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Original Research

Effect of Envenomation on Serum Hepatic Biomarkers in Snake (Echis Ocellatus) Bitten Individuals in Zamko Comprehensive Health Centre of the Jos University Teaching Hospital, North Central Nigeria

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Abstract

Background: Snake bite is a neglected public health issue in many tropical and subtropical countries of the world. About 5.4 million snakebites occur each year, resulting in 1.8 to 2.7 million cases of envenomation yearly. Hepatic markers have been reported to rise 3-6 hours after injection of venom in experimental animals. This study aims to biochemically assess ALT, AST and GGT levels as biomarkers of Echis ocellatus envenomation in victims of snake bite presenting at JUTH Comprehensive Health Centre Zamko 6hours post-bite and compare with values in those bitten by non-venomous snakes.

Methodology: The study was a comparative cross-sectional study where serum levels of AST, ALT and GGT were compared between the study group and the control group.

Results: Of the 150 respondents, 75 from each study group, 90(60.0%) were Male while 60(40.0%) were Female, with a Male to Female ratio of 1.5:1. The most predominant age group was 20-29 years 57(38.0%), the mean age was 39 years. The most predominant occupation was farming 82(54.7%). The majority 82(54.7%) had a secondary level of education. 91(60.7%) were married. A large majority of 123(82.0) had Christianity as their religion. We found a significant increase in the levels of AST (47.45IU/L) and GGT (61.62 IU/L) in the study group compared to AST (25.88IU/L), GGT (29.61IU/L) in the control group at $p<0.05$, while the level of ALT was similar in both groups at $p>0.05$.

Conclusion: This implies that serum levels of AST and GGT can be used to diagnose envenomation in snakebite patients.

Keywords: Envenomation, Snakebite, Hepatocellular, Biomarkers

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Introduction

Snake bite is a neglected public health issue in many tropical and subtropical countries of the world as rightly stated by the World Health Organization (WHO). About 5.4 million snakebites occur each year, resulting in 1.8 to 2.7 million cases of envenoming yearly. There are between 81,410 and 137,880 deaths and around three times as many amputations and other permanent disabilities each year. Most of these occur in Africa, Asia and Latin America.[1]

In Africa, it is estimated that 435,000 to 580,000 snake bites annually need treatment. This Africa's endemic public health problem spares no age or sex group. Envenoming affects children and adults who are mostly farmers in poor rural communities in low- and middle-income countries. The burden is high in countries with weak healthcare systems where medical resources are scarce including drugs and consumables. Health facilities are also sparse thus making accessibility difficult[1].The venomous snakes in Africa are not too different from other continents of the world as they are known to belong to four main families namely, the colubridae, elapidae, viperidae and hydrophidae. The elapid and particularly the viperid snakes are responsible for most bites in the savannah region of Africa.[2]

In Plateau State, Nigeria, snake bite cases are endemic in the Local government areas located in the southern part of Plateau State where the temperature is higher than the LGAs around Plateau areas of Jos which is usually of lower temperature. This is not surprising knowing that snakes are reptiles that lack the ability to adapt to extreme changes in temperature. The commonest species found in Plateau State are Carpet Viper, Puff Adar and Cobra in that order. By far, Carpet Viper is responsible for most of the envenomation in JUTH Zamko Comprehensive Health Centre as indicated by studies done in the centre where 96% of cases of snakes were identified as carpet vipers[3]. However, another study in Plateau state of Nigeria has shown that snake bites are mainly caused by two species of snakes namely Cobra (Naja nigricollis) and Carpet Viper (echiscarinatus)[4] and the majority of the snakes found in the agricultural areas of the state are harmful4. In lower land LGA of Plateau State, snake bites constitute serious public health hazards attributed to the three species described above.

Humans are not necessarily the primary target of snakes as they do not constitute most of their diet but are usually accidental victims[5]. Therefore, not all bites lead to the injection of venom. Greater percentages are dry bites, and the severity of envenomation depends on so many factors like the type and size of snakes and the size of human prey. Children with smaller body surface areas are usually at higher risk of morbidity and mortality since the snake injects the same volume and dose of the venom as adults. Envenomation is the exposure to a poison or toxin resulting from a bite or sting from an animal such as a snake, scorpion, spider, or insect, or from marine life. Relying on information about a bite or sting from patients or primary caregivers may not be objective enough and additional exposures in the case of multiple bites from a single/multiple snakes and or multiple animals may go unreported. Hence, there is a need to study scenically the presence or absence of envenomation in patients who present with a history of bites or stings. Most patients who were bitten by a snake present late to the health facility because of the distance from the farm to the health facility. The transportation to the hospital is also a limiting factor. Many biochemical markers of envenomation have been studied in rats, rabbits, horses and goats but not much in humans. Other researchers focused on parameters of kidney, cardiac and blood injury in snake bite patients. Parameters of hepatic injury in snakebite patients are not well studied. The liver as the center of metabolism that is involved in detoxification is surely one of the targets of envenomation.

