NLR (NEUTROPHIL LYMPHOCYTE RATIO)
AND
SPOT PCR (PROTEIN CREATININE RATIO)
AS
EARLY PREDICTORS OF AKI IN HAEMOTOXIC SNAKEBITE

Dissertation Submitted in partial fulfillment of the requirement for the award of the Degree of

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MAY 2022

CERTIFICATE FROM THE DEAN

This is to certify that this dissertation entitled **"NLR (NEUTROPHIL LYMPHOCYTE RATIO) AND SPOT PCR (PROTEIN CREATININE RATIO) AS EARLY PREDICTORS OF AKI IN HAEMOTOXIC SNAKEBITE"** is the bonafide work of **Dr. PAVITHRAN.S** in partial fulfillment of the university regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, for M.D General Medicine Branch I examination to be held in **MAY 2022.**

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I, Dr. PAVITHRAN.S solemnly declare that, this dissertation entitled **"NLR (NEUTROPHIL LYMPHOCYTE RATIO) AND SPOT PCR (PROTEIN CREATININE RATIO) AS EARLY PREDICTORS OF AKI IN HAEMOTOXIC SNAKEBITE"** is a bonafide record of work done by me at Department of General Medicine, Madurai Medical College and Government Rajaji Hospital, Madurai during July 2021 – December 2021 under the guidance and supervision of **Prof**.**Dr.A.SENTHAMARAI,M.D.,** I also declare that this bonafide work or part of this work was not submitted by me or any others for any award, degree, diploma to any other University, Board either in India or abroad. This dissertation is submitted to The Tamil Nadu Dr. M.G.R Medical University, Chennai in partial fulfillment of the rules and regulations for the award of Degree of Doctor of Medicine (M.D.), General Medicine Branch -I- examination to be held in May 2022.

Place: Madurai

Date: **Dr. PAVITHRAN.S**

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ABBREVIATIONS

NLR – Neutrophil Lymphocyte Ratio

PCR – Protein Creatinine Ratio

AKI- Acute Kidney Injury

R.V – Russel Viper

S.S.V – Saw Scaled Viper

WBCT – Whole Blood Clotting Time

TC - Total Count

DC - Differential Count

CKD – Chronic Kidney Disease

ASV – Anti Snake Venom

FFP – Fresh Frozen Plasma

IV – Intra Venous

ACR – Albumin creatinine Ratio

KDIGO – Kidney Disease – Improving Global Outcome

ABSTRACT

Background: AKI due to venomous snake bite is one of the major public health concern. It causes significant mortality as well as morbidity. Aim of this study was to determine the predictor of AKI at an early stage.

Method; Prospective observational study of patients with snake envenomation at Government Rajaji hospital, Madurai between July 2021 – December 2021 was conducted. Patients data, examination, clinical, laboratory findings were documented. A stepwise statistical analysis done to analyze the data.

Results: among the 75 patients 19 patients went to AKI. Among the AKI patients 15 were required dialysis. On statistical analysis Patients with toxicity have invariably elevated levels of NLR (In AKI PCR cut off ≥13.87 and P-value) with sensitivity 73% and specificity 64% for AKI. Spot PCR has significant correlation with patients progressed to AKI (PCR cut off ≥ 4.46, P value 0.001) with a sensitivity of 94% and specificity of 70%.

Conclusion: Increased NLR is significantly associated toxemia with slight positive correlation with snake bite induced AKI. PCR have significant correlation with patient developing AKI after snake bite.

Keywords: NLR, Spot PCR, AKI, Snake bite

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INTRODUCTION

Introduction

Snake bite is a major public concern throughout the world. Venomous snake bites are acute medical emergency. Despite the advancement in treatment, the morbidity and mortality associated with snake bite still exist at significant level in our country

Snakebite was included in the list of Neglected tropical disease by world health organization in the year 2009. Large proportion of global total number of snake bites are from India. At around 45900 deaths annually in India proposed to be due to snake bite induced.

There are various studies on haematological profile and clinical profile about various snake bites in India. Even there are some relevant studies about neutrophilia in venomous snakebite.

One major complication of snakebite often identified late is snake bite induced kidney injury. Neuroparalysis induced acute respiratory failure and AKI due to snake bite are some of the complications that cannot be managed by primary and rural health care facilities.

If there is early prediction of snakebite induced AKI, timely referral will save many lives as well reduce the mortality and health expenditure. It is proven in many researches and studies that early administration of ASV, prevent the progression of AKI. At least, it prevents the severe renal damage.

Recently, there are numerous indicators such as haematological and urine parameters being studied as a marker of AKI. For example, NGAL (Neutrophil gelatinase-

associated Lipocalin), IL-18, KIM-3 and so. A study conducted in Jipmer, even predicted the persistence of tubular dysfunction after recovery from snakebite induced AKI. It even predicted the progression of CKD from AKI.

Hence, this study aims to study proteinuria by Protein creatinine ratio in a patient with haemotoxic snakebite as well as Neutrophil Lymphocyte ratio as a indicator and predictor of toxic envenomation in snake bite and assess whether it will serve as a early predictor of ACUTE KIDNEY INJURY in snake bite.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Snakes are mysterious species often misunderstood. Some may consider them as fascinating and beautiful creatures, but for the rest they are slithering, crawling and very dangerous beings. There are innumerable mythological stories about snakes throughout the Indian subcontinent. In some cultures, they are portrayed as god , we can even idols and sculptures depicting snakes. The mere sight of snake can be very frightening and spine-chilling. There is a famous Tamil proverb which means that a snake could make an army panic.

According to the latest count, there are 3789 snake species in the world. They are\ divided into 30 different families and numerous subfamilies. Among the total snake species, only about 600 are venomous, in which only around 200 (7%) are able kill or cause significant envenomation in the human. India is home to more than 350 species of snakes, among them around 60 are found to be venomous.

Among the venomous snakes in India, the four lethal venomous snakes are considered to be almost all snakebite related morbidity and mortalities. They are called as Big 4 of Indian snakes.

- INDIAN COBRA (NAJA NAJA)
- RUSSEL VIPER (DABOIA RUSSELII)
- SAW SCALED VIPER (ECHIS CARINATUS)
- COMMON KRAIT (BUNGARUS CAERULEUS)

Figure 1: Big four Indian venomous snakes (cobra, krait, Russel viper, saw scaled viper)

Apart from these snakes, hump nosed pit viper which is considered mildly venomous previously turned out to be lethal one. More number of hump nosed

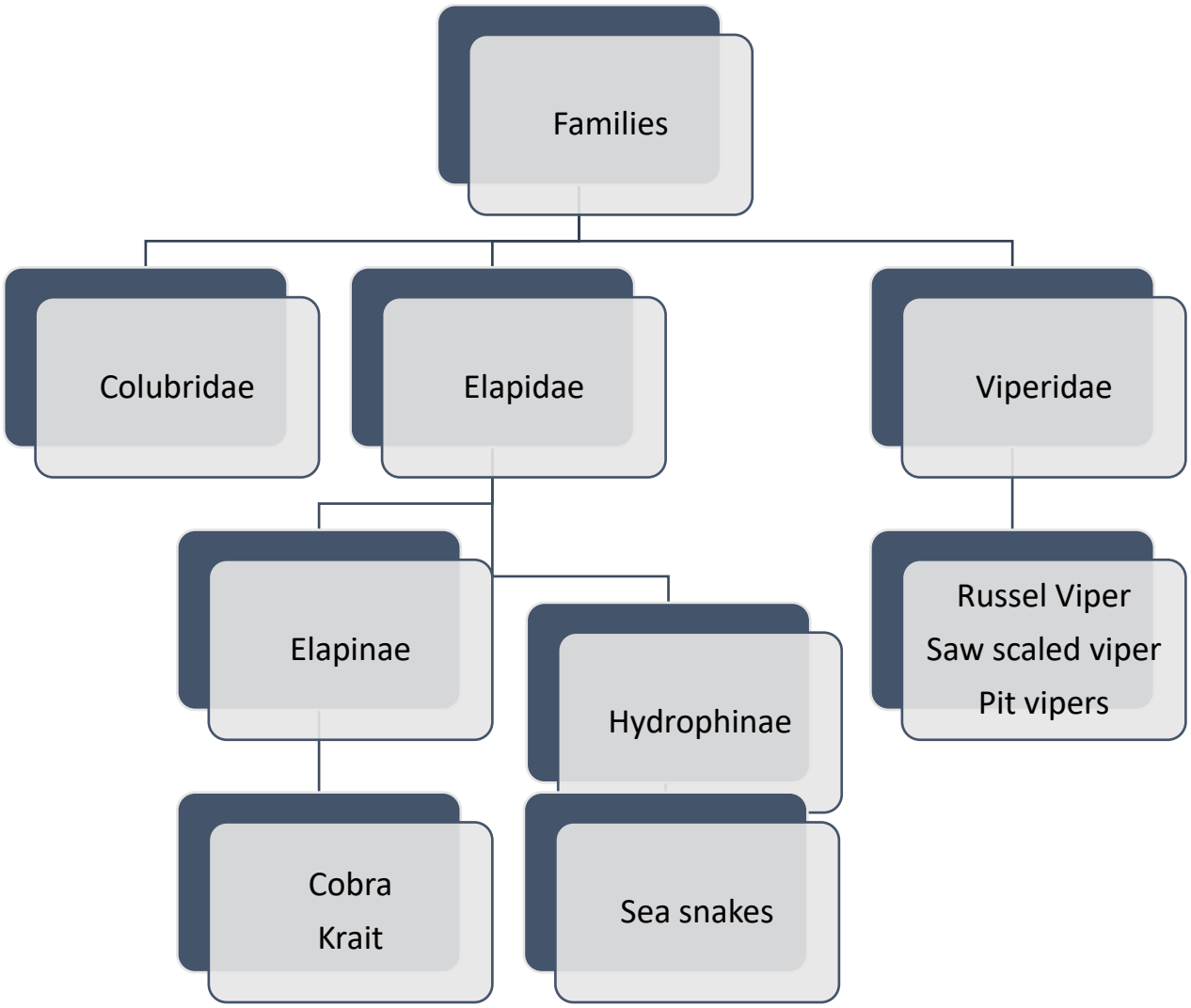
pit viper bites are recorded in Kerala. According to recent survey russel viper causing 43% of venomous snake bites in India. Common krait (18%), Indian spectacled cobra (12%), saw scaled viper (1.7%) and the rest includes hump nosed pit viper as well as other venomous snakes in India.

Snake species in India

Commonly encountered Non- venomous snakes

- Indian Rat Snake (Ptyas mucosa)\
- Common Cat Snake (Boiga trigonata)
- Checkered Keelback (Fowlea piscator) Asiatic water snake
- Indian Rock Python (Python molurus)
- Common Wolf Snake (Lycodon aulius)
- Common Sand Boa (Eryx johnii)
- Banded Racer (Argyrogena fasciolata)
- Banded Kukri Snake (Oligodon arnensis)
- Common Trinket Snake (Coelognathus helena)
- Black Headed Royal Snake (Spalerosophis atriceps)
- Common Bronzeback Tree Snake (Dendrelaphis tristis)
- Dog-faced Water Snake (Cerberus rynchops)

Venomous snakes chart



The Big four (Russel Viper, Saw Scaled Viper, Indian Cobra, Common Krait)

Other venomous Snakes

King Cobra (Ophiophagus Hannah)

Banded krait (Bungarus fasciatus)

Monocled Cobra (Naja kaouthia)

Pit vipers

- Hump Nosed Pit Viper
- Andaman Pit viper
- Bamboo Pit Viper
- Green pit viper
- Himalayan pit viper
- Malabar Pit Viper
- Large Scaled Pit Viper
- Mangrove Pit viper
- Horseshoe Pit Viper

Sea Snakes

- Banded Sea Krait (Laticauda colubrina)
- Blue Lipped Sea Krait (Laticauda laticaudata)
- Beaked Sea Snake (Enhydrina schistose)
- Shaw's Sea Snake (Lapemis curtus)

Apart from the big four snakes, All pit vipers are hemotoxic.

King cobra, monocle cobra and banded krait are neurotoxic.

Sea Snakes are neurotoxic, some of them are myotoxic

Medically important Snakes in India

RUSSEL VIPER

Very dangerous venomous snake in india.it causes major snake bite induced morbidity and mortality in India. It's hemotoxic snake venom can kill a person within 45 min if ASV is not given

Family: **Viperidae**

Scientific Name: **Daboia Ruselii**

Venom Type: **Hemotoxin**

Anti-snake venom**: Available**

Length of an adult: **3.3 Feet**

Lifespan: **10-17 Years**

Resemblance: **Saw Scaled Viper ,Indian Rock Python, Common Sand Boa,**

RUSSEL VIPER

Snakes that resembles Russel Viper

INDIAN ROCK PYTHON

(Non Venomous)

COMMON SAND BOA

(Non Venomous)

SAW SCALED VIPER (Other

Venomous Hemotoxic Snakebite)

COMMON KRAIT

Common krait also known as Indian Krait is one of the species of venomous snake found in the jungle and villages of the Indian subcontinent. It contains neurotoxins that can lead to neuromuscular paralysis, and its bite is life-threatening. Among the big 4 venomous snakes, common krait bite will not produce pain or local symptoms at bite site. It is sluggish and inactive at daytime. However, at night, it is very active as well as aggressive. Early morning neuroparalytic syndrome is one of the presentation to the hospital where the attenders unaware about the snake bite.

