using Sysmex CS-2100, with prothrombin derived fibrinogen method. The clotting tests from community hospital in Nakhon Sawan had been yearly calibrated at Sawanpracharak Hospital. For 20WBCT, the instruction in World Health Organization (WHO) guideline was followed[8]. VCT were performed using modified Lee and White's method. The authors collaborated with all community hospitals in Nakhon Sawan. The protocols for patient enrollment, collecting specimens, 20WBCT, and VCT were distributed and described to the directors, doctors, nurses, and laboratory officers. The protocols were similar to those of Sawanpracharak Hospital. If the patient was transferred from community hospital, the clotting test results from that community hospital were included.

Data analysis

Continuous variables were expressed as medians and interquartile ranges (IQR). Categorical data were expressed in number and percentage. Due to the small number of specimens, association between abnormal clotting test results and outcome (fibrinogen of less than 100 mg/dL and systemic bleeding) were determined by Fisher's exact test. A p-value less than 0.05 indicated statistically significant. Sensitivity, specificity, positive predictive value (PPV), and

Table 1. Characteristics of hematotoxic snake envenomation cases

Characteristics	Number of cases, n (%)		
	Total (30 cases)	GPV (21 cases)	RV (9 cases)
Sex			
Male	17 (56.7)	9 (42.9)	8 (88.9)
Female	13 (43.3)	12 (57.1)	1 (11.1)
Age (years), Median (IQR)	43.0 (33.3 to 57.8)	43.0 (30.0 to 56.0)	41.0 (30.0 to 57.0)
Local complications			
Compartment syndrome	3 (10.0)	3 (14.3)	0 (0.0)
Gangrene	1 (3.3)	0 (0.0)	1 (11.1)
Necrotizing fasciitis	1 (3.3)	1 (4.8)	0 (0.0)
Cellulitis	1 (3.3)	1 (4.8)	0 (0.0)
Hemorrhagic bleb	1 (3.3)	1 (4.8)	0 (0.0)
Systemic complications			
Acute kidney injury	4 (13.3)	0 (0.0)	4 (44.4)
Upper gastrointestinal bleeding	3 (10.0)	1 (4.8)	2 (22.2)
Gross hematuria	1 (3.3)	0 (0.0)	1 (11.1)
Antivenom administration	15 (50.0)	6 (28.6)	9 (100)
Surgical intervention	2 (6.7)	1 (4.8)	1 (11.1)

GPV=green pit viper group; RV=Russell's viper group; IQR=interquartile range

negative predictive value (NPV) of each abnormal clotting test were presented. The statistical analyses were performed using Stata software package version 14.2.

Results

Patients' characteristics and clotting test results

During the study period, thirty-one patients presented with hematotoxic snake envenomation. One case was excluded due to taking aspirin as current medication. Thirty hematotoxic snake envenomation patients were enrolled, including 21 patients (70.0%) bitten by GPV (GPV group), and nine patients (30.0%) bitten by RV (RV group). There were 17 males (56.7%), and 13 females (43.3%). The median age was 43.0 years (IQR 33.3 to 57.8 years) (Table 1). Eight patients had underlying diseases. The common underlying diseases were hypertension (three patients, 10.0%), and hyperlipidemia (two patients, 6.7%). The common occupations were employee (17 patients, 56.7%), farmer (two patients, 6.7%), and student (two patients, 6.7%). Eight patients were referred from the community hospital including three from Takfa Hospital, two from Phayuha Khiri Hospital, two from Phaisali Hospital, and one from Takhli Hospital. The median time from bite to referral was 11.1 hours (IQR 7.5 to 15.6 hours).