Parameters for assessing hepatic functions are numerous, this includes hepatic enzyme levels eg ALT, AST, GTT, total and conjugated bilirubin, total protein and albumin including fibrinogen levels etc. Most hepatic enzymes are nonspecific. However, Alanine amino transaminase (ALT) is pretty specific to the liver and hence a good marker of hepatic injury. Researchers had earlier shown a rise in three hepatic enzymes; Aspartate amino transaminases (AST), Gamma glutaryl transferase (GGT) and ALT in some literature5 and all will be used in this study. In the absence of hemolysis, total and conjugated bilirubin is hepatic specific. This is supported by work done by Jeyarajah et al who reported a raised ALT and bilirubin in patients bitten by Russell viper.[6] Other studies also looked at all the above-mentioned potential hepatic markers of envenomation including total protein and albumin but were not too useful and were not considered in this study.

The current diagnostic method for snakebite envenomation used in the Zamko Comprehensive Health Centre is the 20-minute Whole Blood Clotting Time (WBCT) and that is marred by a lot of false positive and negative results. This problem is not limited to that centre alone, it's a universal issue as indicated by William et al[7] where physicians in India reported problems with the 20min WBCT and requested for a new diagnostic method be developed. The experience in Zamko is that of a serial 20-minute WBCT for 2-5 days until it becomes positive or not. Sometimes patients return to the hospital weeks after the bite with a positive result when they recorded a negative one previously. This means that there are some factors that determine the rate and timing of envenomation from viper's venom. Organ damage may have commenced long before a positive 20-minute WBCT test. This is evidenced by multiple organ damage presented by patients that are 5slow indicators and that delay in Anti-snake venom (ASV) administration may result in significant morbidity and mortality hence the importance of looking for an alternative diagnostic indicator of envenomation in snake bite patients.

This study aims to biochemically compare the serum levels of ALT, AST and GGT in patients bitten by venomous Echisocellatus Snakes with participants bitten by nonvenomous snakes

Materials and Methods

Study Area

This study was carried out at Jos University Teaching Hospital (JUTH) Comprehensive Health Centre Zamko in Langtang Local Government Area of Plateau state, north central Nigeria where snakebite is endemic. The centre is a well-known treatment centre for snakebite patients located in the southern senatorial zone in Plateau State.

Study Population

The study population comprised Echis ocellatus snake-bitten patients with deranged 20WBCT and nonvenomous snake-bitten patients within the selected health facility. Consenting clients who were eligible for the study were recruited using the non-probability consecutive sampling method until the desired sample size was reached.

Sample Size Determination

The sample size was determined using the formula for calculating minimum sample size involving a comparison between 2 means as stated below[8].

N=2(Zα + Zβ) 2 D2/ Δ2

Where:

N= minimum sample size in each group (assuming the proportion of sample size between the two groups= 1:1)

Zα = Two-sided Z value (e.g. Z=1.96 for a significance level of 5% or 95% confidence interval).

Zβ = Power- 0.80 or 80% = 0.841

D = Standard deviations for ALT levels of two groups being compared (e.g. as obtained from a similar study).

D2 = Pooled Variance of distribution of the mean of ALT levels = (sum of the square of both standard deviations) divided by 2.

Δ = Meaningful difference in mean ALT levels between the two groups being compared.

Considerations:

The sample size was calculated based on the following assumptions:

Type I error =0.05 or 5%; Type II error=0.20 or 20%; Power =0.80 or 80%.; Standard deviations for ALT levels of the two groups (Cases and Controls) were 55.2 IU/L and 33.4 IU/L as obtained from a previous study9 Therefore Pooled Variance of distribution of the mean of ALT= (55.22 + 33.42) / 2 ≈ 2,081 and the mean difference in the ALT levels of ALT between Cases and Controls to be detected = 22 IU/L (as suggested by the same study).