- Family: **Elapidae**
- Scientific Name: **Bungarus Caerulus**
- Venom Type: **Neurotoxin**
- Anti-snake venom**: Available**
- Average Length of an adult: **6.5 Feet**
- Lifespan: **10-17 Years**
- Resemblance: **Common wolf snake, Banded krait**

COMMON KRAIT

Snakes Resembling Common Krait

BANDED KRAIT

(Venomous Neurotoxic snake, ASV is not available)

COMMON WOLF SNAKE

(Non venomous)

INDIAN COBRA

The Indian spectacled is a highly venomous snake found in India. There are varied species of cobra in India, however this one is causing more number of bites. It contains neurotoxic venom that will cause neuroparalysis results in respiratory failure

Family: **Elapidae**

Scientific Name : **Naja naja**

Venom Type : **Neurotoxic**

Anti-snake venom : **Available**

Average adult Length : **7 Feet**

Lifespan : **9 Years**

Resemblance **: Oriental** Rat Snake, Banded Racer, Monocled Cobra, Checkered Keelback

INDIAN COBRA

Snakes Resembling Indian Cobra

MONOCLED COBRA

(venomous- neurotoxic)

RAT SNAKE

(Non venomous)

BANDED RACER

(Non venomous)

CHECKERED KEELBACK

(Non venomous)

SAW-SCALED VIPER

The saw-scaled viper is smallest among four venomous snakes in India. It is also called as little Indian viper. Like Russel viper, venom from the saw scale viper is hemotoxic. It lives in sandy areas, scrub lands and rocky habitats.

Family: **Viperidae**

Scientific Name: **Echis Carinatus**

Venom Type: **Hemotoxin**

Anti-snake venom**: Available**

Average adult Length: **2.6 Feet**

Lifespan: **23 Years**

Resemblance: **Common Sand Boa, Common Cat Snake, Russell's Viper**

SAW SCALED VIPER

HUMP-NOSED PIT VIPER

Hump-nosed pit viper is one of the common species in India. They are found in dense forests, tea plantations and hilly areas of South India. This snake is also nocturnal. It has triangular head which is even wider than its neck. It is called Hump Nosed because of nose which is somewhat inverted and broad. Anti-Snake Venom for hump nosed pit viper is yet to be developed.

Family: **Viperidae**

Scientific Name: **Hypnale Hypnale**

Venom Type: **Hemotoxic**

Anti-snake venom: **Unavailable**

Max. Length: **2-3 feet**

Lifespan: **10-15 years**

Morphology of venomous snakes

The venom apparatus of snakes consists of a pair of poison glands, their ducts and a pair of fangs. In venomous snakes the poison glands are situated one on either side of the upper jaw. Each poison gland is sac-like and provided with a narrow duct at its anterior end. During the venomous snake bite, snake using its pair of fangs to inject venom into tissues through the wound. The venom will flow through fang into tissue, some fangs contains through which venom enters. While injecting the venom, if the fang comes in contact with vessels, the venom will disseminate much faster.

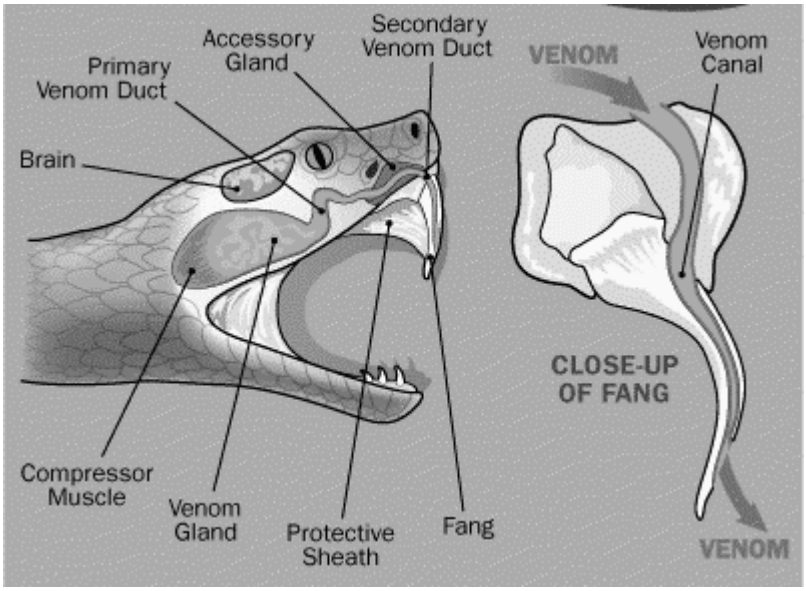
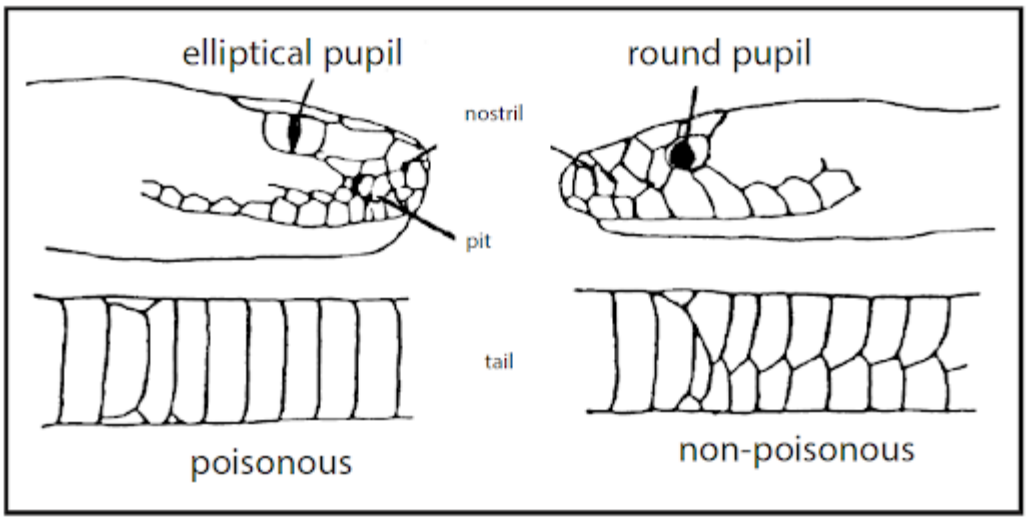


Figure - venom apparatus of snake

Venomous snakes have a typical head shape. Their heads are usually wide at the back and attached to a narrow neck. It will give a triangular-shaped appearance. It is not always accurate, despite it is being considered as a good indicator.

Another indicator is the pits (or holes) that present over their heads. They are present in all pit vipers present in Indian subcontinent. This means that each snake has two pits that appear on their snouts. Pits resemble nostrils and are located midway and slightly below the eye. Non-venomous snakes do not have pits.



When you look into the underbelly of snake, if it has single row of large scales, it is most likely to be venomous snake. If 2 or more rows of scales especially towards the tail end it is non venomous. This will be applied for most of the snakes, but there are some exceptions.

Most of the venomous snakes has vertical pupil and non-venomous will have round pupil. but exceptions are there.

Snake venoms

Snake venoms are mixtures of toxins which contain hundreds of poisonous proteins and enzymes. This results in wide degree of variation in venom nature as different venoms contain different combinations of toxins and quantities thereof. As everyone knows, very many different species of snake have different types of combinations of toxins; however, the variation can go

all the way down to differences between members of the same species. In fact, in some species, an adult's venom can be different to its venom as an infant. The constituents of venom of the same species different in various geographic locations. This renders challenge in making the ideal Anti-snake Venom. This wide range of venoms has the capability to cause neuromuscular paralysis, haemorrhages, tissue damage and necrosis, amongst other things.

Enzymes

1) Acetylcholinesterase

   It acts as the catalyst of the hydrolysis of acetylcholine into choline and acetic acid.it is one of the constituent of elapid venom

2) Hyaluronidase

   It is present in most of the venomous snakes. It hydrolyses hyaluronic acid and enters into the connective tissue and tissue spaces of the cells. SO, it is a main culprit responsible for the development of edema, swelling and progression of cellulitis.it is the enzyme responsible for the rapid absorption of the venom from bite site.

3) Arginine ester hydrolase

   This non-cholinesterase enzyme results in releasing of bradykinin and coagulant effect of some hemotoxic venom may be due to this enzyme also.

4) Phospholipase

It catalyses the hydrolyses of lipids. Phospholipase A2 is one of the factor considered to be responsible for the haemolysis due to snake venom. Direct effect on red cell membrane and indirectly through haemolytic agent, it causes haemolysis. It's effect on neurotoxic venom probably due to its role in disturbing electron transfer by phospholipase in the nerve tissue.

5) Proteinase

This proteolytic enzyme presents in viperid venom abundantly. This enzyme digest tissue protein and peptide leading to marked tissue changes and destruction. It is also responsible for the proteolytic disintegration of fibrinogenesis

6) L- Amino acid oxidase

Almost all snake venom contains this enzyme.it is responsible for yellow colour of the snake venom.

7) Phosphodiesterase

It breaks DNA, RNA and arabinoses derivative. It is found in majority of venomous snakes. It is thought to be responsible for the rapid fall in systolic arterial blood pressure.

8) Nucleotidase

It hydrolyses the phosphate monoesterase which links with DNA and RNA

9) Coagulopathy due to various factor activators

i) Factor V activator

ii) Factor X activator

iii) Indirect prothrombin activator

iv) Direct prothrombin activator

v) Thrombin like enzymes

Non- Enzymatic Proteins in Venom

a) Cardiotoxin

b) Hemorrhagin

c) Neurotoxin

Hemotoxic effect of the venom

Most of the hemotoxic snake venom contains both procoagulant and anti-coagulant effect. Anti-coagulant effect will dominate that results in coagulopathy.

Following mechanisms are responsible for coagulopathy

1) fibrinolysis/ fibrogenolysis action due to direct action on fibrin or fibrinogen
2) direct action of the venom anticoagulant by inhibiting clotting
3) By activation of plasma proactivator of plasminogen or direct act on plasminogen results in activation of fibrinolytic mechanism.
4) Inhibition of the blood clotting factors or the prevention of activation of one of the clotting factors

Neurotoxic effects of venom

Two types of neurotoxins are there

First one is cobra toxin or alpha bungaratoxin which is present in indian cobra, king cobra, most of the sea snakes and in majority of the elapidae family snakes. They produce anti-depolarizing neuromuscular block by acting on the post Junctional membrane of the motor endplate

Second one is beta-bungaratoxin. It acts on pre-synaptic membrane and causes profound reduction in acetylcholine output and produces neuromuscular block.

Beta bungaratoxin is present in common krait.

Different types of snake bites

Dry bites

The snake bites the victim but no venom is injected is called dry bite. Despite that there is a possibility of dry bite, always assume that all the snakebites are venomous bite, it is necessary to manage the bite as a medical emergency.

Venomous bite

When the Snake venom injected through their fangs into the bitten area is called venomous bites. It contains toxins which are used to kill or stun their preys.

Do and Don't After Snakebite

DO 'S

Do the **RIGHT** thing

R - **R**eassure the patient

Remove the ornaments around the bitten limb

I - **I**mmobilise the bitten limb same way as immobilisation of fractured limb using splints.

GH - **G**et to the Nearest Hospital as early as possible

T - **T**ell the doctor if there are any symptoms that had occurred on the way to the hospital

Don’t s

- Do not attempt to catch the live snake or try to kill it
- Do not tie tight ligature or tourniquet around the bitten limb
- Do not clean, cut, rub, abrade the bitten area
- Do not apply any local irritants
- Do not follow any traditional methods for the snake bite as they do not have any proven benefit to patients and because of the delay, it will be deleterious to the patient

Clinical manifestations of snakebite

Venomous snakebite has varied clinical presentation. It depends upon the species of the snake, unprovoked or provoked bite, fed or unfed snake, site of bite, amount of venom injected, dry bite or venomous bite, single or multiple bite, venom injected over the vessel, time duration between bite and ASV administration

Non Venomous Symptoms

It is related to fear and anxiety due to snake bite

- Palpitations, sweating, tremulousness, weakness, difficulty in swallowing and giddiness
- Tachycardia, tachypnea, elevated BP, Paraesthesia, cold extremities, dilated pupils.

Reassurance and transport to nearby healthcare facility as early as possible.

Symptoms due to venomous bite

It can be local or systemic or both

Depends on the species of snake and type of venom injected the clinical

presentations may vary

Four such common presentations are there

- Progressive weakness (Neuromuscular paralysis)
- Bleeding (vasculotoxicity/hemotoxicity)
- Myotoxicity
- Progressive cellulitis

NeuroParalysis

Due to venomous bite from Indian cobra or common krait

Presentation of symptom will be from 30 min – 6 hrs in India Cobra and 6-24 hrs in case of common krait bite.