Snakes were identified by patients' recognition and confirmation with example photos in 18 patients (60.0%) and bringing the snakes or snake carcasses to emergency room in 12 patients (40.0%). Four patients (13.3%) had systemic bleeding, including three patients in RV group, and one patient in GPV group. Reported systemic bleeding were upper gastrointestinal bleeding in three patients (10.0%), and gross hematuria in one patient (3.3%). The median time from bitten to bleeding onset was 7.5 hours (IQR 4.6 to 9.6 hours). The median time from bites to first abnormal clotting tests was 5.5 hours (IQR 3.7 to 6.5 hours). Acute kidney injury was reported in four patients, all were in the RSV group. Two patients underwent wound debridement in the operating room (Table 1). There was no death. Thirty-one doses, 141 vials, of antivenom were administered in 15 patients. The indications of antivenom were described in Table 2.

One hundred sixty blood specimens were collected. Of the 128 specimens tested for VCT, VCT of 20 or more were reported in 19 specimens. Of the 99 specimens tested for 20WBCT, unclotted 20WBCT were reported in 12 specimens. Of the 100 specimens tested for fibrinogen concentration, fibrinogen of less

Table 2. Indication of antivenom in green pit viper group and Russell's viper group

Indication of antivenom	Number of antivenom administration course, n (%)		
	Total (31 courses)	GPV (10 courses)	RV (21 courses)
Venous clotting time more than 20 minutes	20 (64.5)	4 (40.0)	16 (76.2)
Unclotted 20-minute whole blood clotting test	11 (35.5)	3 (30.0)	8 (38.1)
Clinical systemic bleeding	9 (29.0)	2 (20.0)	7 (33.3)
International normalized ratio more than 1.2	5 (16.1)	1 (10.0)	4 (19.0)
Platelet count less than 50,000/mcL	2 (6.5)	2 (20.0)	0 (0.0)

GPV=green pit viper group; RV=Russell's viper group

than 100 md/dL were reported in eight specimens. Of the 101 specimens tested for complete blood count, platelet count of less than 50,000/mcL was reported in one specimen. Of the 102 specimens tested for PT and INR, there were 68 specimens with PT of 13 seconds or more, and 19 specimens with INR of 1.2 or more. Of the 87 specimens tested for PTT, which has a normal range 28 to 38 second, none was reported to have a PTT of 38 seconds or more.

Fifty-one specimens were collected after receiving antivenom, and there were five INR specimens, three platelet specimens, two fibrinogen specimens, and one VCT specimen that appeared to have abnormal results after receiving antivenom. All of the clotting tests had been followed every six hours and returned to be within normal range within 18 hours after receiving the antivenom.

Of the specimens with fibrinogen of less than 100 mg/dL, three specimens were without further antivenom administration due to no clinical of bleeding and normal clotting tests (two specimens taken from the patient who received antivenom before, and one specimen taken without prior antivenom). The fibrinogen concentration was followed and returned to be more than 100 mg/dL at the next six hours.

Association between abnormal clotting tests and fibrinogen less than 100 mg/dL

Factors associated with fibrinogen of less than 100 mg/dL were VCT of 20 minutes or more (p=0.01), unclotted 20WBCT (p=0.01), PT of more than 13 seconds (p=0.04), and INR of 1.2 or more (p<0.01). Sensitivity, specificity, PPV, NPV are described in Table 3.

In GPV group, factors associated with fibrinogen of less than 100 mg/dL were VCT of 20 minutes or more (p=0.04) and INR of 1.2 or more (p=0.03) (Table 4). In RV group, factors associated with fibrinogen of less than 100 mg/dL was INR of 1.2 of more (p=0.03) (Table 5).

Association between abnormal clotting tests and systemic bleeding

The clotting tests performed at the time with systemic bleeding included seven VCT specimens, seven 20WBCT specimens, six platelets count specimens, five PT specimens, five PTT specimens, five INR specimens, and five fibrinogen specimens.

Factors associated with systemic bleeding were VCT of 20 minutes or more (p<0.01), unclotted 20WBCT (p<0.01), INR of 1.2 or more (p=0.04), and fibrinogen of less than 100 mg/dL (p=0.01). Sensitivity, specificity, PPV, NPV were described in Table 6.