Substituting:
N= 2 X (Zα + Zβ) 2 d2/ Δ2;N=2 X (1.96+0.84)2 X 2,081/ 222;N=2 X (2.8)2 X 2,081 / 484;
N= 2X 7.84 X 2,081/ 484; N≈ 67 participants per group
The sample size was adjusted to compensate for non-response as follows:
Population correction factor (PCF) for a population less than 10,000 (nf) = N / [1+ (N/sample frame)](10)= 67/ [1 + (67/3,081)]= 66
Allowing for 10% missing or incomplete data rate; = (10/100 x nf) + nf= (10/100 x 66) + 66 = 73 per group. A total of 146 subjects (73 cases and 73controls) were considered for this study.

Inclusion Criteria
Echis ocellatus snake-bitten patients prior to administration of ASV, those bitten but with deranged 20WCBT, those who are 18 - 80years old, Echis ocellatus snake-bitten patients that reported to the hospital within 6 hours of bite, bitten patients with no known acute or chronic diseases of the Liver/kidney, muscle, Sickle Cell Anaemia (SCA) on hepatotoxic drugs like hydroxyurea, and not known alcoholic.

Exclusion Criteria
Known alcoholics, known viral hepatitis patients or any liver diseases, non-consenting participants, all known acutely ill clients, snake bite patients who receive ASV already, snake bite patients with normal 20WCBT, Individuals with known chronic diseases e.g. Hypertension, Renal/Liver disease, Tuberculosis, Diabetes Mellitus, Epilepsy, Malignancy, Sickle Cell Anaemia, and Hepatotoxic drugs such as isoniazid.

Study Design
A hospital-based comparative cross-sectional study. The participants were recruited using the non-probability consecutive sampling method. All consenting adult participants who met the inclusion criteria were recruited until the desired sample size was obtained. The study was carried out within 6 months. Sample collection for serum ALT, AST and GGT was done in the first 3 months.

Ethical Considerations and Consent
Ethical Clearance was obtained from the Ethics Committee of Jos University Teaching Hospital (JUTH). Informed consent was obtained from all participants after due explanation of the research work, procedure and its objectives. all participant's data was treated witha high level of confidentiality.

Data Collection/Sampling Method
Each participant who met the inclusion criteria was recruited by an interviewer-administered a structured questionnaire which was filled out by the researcher where necessary information including socio-demographic characteristics was collected. 5mililitres of venous whole blood were taken from snake bite patients at the point of 20WBCT to avoid multiple venipuncture and those bitten by nonvenomous snakes (control participants) into an appropriately labelled plain vacutainer bottle, thereafter samples were separated with the aid of a centrifuge at 4000 rpm for 5minutes and automated micropipette. Serum harvested were transferred to cryotubes in aliquots of 1mL, transported on dry ice to JUTH special laboratory and assayed using standard protocols for serum ALT, AST and GGT respectively.

Statistical Analysis
ANOVA was used to compare the serum levels of ALT, AST and GGT in the control group and study group, descriptive statistics was used to show the socio-demographic characteristics of participants, and all tests were carried out at a 95% confidence interval, using SPSS version 22.0. Results were presented using contingency tables.