Neurotoxic snake venom, whether it is alpha or beta bungaratoxin, it will cause descending neuroparalysis

First symptom will be Ptosis

Subsequently patient may develop

- Diplopia – double vision
- Dysphagia- difficulty in swallowing
- Dysarthria – difficulty in articulation

- Dysphonia – difficulty in producing voice
- Dyspnoea – breathing difficulty

Afterwards, paralysis of intercostal and diaphragmatic muscle results in respiratory paralysis which is acute life threatening emergency.

Impending respiratory failure in neurotoxic snakebite can be assessed by following methods

- Neck muscle weakness
- Diminished or absent deep tendon reflexes
- Single breath count in one exhalation (>30 is normal)
- Breath holding time – breath held in inspiration > 45 sec
- Able to complete a sentence in a single breath

These methods can identify the impending respiratory failure and patient can be referred to higher centre where advanced airway management is available.

EMNPS – Early Morning Neuroparalytic Syndrome

Because of common krait's nocturnal habitat, it usually bites the victim in the early morning. And also it has fine slender fangs which won't produce pain mostly. It doesn't produce local reaction like other venomous snakes. So, the victim or attender will be unaware about the snakebite until some neurological symptoms start appearing.

Patient usually brought by the attender with unexplained respiratory distress, epigastric pain with nausea, vomiting followed by neurological signs sudden onset of acute flaccid paralysis of descending type (locked in) may be the presenting feature which is called as EMNPS.

Careful clinical examination with clinical correlation as well as knowledge about endemicity of neurotoxic snakes will avoid unnecessary investigations as well as undue delay in initiation of treatment.

Hemotoxic envenomation

Snakes belongs to viperidae family namely Russel viper , saw scaled viper and pit vipers contains hemotoxic venom.

Local manifestations

Local swelling/edema around the bite site

Progressive ascending cellulitis

Formation blisters/necrosis/sometimes compartment syndrome

Systemic manifestations

Visible systemic bleeding manifestations such as

- Gum bleeding
- Epistaxis
- Ecchymotic patches

- Sub conjunctival edema
- Continuos bleeding from the bite site
- Rarely hematemesis/hemoptysis
- Hematuria

Venom induced disseminated intravascular coagulation

Life threatening bleeding manifestations like intracranial bleed, retroperitoneal bleed.

Acute kidney injury

Refractory shock

Multi organ dysfunction syndrome

Myotoxicity

Mostly present in sea snakebite

Clinical features will be muscular ache, muscle swelling and involuntary contraction of muscles

Rhabdomyolysis and tissue necrosis due to myotoxic snake venom leads to hyperkalaemia, cardiac dysrhythmias and acute kidney injury

Life threatening complications of snakebite

- Hypotension followed by refractory shock
- Acute respiratory failure in neurotoxic snakebite
- Acute kidney injury
- Compartment syndrome
- Secondary bacterial infection in wound and sepsis
- Disseminated intravascular coagulation
- MODS
- ARDS

Other rare complications

Acute visual loss (CRAO and other mechanism related)

Systemic capillary leak syndrome

Delayed complications

ASV induced serum sickness like reaction

Delayed recurrent coagulopathy

Russel viper induced hypopituitarism

Some AKI progressed to CKD

	Indian cobra	Common krait	Russel viper	Saw scaled viper	Pit vipers
Local tissue damage	Yes	No	Yes	Yes	Yes
Hemotoxicity	No	No	Yes	Yes	Yes
Neurotoxicity	Yes	Yes	Yes	No	No
AKI	No	No	Yes	Yes	Yes
Atrophine/ Neostigmine	Respond	No	No	No	No

Investigations

First and foremost, investigation is WBCT

- Simple, but relevant bedside test
- Take a new, washed, clean glass test tube
- Place a 2ml of patient's venous blood
- It should be kept untouched and undisturbed for 20 minutes at ambient room temperature
- If the blood is clotted, may repeat it again if indicated
- If the blood is not clotted, it is due to hemotoxic venom induced consumption coagulopathy
- It indicates plasma fibrinogen concentration is less than 0.5g/l

Other investigations

Electrocardiogram

Complete blood count including total and differential count

Platelet count

Renal function tests including Serum creatinine and blood urea

If needed

Liver function test

Serum electrolytes

Blood peripheral smear

PT and APTT

Creatinine phosphokinase

Cholinesterase

Treatment

After admission and monitoring for signs and symptoms of Envenomation. If there is any signs of envenomation, Anti snake venom will be the main modality of treatment.

ASV – Anti snake Venom

ASV acts by bind, stun, neutralise and eliminate the venom from systemic circulation if it is administered timely and appropriately. Success rate of ASV depends on timing of ASV administration, selection of appropriate mono/polyvalent anti-snake venom, venom diversity and its antigenic property

In India ASV is Polyvalent which contains anti-venom of all big 4 snakes

(Russel viper, saw scaled viper, common krait, Indian cobra)

1 ml of Indian polyvalent anti-snake venom will neutralize

- 0.6 mg of Indian Cobra
- 0.6 mg of Russel Viper
- 0.45mg of Common krait
- O.45 mg of saw scaled viper

Available formulations of ASV

Freeze dried form (heat stable/shelf life of 5 year)

Near liquid form (heat labile- require cold chain for its maintenance 2-8°C, Refrigerated shelf life is 2 years)

Indications of anti-snake venom

- Coagulopathy
- Acute kidney injury
- Neurotoxic signs
- Cardiovascular abnormalities such as hypotension and shock
- Local signs and symptoms

Administration

It has to administered through intravenous route

Intra muscular, subcutaneous route, local infiltration is not recommended

Test dose aren't needed

It should be given by diluting in saline and in a slow IV infusion preferably over one-hour period

ASV in children and pregnant women should be given as same dose as in adults.

ASV reactions

Early anaphylactic reactions

It occurs in 10-180 minutes of start of therapy

It is characterised by intense itching starting from scalp, dry cough, nausea, vomiting, abdominal colic, diarrhoea.

Rarely life threatening anaphylaxis may set in as hypotension, bronchospasm and angioedema.

With first sign of reaction 0.5 mg of epinephrine should be given intramuscularly into anterolateral aspect of thigh.

Pyrogenic reaction occurs 1-2 hr after treatment, it presents as chills, rigor, fever and hypotension.

Late reaction (serum sickness type)

It occurs 1-12 days after the treatment with ASV. Features includes nausea, vomiting, myalgia, arthralgia, recurrent utricaria, diarrhoea, immune complex nephritis and rarely encephalopathy.

Other management modalities

In case of neurotoxic snakebite, due to India cobra or a suspected Indian cobra bite, on the first symptom of neurotoxicity

Injection atropine 0.6mg followed by injection neostigmine 1.5 mg IV stat

↓

Repeat Inj. Neostigmine 0.5 mg / atropine 0.6mg every 30 min for 5 doses

If there is improvement, it can be repeated after the 5 doses, In 1 hr, 2 hr, 6 hr and 12 hrs.

If there is no improvement, it can be stopped after 3 doses.

For krait bite, injection calcium gluconate 10 ml IV over 5-10 mins every 6 hours, can be give till neuroparalysis recovers (5-7 days)

In Respiratory failure by neurotoxic venom, assisted ventilation may be necessary such as mechanical ventilation.

Haemolysis in case of acute kidney injury

For coagulopathy, if it is persisted even after the maximum doses of anti-snake venom, treated with Fresh Frozen Plasma (FFP)

For local wound tissue necrosis, surgical wound debridement may be needed.

For compartment syndrome, fasciotomy need to be done.

For secondary infection, intravenous broad spectrum antibiotics can be given

IV fluids for hypotension/shock.

AKI in snake bite

Acute kidney injury is one of the notorious complications of snake bites. It some rural areas it remains unidentified that leads significant morbidity as well as mortality. The progression of AKI can be prevented if the patient's venom is neutralised by anti-snake venom. Once the AKI sets in, there is a need of higher centre with dialysis and intensive care facility. In resource poor areas it is even more difficult.

Among venomous snakes in India, two predominant hemotoxic snakes namely Russel viper and saw scaled viper are known to cause AKI in bitten patients.

AKI in snakebite is one of the delayed manifestations of snakebite, despite some of the patients may present earlier. So, all the patients who were treated for these two venomous bite should be observed for the development of AKI, even if their earlier symptoms were subsided due to administration of ASV. There are certain conventional parameters that predicts the progression of AKI such as urine output, serial measurements of urea and creatinine. But it will be useful when there is a marker that predict the occurrence of AKI very soon after snakebite.

AKI – Definition

According to KDIGO – The Kidney Disease- Improving Global Outcomes It is defined as abrupt decrease in kidney function, results in the retention of urine and other waste products of nitrogen and dysregulation of extracellular volume and electrolytes.

It includes

- Increase in serum creatinine ≥ 0.3 mg/dl within 48 hour
- Increase in serum creatinine ≥ 1.5 times baseline, which is known or presumed to have occurred within the past 7 days

- Urine volume < 0.5 ml/kg/hr for 6 hours

Stages of AKI

KDIGO definition of acute kidney injury

Stage	Creatinine Criteria	Urine Output Criteria
1	Cr 1.5-1.9 times baseline, OR Cr increase >0.3 mg/dL	< 0.5 ml/kg/hr x 6-12 hours
2	Cr 2-2.9x baseline	<0.5 ml/kg/hr for >12 hours
3	Cr > 3x baseline, OR Cr > 4 mg/dL, OR Initiation of dialysis	<0.3 ml/kg/hr for >24 hours, OR Anuria > 12 hours

Pathogenesis of Acute kidney injury in snakebite

Despite there were plenty of researches and studies were done, still the exact mechanisms and pathophysiology of snake venom induced AKI is not precisely known. Currently it is proposed that many factors are responsible for the development of AKI in snake bite patients

Intravascular haemolysis

Haemolysis results from one main constituent of venom " Phopspholipase A2". It causes haemolysis by direct hydrolytic effect on RBC membrane phospholipids and indirectly through production of strong haemolytic component called lyolecithin. Following the Russel viper bite, 50% of patients showed evidence of intravascular haemolysis like hemoglobinuria, anemia, abnormal peripheral blood smear, raised free haemoglobin, jaundice and reticulocytosis.

DIC

Hemotoxic venom, especially from viperidae family, have multiple numbers of peptides and proteins which are known to activate or inactivate various clotting mechanisms.

Prothrombin activators of different types present in snake venom. Russel Viper venom contain a factor V activating serine proteinase. RVV will convert Factor V to Factor Va and factor IX to factor IXa. It also contains potent activator of coagulation factor X. Snake venom also contains number of components, including those causing aggregation as well as inhibition of platelet aggregation.

Hemotoxic venom also contains proteins that has anticoagulant activation properties. They will activate protein C that inhibits factor Va and VIIIa. In another way, it inhibits factor IX and X also.

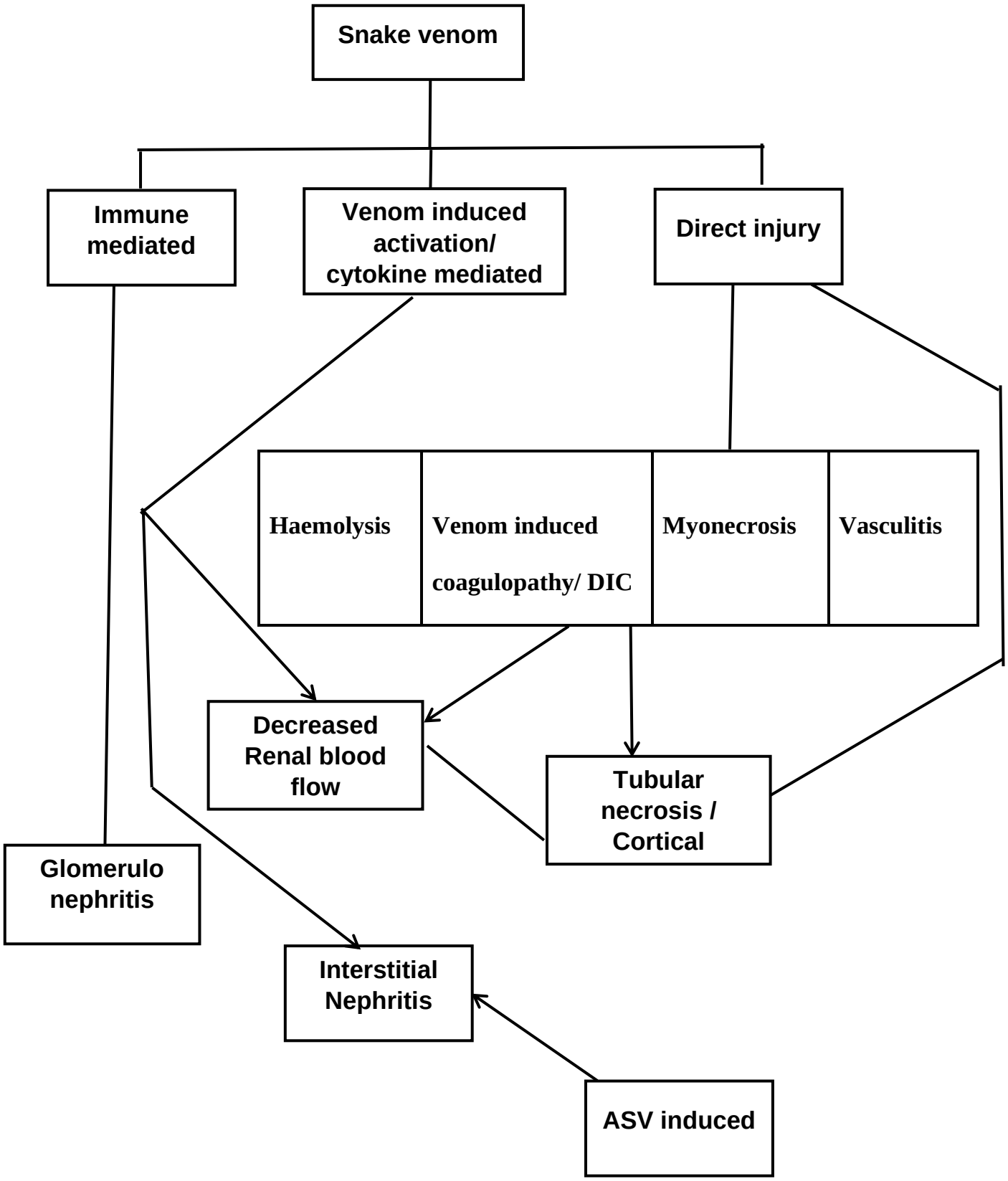
The final coagulation disturbances result from the collective action of anticoagulant, procoagulant activity, fibrolytic and fibrogenolytic activity. Many of the experimental studies were proven that DIC plays major role in snake bite induced AKI. They produce MAHA- microangiopathic haemolytic anemia and thrombocytopenia and also clogs the renal microvasculature results in cortical necrosis.