In the GPV group, factors associated with systemic bleeding were platelets of less than 50,000/mcL (p=0.03), and INR of 1.2 or more (p=0.03) (Table 7). In the RV group, factors associated with systemic bleeding were VCT of 20 minutes or more (p<0.01), unclotted 20WBCT (p<0.01), and fibrinogen of less than 100 mg/dL (p=0.049) (Table 8).

Discussion

The present study analyzed clotting tests with fibrinogen of less than 100 mg/dL and systemic bleeding from patients bitten by GPV or RV. Serum fibrinogen are the common final substrate of the coagulation cascade[3]. However, there is no clear threshold for clinically significant hypofibrinogenemia[4]. Fibrinogen concentration of less than 100 mg/dL is associated with an increasing risk of systemic bleeding[5], therefore fibrinogen concentration of less than 100 mg/dL is used as a marker of systemic bleeding risk in the present study.

In the present study, the authors found that factors significantly associated with fibrinogen of less than 100 mg/dL were VCT of 20 minutes or more, unclotted 20WBCT, and INR of 1.2 or more.

Table 3. Association between clotting tests and fibrinogen <100 mg/dL in green pit viper group and Russell's viper group

Clotting tests	Numbers of specimens		p-value*	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
	Fibrinogen <100 mg/dL	Fibrinogen ≥100 mg/dL					
Venous clotting time			0.01				
<20 minutes	3	69		Reference			
≥20 minutes	3	4		50.0	94.5	42.9	95.8
20-minute whole blood clotting test			0.01				
Clotted	6	65		Reference			
Unclotted	4	6		40.0	91.6	40.0	94.2
Platelet count			1.00				
≥50,000/mcL	7	82		Reference			
<50,000/mcL	0	1		0.0	98.8	0.0	92.1
Prothrombin time			0.04				
<13 seconds	0	33		Reference			
≥13 seconds	8	59		100	36.9	11.9	100
International normalized ratio			<0.01				
<1.2	2	78		Reference			
≥1.2	6	11		75.0	87.6	35.3	97.5

PPV=positive predictive value; NPV=negative predictive value

* p-value by Fisher's exact test

Table 4. Association between clotting tests and fibrinogen <100 mg/dL in green pit viper group

Clotting tests	Numbers of specimens		p-value*	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
	Fibrinogen <100 mg/dL	Fibrinogen ≥100 mg/dL					
Venous clotting time			0.04				
<20 minutes	1	50		Reference			
≥20 minutes	1	0		50.0	100	100	98.0
20-minute whole blood clotting test			0.25				
Clotted	3	52		Reference			
Unclotted	1	3		25.0	94.6	25.0	94.6
Platelet count			1.00				
≥50,000/mcL	3	62		Reference			
<50,000/mcL	0	1		0.0	98.4	0.0	95.4
Prothrombin time			0.24				
<13 seconds	0	29		Reference			
≥13 seconds	4	40		100	42.0	9.1	100
International normalized ratio			0.03				
<1.2	2	65		Reference			
≥1.2	2	4		50.0	94.2	33.3	97.0

PPV=positive predictive value; NPV=negative predictive value

* p-value by Fisher's exact test

Table 5. Association between clotting tests and fibrinogen <100 mg/dL in Russells' viper group

Clotting tests	Numbers of specimens		p-value*	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
	Fibrinogen <100 mg/dL	Fibrinogen ≥100 mg/dL					
Venous clotting time			0.20				
<20 minutes	2	19		Reference			
≥20 minutes	2	4		50.0	82.6	33.3	90.5
20-minute whole blood clotting test			0.06				
Clotted	1	13		Reference			
Unclotted	3	3		75.0	81.3	50.0	92.9
Platelet count			NA[1]				
≥50,000/mcL	4	20		Reference			
<50,000/mcL	0	0		0.0	NA[1]	NA[1]	83.3
Prothrombin time			1.00				
<13 seconds	0	4		Reference			
≥13 seconds	4	19		100	17.4	17.4	100
International normalized ratio			0.03				
<1.2	0	13		Reference			
≥1.2	4	7		100	65.0	36.3	100