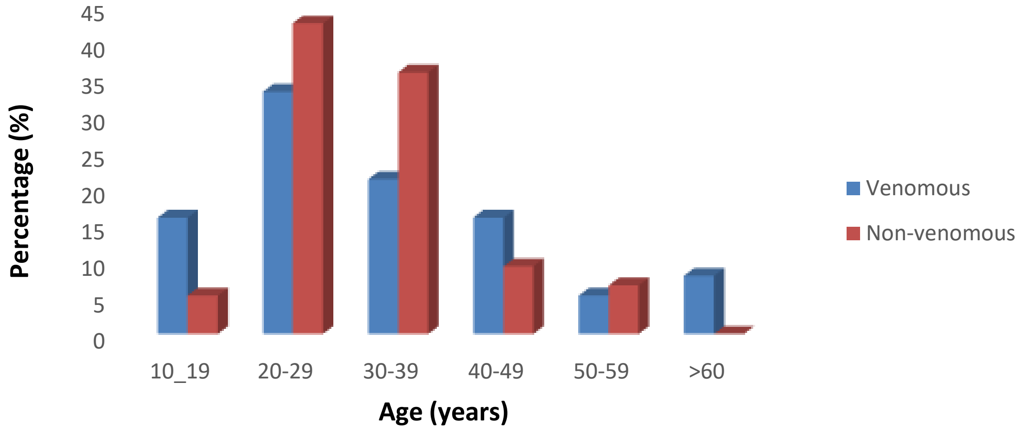
Results

Table 1: Sociodemographic distribution of respondents in the two-study group

		Study group				
Variables	**Response**	**Venomous**	**Control**	**TOTAL**	**p-value**	**χ2**
Sex	Male	45(60.0)	45(60.0)	90(60.0)	0.001	0.999
	Female	30(40.0)	30(40.0)	60(40.0)		
	Sex ratio (M: F)	1.5:1	1.5:1	1.5:1		
	TOTAL	**75(100)**	**75(100)**	**150(100)**		
Edu. level	No Formal Edu.	8(10.7)	4(5.3)	12(8.0)	2.477	0.479
	Primary	24(32.0)	20(26.7)	44(29.3)		
	Secondary	37(49.3)	45(60.0)	82(54.7)		
	Tertiary	6(8.0)	6(8.0)	12(8.0)		
	TOTAL	**75(100)**	**75(100)**	**150(100)**		
Marital status	Single	30(40.0)	29(38.7)	59(39.3)	0.028	0.867
	Married	45(60.0)	46(61.3)	91(60.7)		
	TOTAL	**75(100)**	**75(100)**	**150(100)**		
Religion	Islam	8(10.7)	10(13.3)	18(12.0)	3.073	0.215
	Christianity	60(80.0)	63(84.0)	123(82.0)		
	Traditionalist	7(9.3)	2(2.7)	9(6.0)		
	TOTAL	**75(100)**	**75(100)**	**150(100)**		

The result is significant where $p<0.05$ at 95% C.I

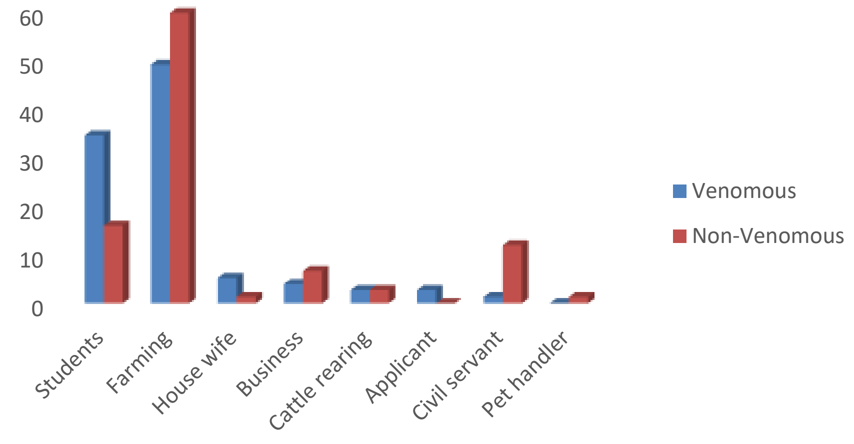
Of the 150 respondents, 75 from each study group, 90(60.0%) were Male while 60(40.0%) were Female, with a male-female ratio of 1.5:1. The most predominant age group was 20-29 years 57(38.0%), the mean age was 39 years (Fig 1). The most predominant occupation was farming 82(54.7%). The majority 82(54.7%) had a secondary level of education. 91(60.7%) were married. A large majority of 123(82.0) had Christianity as their religion.



$\chi 2=15.101$; $p=0.010$

Mean age(years)=39±3.43

Fig 1: Age distribution of respondents in the two study groups



$\chi 2=17.638$;$p=0.014$

Fig 2: Occupational distribution of respondents in the two study groups

Table 2: Comparative Serum levels of ALT, AST and GGT in participants bitten by venomous (Echis ocellatus) snakes with participants bitten by nonvenomous snakes that present to JUTH Zamko

Study groups	**ALT(IU/L)**	**AST(IU/L)**	**GGT(IU/L)**
Venomous	47.45±15.96	61.62±9.93	42.81±2.93
Non-Venomous (Control)	25.88±0.59	29.61±0.79	25.65±1.05
F	**3.310**	**32.634**	**53.721**
p-value	**0.179**	**0.002**	**0.001**

Result is significant where (p<0.05); Values are Mean±SEM

Table 3: Multi-variate logistic regression of some independent variables with AST, GGT observed in patients bitten by venomous snakes and nonvenomous snakes at JUTHZamko