Hypotension

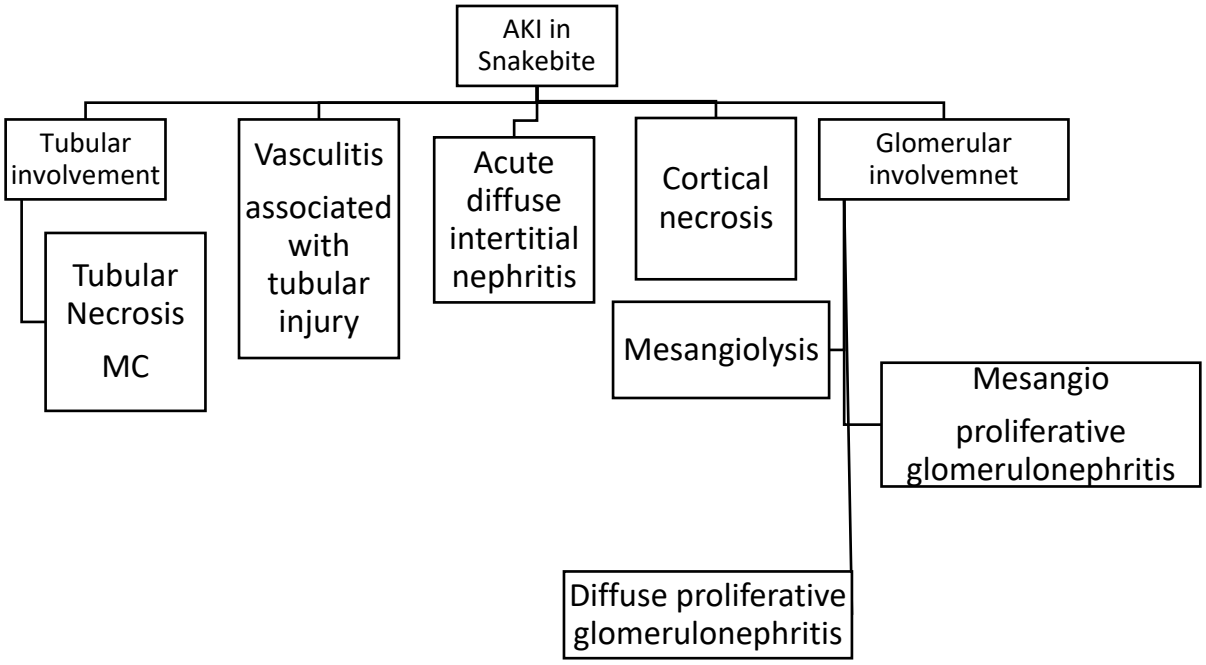
There are very many causes of hypotension due to snakebite. Acute envenomation will cause vasodilation and increased capillary permeability due to the effect of the venom. Because of coagulopathy, there will be bleeding into tissues, interstitial spaces and also externally through wound. Finally, some of the enzymes in viper venom will cause direct myocardial depression. All those above mentioned mechanism can lead to hypotension and shock that results in decreased RBF, and resultant precipitation of AKI.

Direct Venom Related Nephrotoxicity

Many experiments that were done in rhesus monkeys, Sprague dawley rats by injecting viper venom into them. It results in complete lysis of vascular smooth muscle cells, varying degree of epithelial injury in tubules, complete disintegration of mesangial cells. It has demonstrated that viper venom is capable of causing direct renal damage that too in dose dependent manner.


Snake venom
Immune mediated
Venom induced activation/ cytokine mediated
Direct injury
Haemolysis
Venom induced coagulopathy/ DIC
Myonecrosis
Vasculitis
Decreased Renal blood flow
Tubular necrosis / Cortical
Glomerulo nephritis
Interstitial Nephritis
ASV induced

Various modes of renal involvement in Snake bite induced Acute Kidney Injury



NLR – Neutrophil Lymphocyte Ratio

NLR is gained popularity recently. In the literature, the NLR is studied as an independent prognostic factor of morbidity and mortality in several conditions, such as cancers and cardiovascular diseases. NLR is also usually elevated in infections, inflammations, metabolic derangements, exposure toxin and post-operative complications. Nevertheless, none of these studies based their cut-off on data coming from population in good health, and none on data coming from normal controls. Some of these studies used their cut-off value on the basis of the median, higher quartile or values determined by the use of receiver-operating curves.

Snake venom exert a reaction to host that results in increased TNF and various interleukins (IL-6, IL-7, IL-8, IL-12, IL-17) which is similar to that of other inflammatory and infectious conditions. But measuring these biomarkers are difficult and expensive. In contrast, NLR is a simple index derived from routine blood tests which might provide equal and valuable information. Because it is a ratio, NLR is relatively more stable than individual leukocytic parameters that are easily altered by many simple conditions (e.g. dehydration, over hydration, diluted blood specimens, and in vitro blood specimen handling).

NLR in snakebite

There is significant leukocytosis, neutrophilia and lymphocytopenia in patients with snakebite envenomation has been reported in various studies like Moreira et al (2009), Zornetta et al. (2012); Elbey et al. (2015).
Increased NLR ratio is associated increased envenomation and strongly correlation with increased morbidity and mortality.

There is a strong correlation between snake envenomation and inflammatory syndrome and innate immune response that might contribute to the local and systemic inflammatory events with induction of neutrophil activation is suggested by Zornetta et al. (2012) .

The neutrophil elevation in snake bite due to demargination of neutrophils from the endothelium, delay of neutrophil apoptosis, and effect of growth factors on stem cells. Whereas, lymphocytopenia occurs in response to physiological stress-induced margination to the reticulo-endothelial system, redistribution and accelerated apoptosis. The elevation of NLR is set to be started as early as one-hour after envenomation.

SPOT PCR

SPOT Protein Creatinine Ratio

Proteinuria is excretion of protein in the urine. Normally small amount of low molecular weight proteins and trace amounts of albumin are filtered by glomerulus from the plasma and reabsorbed in the tubules. Daily normal excretion of protein in urine is less than 150g.

Among the total protein excretion, constituents include mucoproteins (mainly Tamm–Horsfall protein), blood-group proteins, albumin, immunoglobulins, mucopolysaccharides and very small amounts of hormones and enzymes.

Proteinuria is physiological in healthy individuals, even considered physiological even it is excreted beyond the normal range in some conditions like orthostatic proteinuria. But pathological proteinuria is a marker of underlying renal dysfunction.it can be considered as glomerular proteinuria, tubular proteinuria and overflow proteinuria. Proteinuria is recognised as diagnostic marker, prognostic marker, assessment of progression of certain diseases.

Commonly used to methods to measure the proteinuria includes Urine dipstick, 24-hr urinary protein excretion, Spot urine protein creatinine ratio and Albumin Creatinine ratio. Both urine dipstick and ACR are being used to detect albumin and the remaining two were used calculate the total protein excretion including albumin.

The 24-hour urine collection test is the gold standard method of assessing the urinary protein excretion in patients with renal diseases. But it is cumbersome procedure that require lot of time and skill as well as cooperation from the patient.

The Urine Protein Creatinine Ratio in a single voided sample was first Established during 1983.Since then it is becoming widely accepted marker to assess the renal function. Majority of studies were found the correlation

between the protein content of twenty-four-hour urine collection and the PCR in a single voided sample. It has been recommended by the National Kidney Foundation-K/DOQI guidelines.

It is possible to measure albumin creatinine ratio, but it is usually required for detection of the early stages of diabetic nephropathy. In this study, it is decided to measure the proteinuria which includes not only albumin but also tubular and other proteins.

Spot PCR is considered to be normal when the ratio is <0.3. More than 1 considered as high range as more than 3.5 considered as nephrotic range Proteinuria. but in our study raise in PCR value rather than cut off range has taken into account.

AIM & OBJECTIVES

AIMS AND OBJECTIVES

- The aim of the study is to determine the PREDICTORS of AKI following hemotoxic snake bite in patients presenting to our institute

- Early identification of AKI in Haemotoxic snake bite patients

MATERIALS AND METHODS

MATERIALS AND METHODS:

SOURCE OF DATA

Patient admitted to Madurai Medical College with alleged history of

snake bite which show haemotoxic envenomation signs will be included in the study.

METHOD OF COLLECTING THE DATA*:*

The study will be conducted in 75 snake bite patients admitted within 24 hours in Government Rajaji Hospital, Madurai during the study period from July 2021 – December 2021.

STUDY METHOD

Longitudinal prospective study

DEFINING CRITERIA

- Evidence of bite by a venomous snake included presence of fang marks consistent with a snake bite at the alleged site of bite
- Identification of snake if possible, either as per patient's history or if a dead snake is brought by a patient or attenders
- Evidence of local toxicity/systemic envenomation (specifically haemotoxicity in the form of bleeding manifestations and/or prolonged whole blood clotting time) with alleged h/o snake bite

INCLUSION CRTIERIA:

Patient with definitive history of snake bite comes within 24 hrs of bite, with signs of envenomation like bleeding manifestation and prolonged clotting time.

EXCLUSION CRITERIA:

- Snakebite with no signs of envenomation
- Snakebite with envenomation other than haemotoxicity
- Diabetes mellitus
- Hypertension
- Urinary tract infections,
- Pre-existing renal disease
- Acute illness/infection/fever
- Pregnancy
- Usage of nephrotoxic drugs for the last three months.
- H/o NSAID drugs abuse
- Age more than 60 years

Laboratory Assessment

- Random urine samples will be collected on admission and every 24hrs for 3days
- Urinary protein will be measured by spot PCR (Protein creatinine ratio)

- WBCT on admission
- Hematological investigations include CBC (Hemoglobin, TC, DC, PLATELET COUNT) by auto analyzer and Complete hemogram with Peripheral smear. (by pathology)
- Biochemical tests include blood urea, serum creatinine, RBS on admission and every 24 hours if needed

DATA AND STATISTICAL ANALYSIS

The collected data was analyzed using mean, mode for demographic data and frequency percentage for the analysis of the clinical data. Statistical Analysis was done using SPSS software version 23.0. A ‘p’ value less than 0.05($p<0.05$) is considered significant

STATISTICAL ANALYSIS

Statistical analysis was performed with IBM SPSS version 26 (SPSS Inc., Chicago, IL). Descriptive statistics was computed. Data were tested for normality using Shapiro wilks normality test. Due to the skewed data levels, mann whitney U test was used for between group analysis. Chi square test was used to analyse categorical variables. Receiver Operating Characteristic Curve was used to find out cut-off point of markers in predicting AKI. A significance was set as $p < 0.05$.

The non parametric Friedman test was used to compare urea and creatinine levels of both AKI and Non AKI grp group measured at 3 occasions. A post hoc Dunn pairwise test was used for pairwise comparison at all possible combinations to examine where the differences actually occur. Hence it is a multiple comparison bonferroni correction [p value/ no.of. Dunn test used] has been done.