PPV=positive predictive value; NPV=negative predictive value

* p-value by Fisher's exact test, [1] Cannot be calculated; all specimen had platelets ≥50,000/mcL

Table 6. Association between clotting tests and systemic bleeding in green pit viper group and Russell's viper group

Clotting tests	Numbers of specimens		p-value*	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
	With bleeding	Without bleeding					
Venous clotting time			<0.01				
<20 minutes	1	108		Reference			
≥20 minutes	6	13		85.7	89.3	31.6	99.1
20-minute whole blood clotting test			<0.01				
Clotted	1	86		Reference			
Unclotted	6	6		85.7	93.5	50.0	98.9
Platelet count			0.06				
≥50,000/mcL	5	95		Reference			
<50,000/mcL	1	0		16.7	100	100	95.0
Prothrombin time			0.29				
<13 seconds	0	34		Reference			
≥13 seconds	5	63		100	35.0	7.4	100
International normalized ratio			0.04				
<1.2	2	81		Reference			
≥1.2	3	16		60.0	83.5	15.8	97.6
Fibrinogen			0.01				
≥100 mg/dL	2	90		Reference			
<100 mg/dL	3	5		60.0	94.7	37.5	97.8

PPV=positive predictive value; NPV=negative predictive value

* p-value by Fisher's exact test

Table 7. Association between clotting tests and systemic bleeding in green pit viper group

Clotting tests	Numbers of specimens		p-value*	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
	With bleeding	Without bleeding					
Venous clotting time			0.13				
<20 minutes	1	69		Reference			
≥20 minutes	1	4		50.0	94.5	20.0	98.6
20-minute whole blood clotting test			0.11				
Clotted	1	69		Reference			
Unclotted	1	3		50.0	95.8	25.0	98.6
Platelet count			0.03				
≥50,000/mcL	1	65		Reference			
<50,000/mcL	1	0		50.0	100	100	98.5
Prothrombin time			1.00				
<13 seconds	0	30		Reference			
≥13 seconds	2	42		100	41.7	4.6	100
International normalized ratio			0.03				
<1.2	2	66		Reference			
≥1.2	0	6		0.0	91.7	0.0	97.1
Fibrinogen			0.11				
≥100 mg/dL	1	68		Reference			
<100 mg/dL	1	3		50.0	95.8	25.0	98.6

PPV=positive predictive value; NPV=negative predictive value

* p-value by Fisher's exact test

Table 8. Association between clotting tests and systemic bleeding in Russell's viper group

Clotting tests	Numbers of specimens		p-value*	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
	With bleeding	Without bleeding					
Venous clotting time			<0.01				
<20 minutes	0	39		Reference			
≥20 minutes	5	9		100	81.3	35.7	100
20-minute whole blood clotting test			<0.01				
Clotted	0	17		Reference			
Unclotted	5	3		100	85.0	62.5	100
Platelet count			NA[1]				
≥50,000/mcL	4	30		Reference			
<50,000/mcL	0	0		NA[1]	NA[1]	NA[1]	NA[1]
Prothrombin time			1.00				
<13 seconds	0	4		Reference			
≥13 seconds	3	21		100	16.0	12.5	100
International normalized ratio			0.07				
<1.2	0	15		Reference			
≥1.2	3	10		100	60.0	23.1	100
Fibrinogen			0.049				
≥100 mg/dL	1	22		Reference			
<100 mg/dL	2	2		66.7	91.7	50.0	95.7

PPV=positive predictive value; NPV=negative predictive value

* p-value by Fisher's exact test, [1] Cannot be calculated; all specimen had platelets ≥50,000/mcL

Unclotted 20WBCT associated with fibrinogen of less than 100 mg/dL was similar as in the previous studies in patients bitten by *Bothrops* snake in Brazil, *Oxyuranus scutellatus canni* (Papuan Taipan) in Papua New Guini[9,10]. In the study of 97 GPV envenomation patients, 20WBCT, VCT, PT, and INR were associated with hypofibrinognemia[5]. The explanation for INR of 1.2 or more associated with fibrinogen of less than 100 mg/dL was probably that, the prolongation of PT was due to low fibrinogen level, and hyperfibronolysis resulting in fibrin degradation product and fibrin polymerization interference[11].