		Unstandardized Coefficient		Standardized Coefficient	
	Model	B	SEM	Beta	p-value
AST	(Constant)	8.942	78.732		**0.910**
	Age	3.158	5.967	.061	**0.597**
	Sex	-7.230	10.713	-.057	**0.501**
	Hypertension	17.381	16.070	.124	**0.281**
	Diabetes mellitus	-8.148	27.826	-.025	**0.770**
	Smoking	6.089	18.713	.027	**0.745**
	Alcohol	15.335	11.264	.117	**0.176**
	BMI	-6.500	4.741	-.116	**0.173**
GGT	(Constant)	34.976	26.031		**0.181**
	Age	2.494	1.973	.146	**0.208**
	Sex	-4.261	3.542	-.100	**0.231**
	Hypertension	3.887	5.313	.084	**0.466**
	Diabetes mellitus	-7.147	9.200	-.067	**0.439**
	Smoking	6.854	6.187	.093	**0.270**
	Alcohol	-2.999	3.724	-.069	**0.422**
	BMI	-1.294	1.568	-.070	**0.410**

Dependent variables (ALT, AST, GGT): Predictors(constant) Age, sex, Hypertension, Diabetes mellitus, smoking, Alcohol, BMI

Table 4: Some vital signs of patients who presented to JUTH Zamko with the incidence of snake bite by venomous (Echis ocellatus) snake and nonvenomous snakes

	Presenting BP (mmHg)	**No. Observed**	**Venomous (%)**	**Nonvenomous (%)**	**p-value**
	<99	1	1(100.0)	-	
Systolic	100-120	57	44(77.2)	13(22.8)	
	121-140	72	23(31.9)	49(68.1)	0.001
	>141	20	7(35.0)	13(65.0)	
	TOTAL	**150**	**75(50.0)**	**75(50.0)**	
Diastolic	<79	83	34(41.0)	49(59.0)	
	80-90	56	37(66.1)	19(33.9)	0.016
	91-100	5	1(20.0)	4(80.0)	
	>101	6	3(50.0)	3(50.0)	
	TOTAL	**150**	**75(50.0)**	**75(50.0)**	
Pulse rate (Bpm)					
	<59	9	4(44.4)	5(55.6)	
	60-100	135	65(48.1)	70(51.9)	0.043
	>101	6	6(100.0)	-	
	TOTAL	**150**	**75(50.0)**	**75(50.0)**	

The results are significant where ($p<0.05$)

Discussion

A total of153 patients bitten by snakes were recruited in this study. However, two patients died before the questionnaires were administered and 1 declined. 150 consenting respondents participated in this study, 75 cases; those that were bitten by venomous snakes and another 75 as control; that is those that were bitten by non-venomous snakes. The majority 90(60.0%) of the total respondents were males while 60(40.0%) were females, with a Male to Female ratio of 1.5:1. This is consistent with the clinical update report on the management of snakebite 2022 by Ravikar et al[11] and work done in Tanzania that reported similar male to female ratio.[12]The most predominant age group commonly affected by snakebite was 20-29 years 57(38.0%), and the mean age was 39 years (Fig 1) which varies with the Tanzania study which reported 18 years as the mean age group though both are within the productive age bracket. Previous works done on victims of snakebites in Zamko, Langtang LGA of Plateau State of Nigeria where this study was done affirm similar age ranges between 25-49 years[13] and 15-44years.(Ekwere et al[2].The most predominant occupation was farming 82(54.7%). This is similar to findings in the Tanzania study and previous works done in Zamko[3,13]. The majority 82(54.7%) had a secondary level of education. 91(60.7%) were married. A large majority of 123(82.0) had Christianity as their religion.

The current diagnostic test for the determination of envenomation in a patient bitten by a snake worldwide is the 20-minute WBCT test as indicated by the 2022 clinical update report on snake bite [(11).] The need for a new test or an adjuvant test arises when in some instant, the test turns out negative when indeed envenomation is ongoing. For centres that have laboratory support, diagnostic sensitivity and specificity of the 20-minute WBCT test can be improved upon by assessing hepatic enzyme levels. Rise in hepatic enzymes was earlier shown to occur early enough in experimental animals however, [17,18,19] up until now, no laboratory human studies in sight reported this correlation. The results of this study revealed that there was a significant difference in the level of AST and GGT in the two study groups at ($p<0.02$ and 0.01) respectively (table 2), while the level of ALT was not significantly higher in cases when compared with the control groups at a ($p<0.179$). However, a significant rise in ALT was noted in some patients who demonstrated a markedly high liver enzyme. For instance, in all the cases that showed levels of AST and GGT greater than 4 times the upper limit of normal, ALT levels were also noted to rise alongside.