OBSERVATION AND RESULTS

Observation and Results

Base line characteristics of population

This study has been done on population of 75 who came to Government Rajaji hospital, Madurai with alleged history of snakebite

		N	%
Gender	Male	58	77.3
	Female	17	22.7
Age	10-19 years	5	6.7
	20-29 years	24	32
	30-39 years	23	30.7
	40-49 years	16	21.3
	50-60 years	7	9.3
Snake identified	unknown	44	58.7
	R.V	19	25.3
	S.S.V	12	16
Bleeding manifestations	Nil	72	96
	Bleeding gums	2	2.7
	Hematuria	1	1.3

Table – shows demographic data collected in this study from the patients

	Minimum	Maximum	Mean	Std. Deviation
AGE	16.0	55.0	34.5	10.0
TC	6460	26290	13552	4535
NEUTROPHILS	33.0	95.0	84.0	10.7
LYMPHOCYTES	4.0	57.0	12.4	8.9
NLR	0.6	23.8	10.4	6.3
URINE PROTEIN	5.0	176.0	38.1	53.8
URINE CREATININE	12.0	76.0	30.7	14.5
PCR	0.1	8.3	1.4	2.2

Table: Lab parameters collected in this study

Gender Distribution Of Snakebite Patients

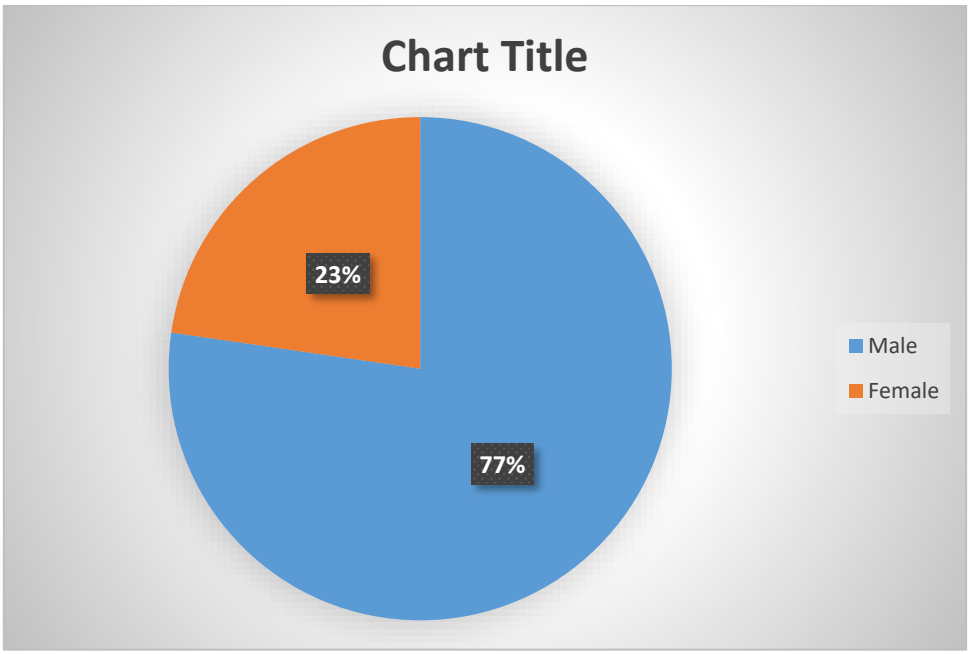
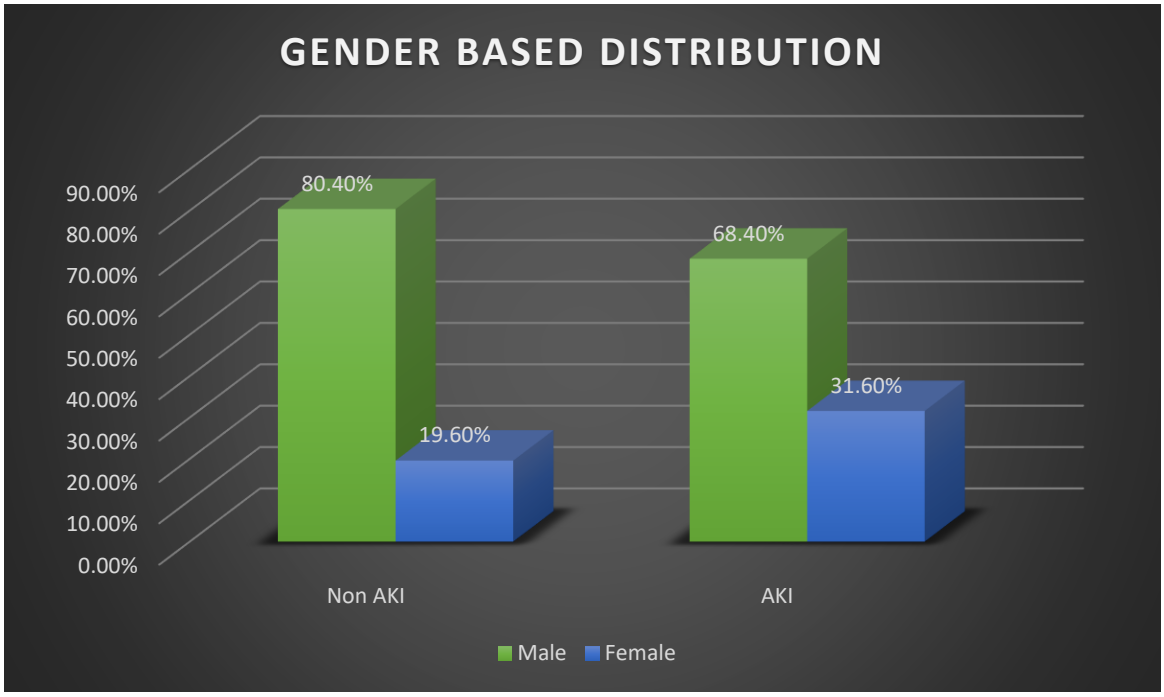


Chart: Gender distribution of total study populations

Among the total number of patients, some went in for AKI., though the proportion of female patients were low, one third of them went in for AKI

	Non AKI	Non AKI	AKI		P value
Male	45	80.40%	13	68.40%	0.221
Female	11	19.60%	6	31.60%	

Chi square test ; * shows ($p<0.05$)



Graph: Distribution of male and female patients with AKI and without AKI

Age distribution of cases

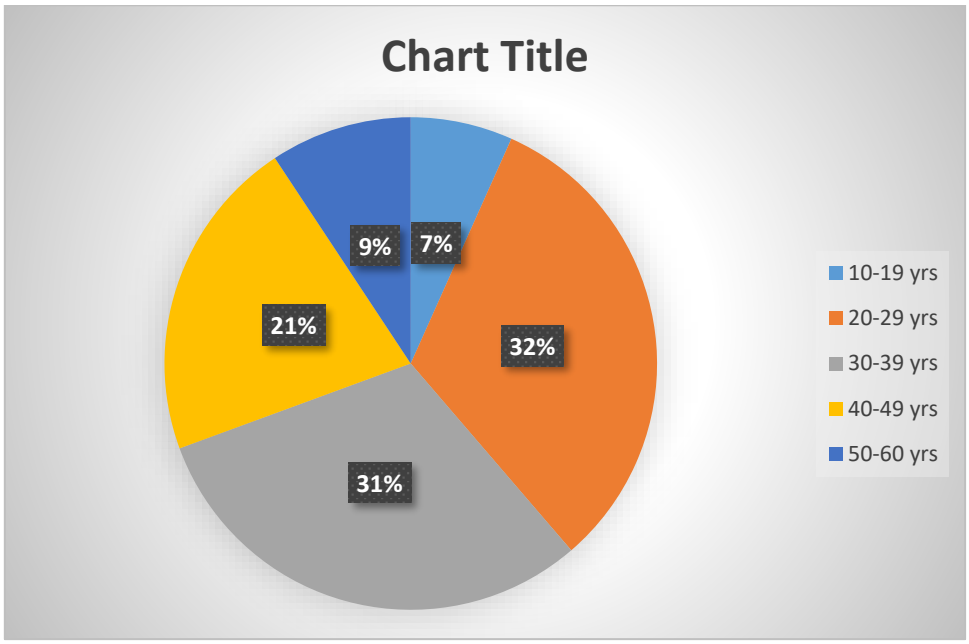


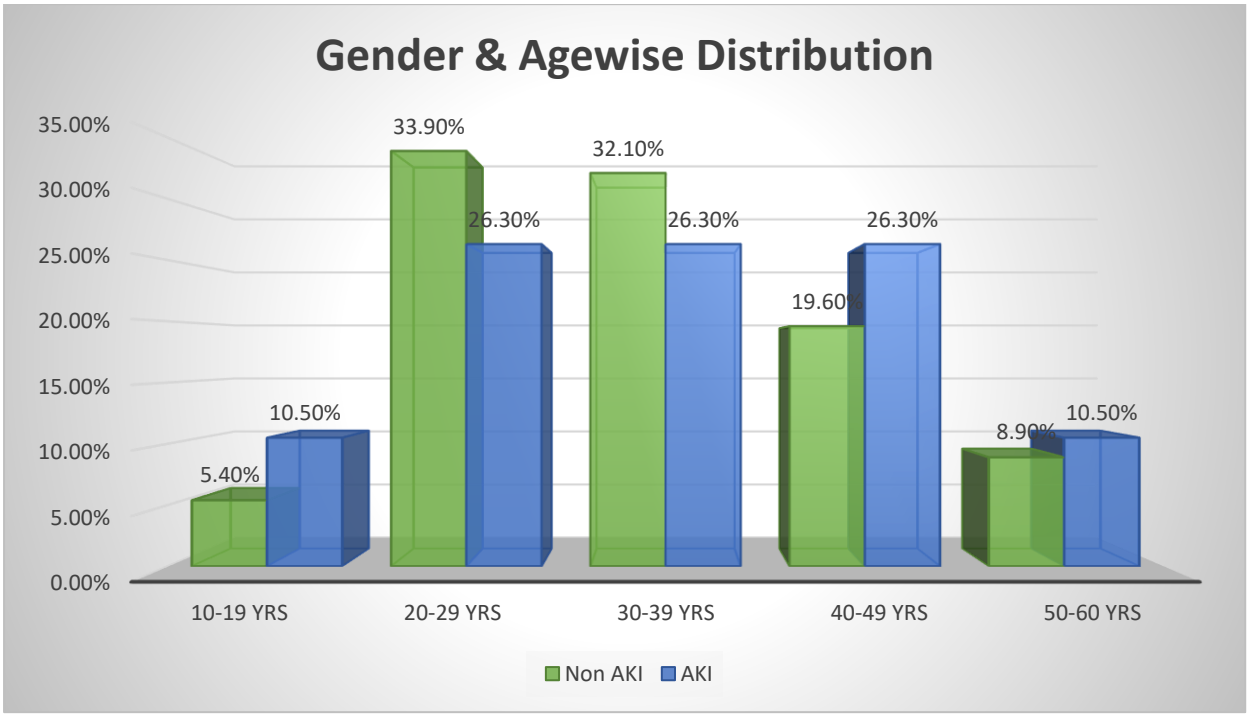
Chart: Age wise distribution of study populations

	Non AKI	Non AKI (%)	AKI	AKI (%)	P value
10-19 yrs	3	5.40%	2	10.50%	0.858
20-29 yrs	19	33.90%	5	26.30%	
30-39 yrs	18	32.10%	5	26.30%	
40-49 yrs	11	19.60%	5	26.30%	
50-60 yrs	5	8.90%	2	10.50%	

Chi square test; * shows (p<0.05)

Table : Age wise distribution of snakebite patients

Most of our patients in the present study were in the age group of 20-40 years (69%).