Factor associated with systemic bleeding in the present study were VCT of 20 minutes or more, unclotted 20WBCT, and fibrinogen of less than 100 mg/dL. In RV group, unclotted 20WBCT was associated with systemic bleeding ($p<0.01$) with 100% sensitivity and 85% specificity. In contrast to the study of cases bitten by RV in Sri Lanka, which reported that 20WBCT had low sensitivity about 40% (95% CI 32 to 49) to predict systemic bleeding risk[7]. The different findings on 20WBCT sensitivity may be from the toxin variations between RV in the regions[12].

In GPV subgroup, the authors found that platelets of less than 50,000/mcL and INR of 1.2 or more were associated with systemic bleeding. Only one GPV bitten patient reported systemic bleeding in the present study. The number of specimens taken during bleeding in GPV case were only two specimens. Due to underpower, the authors could not find association of other clotting test results with systemic bleeding in GPV group. Further study with higher number of bleeding cases should be performed to determine the association between systemic bleeding with clotting test results in GPV envenomation.

In the present study result, five INR specimens, three platelet specimens, two fibrinogen specimens, and one VCT specimen were still abnormal after receiving antivenom. GPV-antivenom directly neutralized to the systemic toxin, thrombin-like effect, and anti-fibrinolysis effect of GPV toxin. RV-antivenom neutralized to RV-toxin that activated factor X to factor Xa[13]. Therefore, INR, which represents factor VII and extrinsic coagulation pathway and not the action side of antivenom, would still be abnormal. The other clotting tests, which do not represent the action site of antivenom, may be still abnormal after antivenom.

In the present study, three patients had fibrinogen of less than 100 mg/dL without further antivenom administration due to no clinical of bleeding and normal clotting tests. The authors could not find literature to explain that result. However, the authors suggest that close observation may be safe in hypofibrinogenemic patients with normal other clotting tests and no clinical bleeding.

Therefore, the authors summarized that unclotted 20WBCT, VCT, and INR were useful tests that were significantly associated with fibrinogen of less than 100mg/dL and systemic bleeding in the same direction as recommendation from WHO, management of snakebites in Southeast Asia[8].

Limitation

The present study had some limitations, due to low incidence of bleeding, association between systemic bleeding and some abnormal clotting test results may be undetected in both GPV and RV subgroups. Absence of the PT, PTT, INR, and fibrinogen level at the community hospital in referred patients were resulting in lack of other clotting test results to compare with VCT and 20WBCT. However, the specimens included in the present study analysis were the specimens taken for fibrinogen and other clotting tests at the same time. Due to varieties of both GPV and RV worldwide, the present findings are not generalized to envenomation in the other regions.

Conclusion

VCT of 20 minutes or more, unclotted 20WBCT, and INR of 1.2 or more are useful tests that significantly associated with fibrinogen of less than 100 mg/dL and systemic bleeding in GPV and RV.

What is already known on this topic?

Serum fibrinogen of less than 100 mg/dL is recommended for predicting systemic bleeding risk in hematotoxic snake bite patients, but it is not widely available.

What this study adds?

VCT of 20 minutes or more, unclotted 20WBCT, and INR of 1.2 or more are associated with serum fibrinogen of less than 100 g/dL and systemic bleeding in GPV and RV envenomation.

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Conflicts of interest

The authors declare no conflict of interest.

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