The rise in plasma AST and GGT about six hours post-bite is in keeping with several studies in experimental animals.[19,20]Putting the type of snake venom (echis ocellatus) into consideration, one may think that the source of the AST is from hemolyzed red blood cells as a result of the haematotoxic envenomation but when you put the elevated GGT levels also into consideration, it supports hepatic origin. All though ALT which is more specific to the liver did not rise significantly in the study group compared to the control group, it's probably because it requires more than 6 hours to rise significantly, or the dose of the venom may not have been enough to cause an early rise in its levels as indicated in experimental animals. A dose-dependent rise in the levels of ALT, AST and GGT in mice was demonstrated in several studies.[19] This pattern of elevated hepatic enzyme in this study indicates that the echis ocellatus venom-like is cytotoxic and often leads to some form of infiltrative injuries to the hepatocytes as the venom circulates in the human body. This is because the location of ALT in the hepatocytes is cytoplasmic while that of AST is more mitochondrial in origin. Cytoplasmic AST is less in quantity compared to the mitochondrial AST. The total hepatic AST is higher in quantity compared to the levels of ALT.[21] The implication of these is that inflammatory conditions will elevate more of ALT while infiltrative injuries will cause an elevation in AST rather than ALT as is the case in this study. The elevated GGT may be a result of acute intrahepatic obstruction somehow caused by the echis ocellatus envenomation or other mechanisms yet to be understood. Elevated GGT is usually seen in some hepatic obstruction from conditions like fatty liver disease or alcoholism which are usually chronic conditions. Alkaline Phosphatase (ALP) if done may have given extra clues as to the cause of the elevated GGT. High ALP will be supporting a post-hepatic origin.

Snake venom contains a thrombolytic enzyme and causes tissue necrosis, hypotension, coagulopathy, thrombocytopenia, spontaneous bleeding, electrolyte derangements with worsening anaemia and severe metabolic acidosis.[22] Serum levels of negative and positive acute phase proteins can be explored as additional tests that should be done to add to the traditional 20MWBCT test in order to improve the diagnostic accuracy of envenomation. Other biomolecules like total and conjugated bilirubin, urea, creatinine, ALP, full blood count, clotting time, lipid profile, thyroid function test, glucose and other biochemical profile may give us a clue as to the biochemical characteristics of echis envenomation. Perhaps, this profile may help to distinguish even the kind of snake that was involved. Since each snake belongs to a class that is unique to it, the biochemical profile of the patients bitten by those groups of snakes may also be unique.

The results of this study also indicated that other sociodemographic variables did not have a significant effect on the levels of the hepatic enzymes levels as indicated by the multivariate logistic regression of independent predictors. Body mass Index, obesity, alcohol intake and Diabetes mellitus may have an effect on the levels of the hepatic enzymes in literature but there was no significant association with elevated levels of hepatic enzyme in this study. Anxiety is a common factor that is usually exhibited by snakebite patients. Anxiousness was examined by accessing the pulse rate and blood pressure of both the control and the study groups and the results showed a significant difference in the levels of the blood pressure and pulse rates of the study group compared to the control group. This means that other factors may have contributed to an even higher pulse rate and blood pressure other than anxiety alone.

Accurate timing of exposure was difficult. The research was limited by the knowledge of the timing of the bite. Total reliance on information from patients and relatives who don't usually note the time of bite during the panic period post-bite and will only give an estimated time.

In reported studies on experimental animals, a known dose of snake venom was injected in these animals therefore, an accurate dose-dependent rise in the hepatic enzymes was accurately measured at a particular time. This was not the case in this study. Several factors may have affected the dosage of venom injected into these victims that we cannot standardise.

Conclusion and Recommendation

Snakebite is a neglected public health issue worst in sub-Saharan Africa. The condition affects more males than females, affects younger age groups and farming is an occupational risk factor. The above findings guarantee that serum AST and GGT levels may be used for the diagnosis of envenomation in snakebite patients all over the world where material and human resources are available for a quality liver enzyme assay. In our settings, the Government and private sectors should investigate investing in equipment and manpower to ensure the availability of such assays in rural centres like Zamko to enable seamless diagnosis of envenomation with liver enzyme levels. A complete biochemical profile of snakebite patients should be researched with available resources and time. This may unveil other biochemical indicators of envenomation that may be earlier than the above and provide additional evidence for clinicians in the management of snake bite patients.

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Conflict of Interest
The authors declared that there is no competing interest

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