Graph: shows Male & female ratios in agewise distribution

Snake species in our study

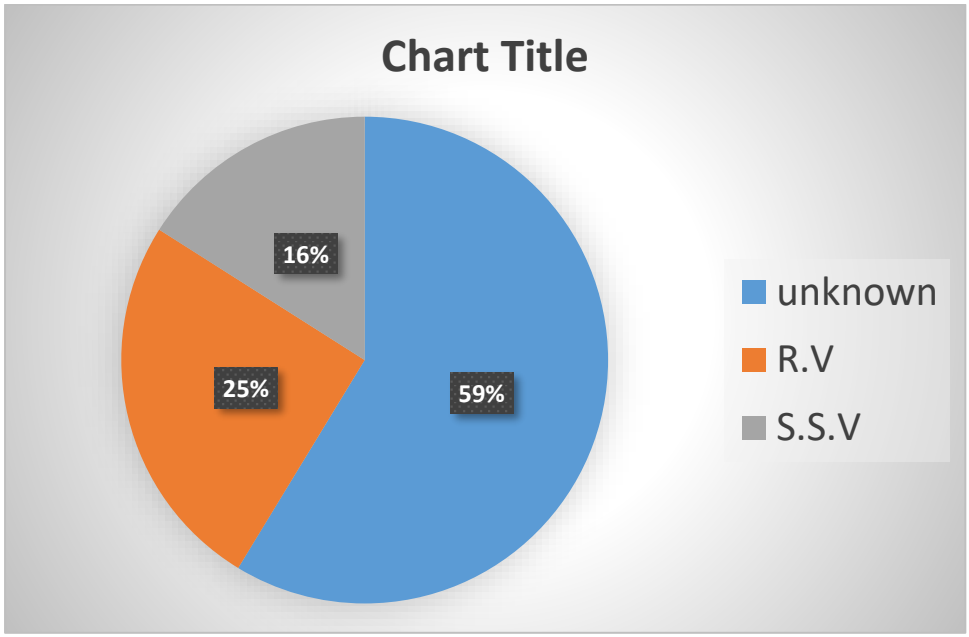
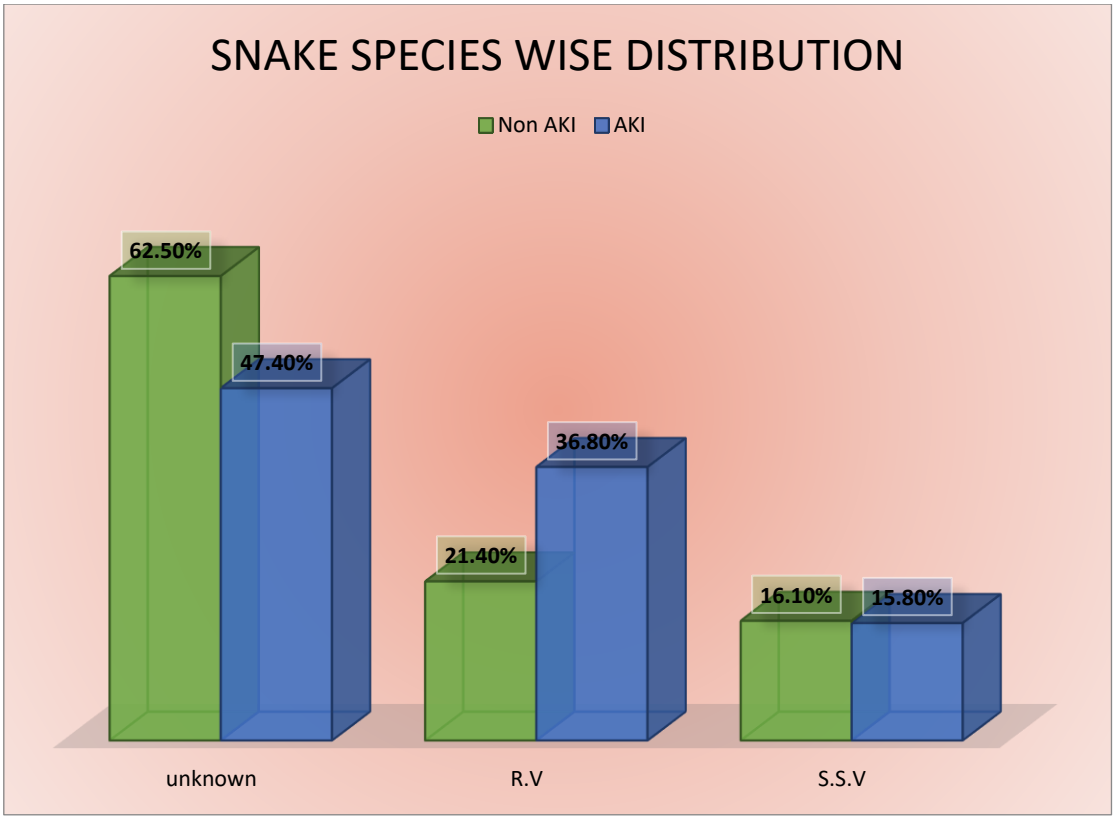


Chart: Distribution of snake species

	Non AKI	Non AKI	AKI	AKI	P value
Unknown	35	62.50%	9	47.40%	0.390
Russel Viper	12	21.40%	7	36.80%	
Saw Scaled Viper	9	16.10%	3	15.80%	

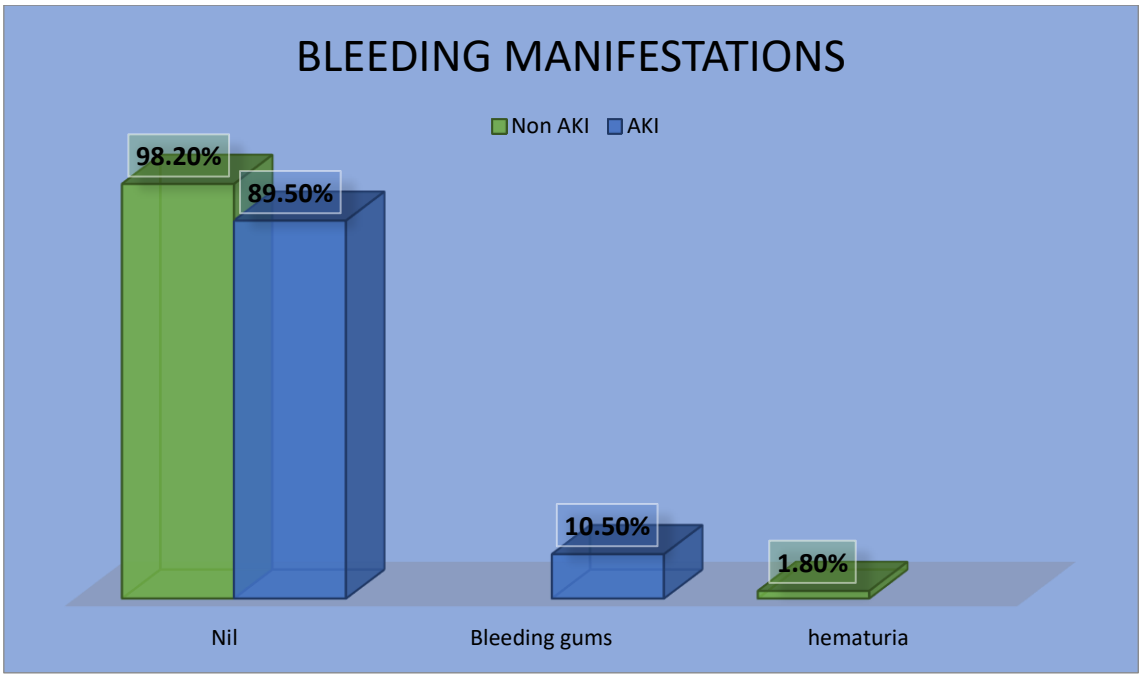
Chi square test: * shows ($p<0.05$)

Table: Distribution of patients bitten by Russel viper and Saw scaled viper and unidentified snakes



Graph: Shows specieswise distribution of patients with AKI and without AKI

All the patients in this study were positive for whole blood clotting time, few showed some bleeding manifestations



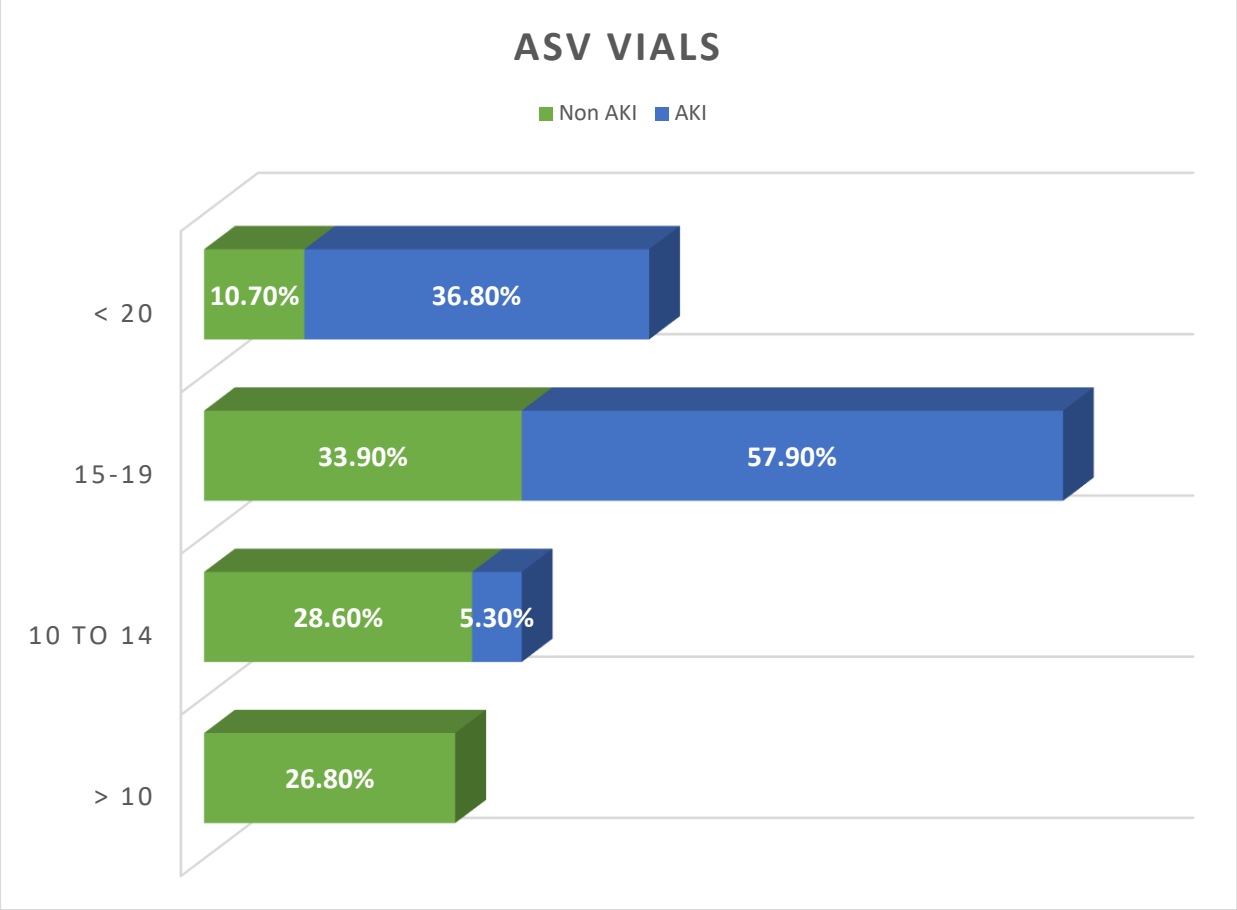
Graph: shows that majority of patients didn't present with specific bleeding manifestations

ASV Vials

	Non AKI	Non AKI	AKI	AKI	p value
> 10	15	26.80%	0		0.001*
10 to 14	16	28.60%	1	5.30%	
15-19	19	33.90%	11	57.90%	

Chi square test; * shows (p<0.05)

Table: ASV vials usage distribution



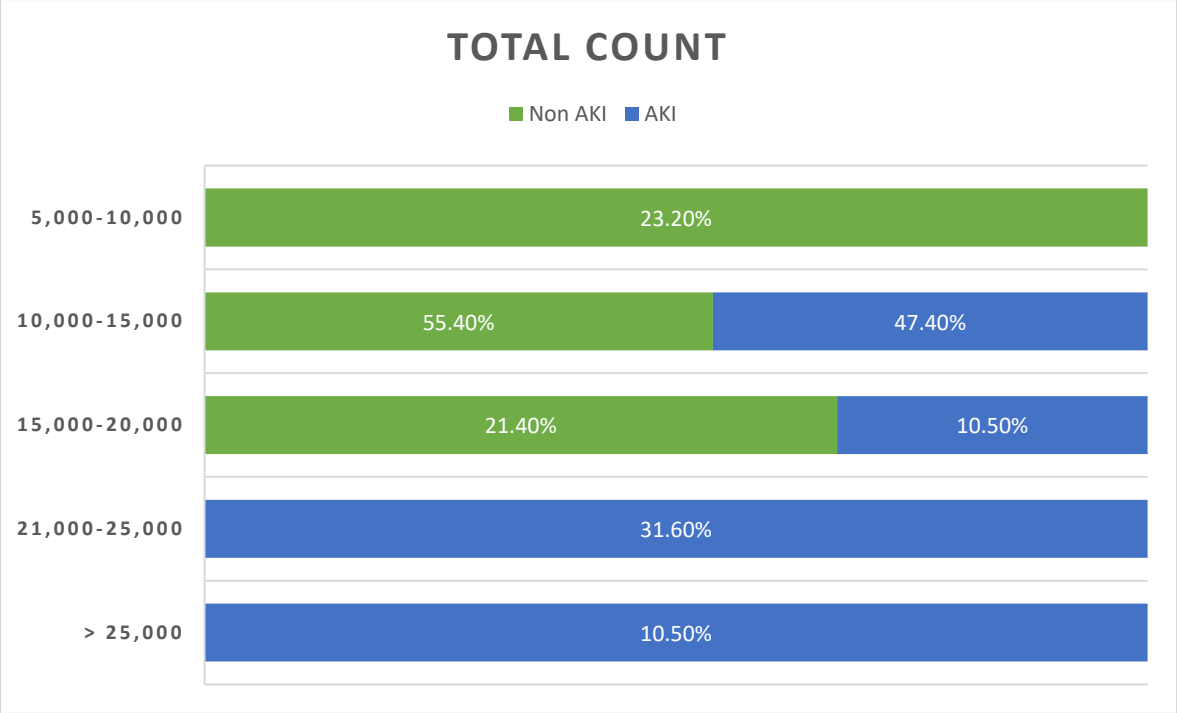
Graph: shows usage of ASV vials in our study and their of percentage distribution in AKI and Non-AKI patients

Total Count

	Non AKI	Non AKI	AKI	AKI	p value
> 25,000	0		2	10.50%	
21,000-25,000	0		6	31.60%	
15,000-20,000	12	21.40%	2	10.50%	0.001*
10,000-15,000	31	55.40%	9	47.40%	
5,000-10,000	13	23.20%	0		

Chi square test; * shows (p<0.05)

Table: Distribution of haemotoxic snake patients in this study according to their total count



Graph: Distribution of total count in AKI and Non AKI patients

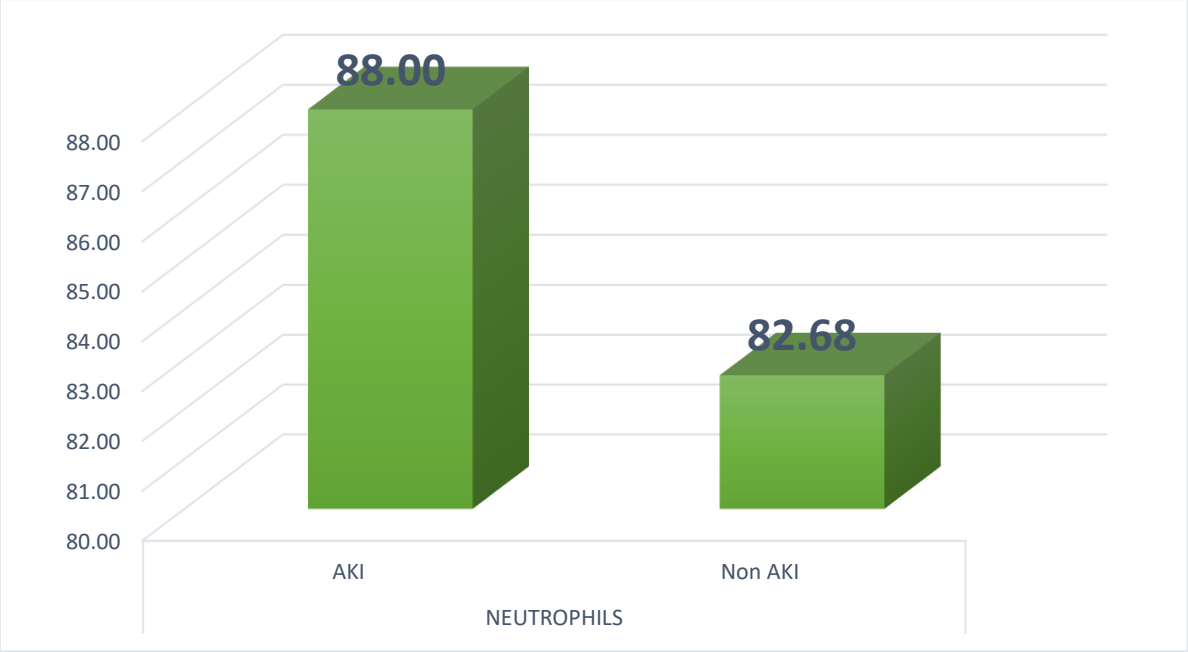
Mean and Standard Distribution

	AKI	Mean	Std. Deviation	p value
AGE	AKI	34.89	10.96	0.831
	Non AKI	34.41	9.78	
TC	AKI	17690.53	5748.95	0.001*
	Non AKI	12148.39	2989.01	
NEUTROPHILS	AKI	88.00	8.75	0.011*
	Non AKI	82.68	11.05	
LYMPHOCYTES	AKI	8.53	5.79	0.006*
	Non AKI	13.70	9.47	
NLR	AKI	13.87	6.44	0.005*
	Non AKI	9.19	5.81	
URINE_PROTEIN	AKI	114.37	54.54	0.001*
	Non AKI	12.29	15.45	
URINE_CREATININE	AKI	28.58	10.07	0.961
	Non AKI	31.43	15.78	
PCR	AKI	4.46	2.59	0.001*
	Non AKI	0.37	0.22	

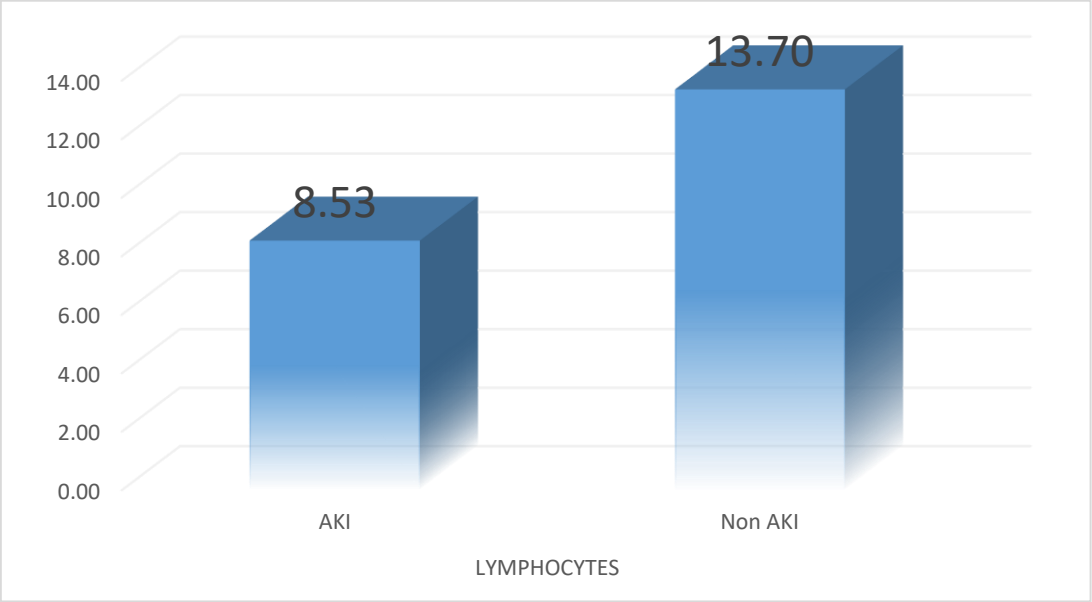
Mann whitney U test ; * shows ($p<0.05$)

Table: Mean and Standard deviation of all values according to AKI and Non AKI

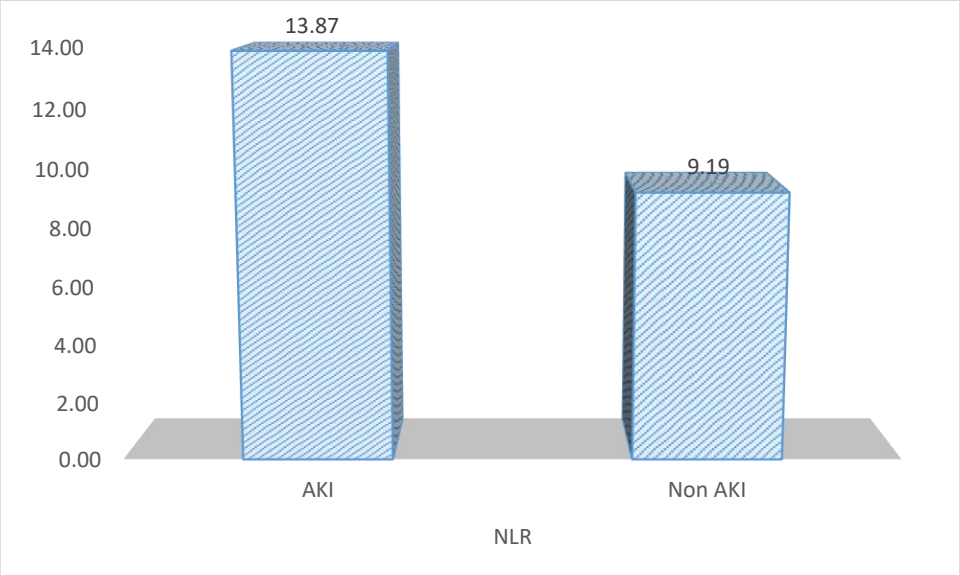
Neutrophil Lymphocyte Ratio - NLR



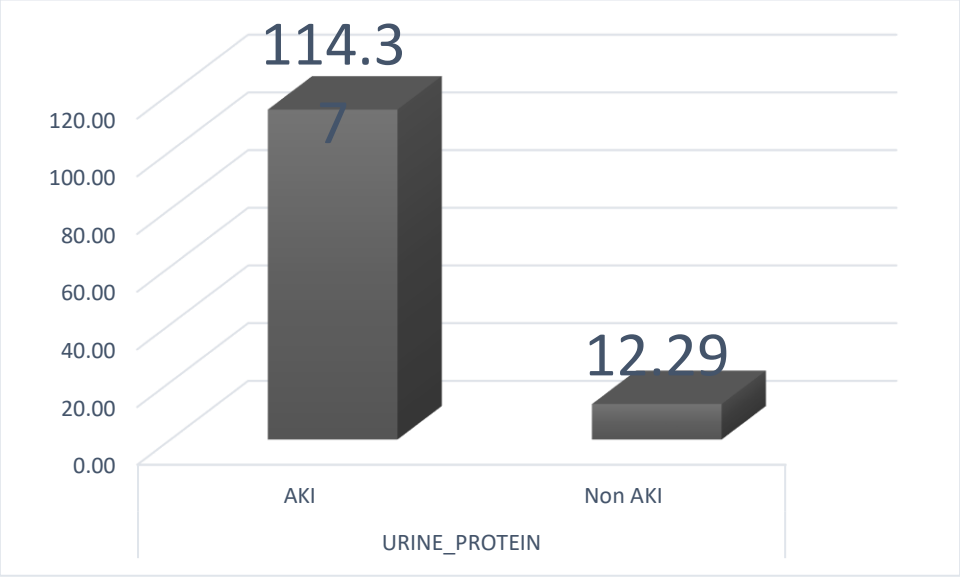
Graph: Neutrophils in hemotoxic snakebite patients



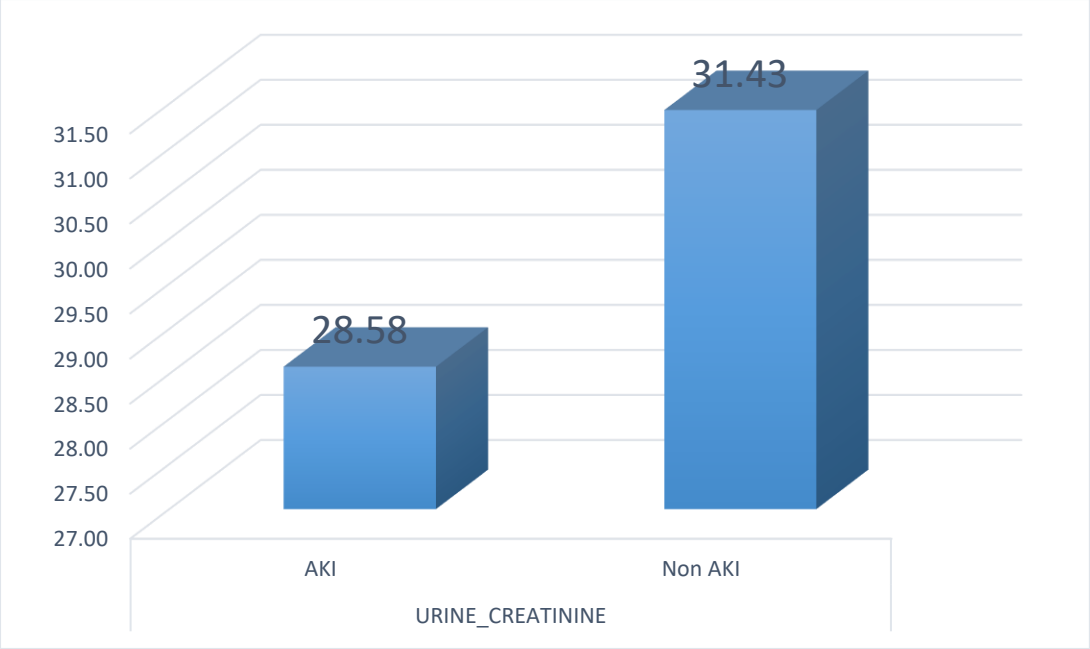
Graph: Lymphocytes in hemotoxic snakebite patients



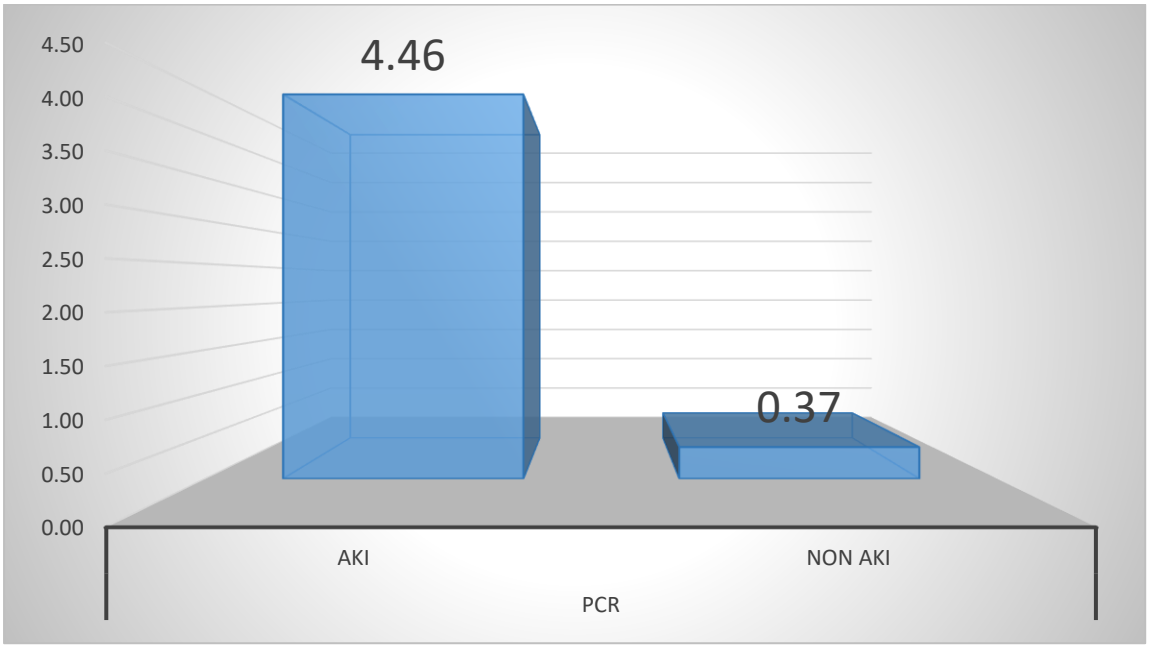
Graph: NLR in hemotoxic snakebite patients



Graph: Urine Protein in hemotoxic snakebite patients



Graph: Urine Creatinine in hemotoxic snakebite patients



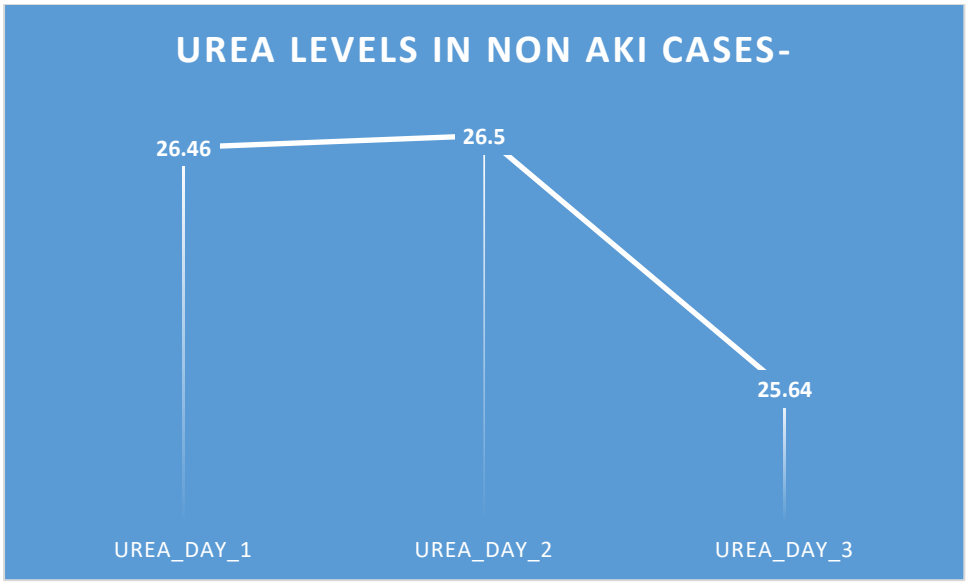
Graph: PCR in AKI and Non AKI patients

Urea levels in Non AKI patients

Non AKI	Mean	Std. Deviation	p value
UREA_DAY_1	26.46	7.153	
UREA_DAY_2	26.5	5.437	0.44
UREA_DAY_3	25.64	4.852	

Friedman's RMANOVA; NS

Table: Urea levels in Day 1-3 in snakebite patients without AKI



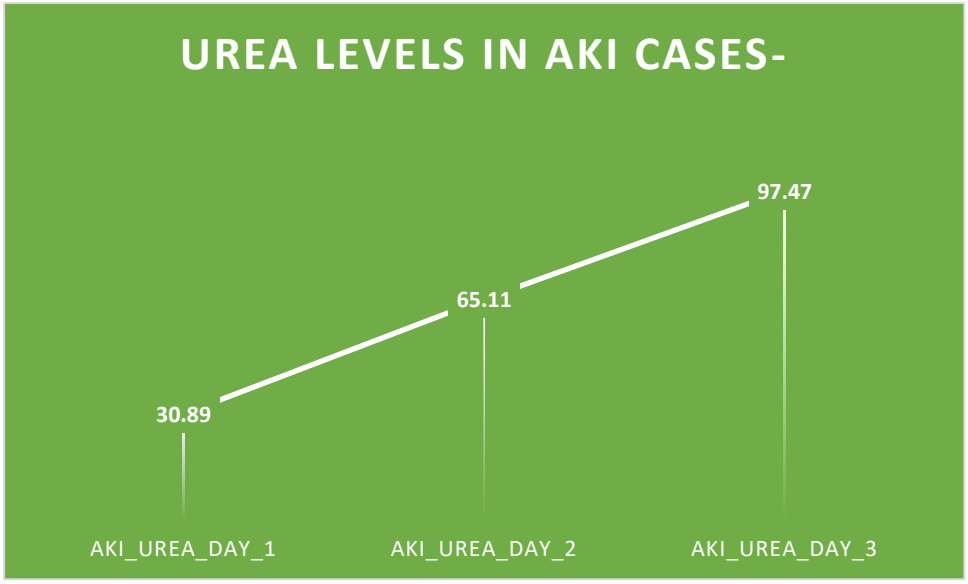
Graph : Urea levels in Day 1-3 in snakebite patients without AKI

Urea level in AKI patients

AKI	mean	SD	P value
AKI_UREA_DAY_1	30.89	7.094	
AKI_UREA_DAY_2	65.11	16.038	0.001*
AKI_UREA_DAY_3	97.47	21.373	

Friedman's RMANOVA; * (p<0.05)

Table: Urea levels in Day 1-3 in snakebite patients with AKI



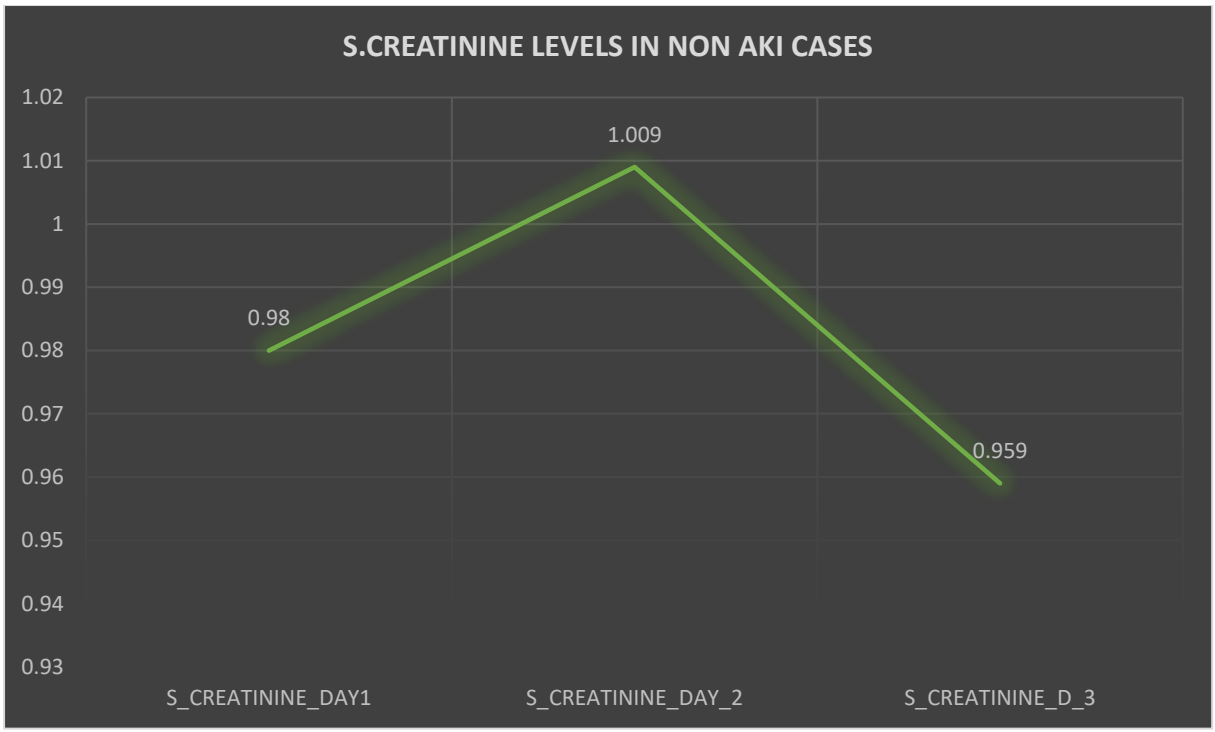
Graph: Urea levels in Day 1-3 in snakebite patients with AKI

Creatinine level in Non AKI patients

Non AKI	Mean	Std. Deviation	p value
S_CREATININE_DAY1	0.98	0.2058	
S_CREATININE_DAY_2	1.009	0.1676	0.097
S_CREATININE_D_3	0.959	0.1616	

Friedman's RMANOVA; NS

Table: creatinine levels in Day 1-3 in snakebite patients without AKI



Graph : Creatinine levels in Day 1-3 in snakebite patients without AKI

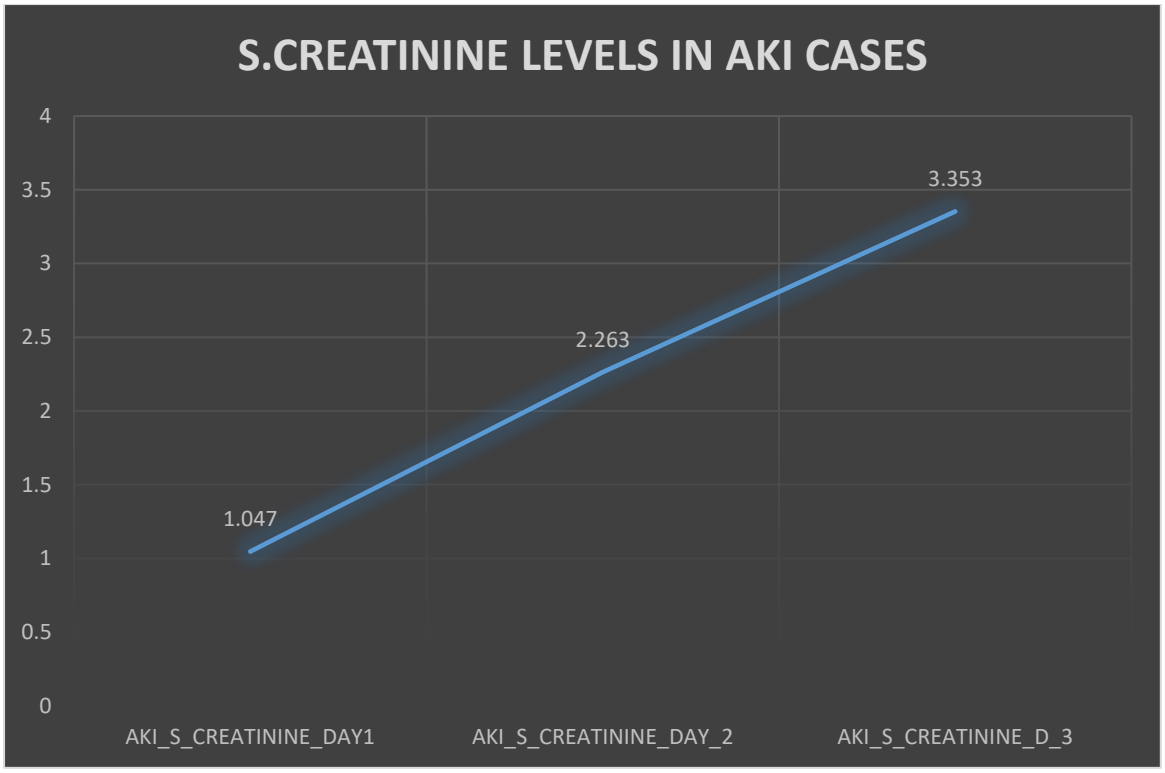
Creatinine levels in AKI patients

AKI	Mean	Std. Deviation	p value
AKI_S_CREATININE_DAY1	1.047	0.1429	
AKI_S_CREATININE_DAY_2	2.263	0.6743	0.001*
AKI_S_CREATININE_D_3	3.353	0.9507	

Friedman's RMANOVA; * (p<0.05)

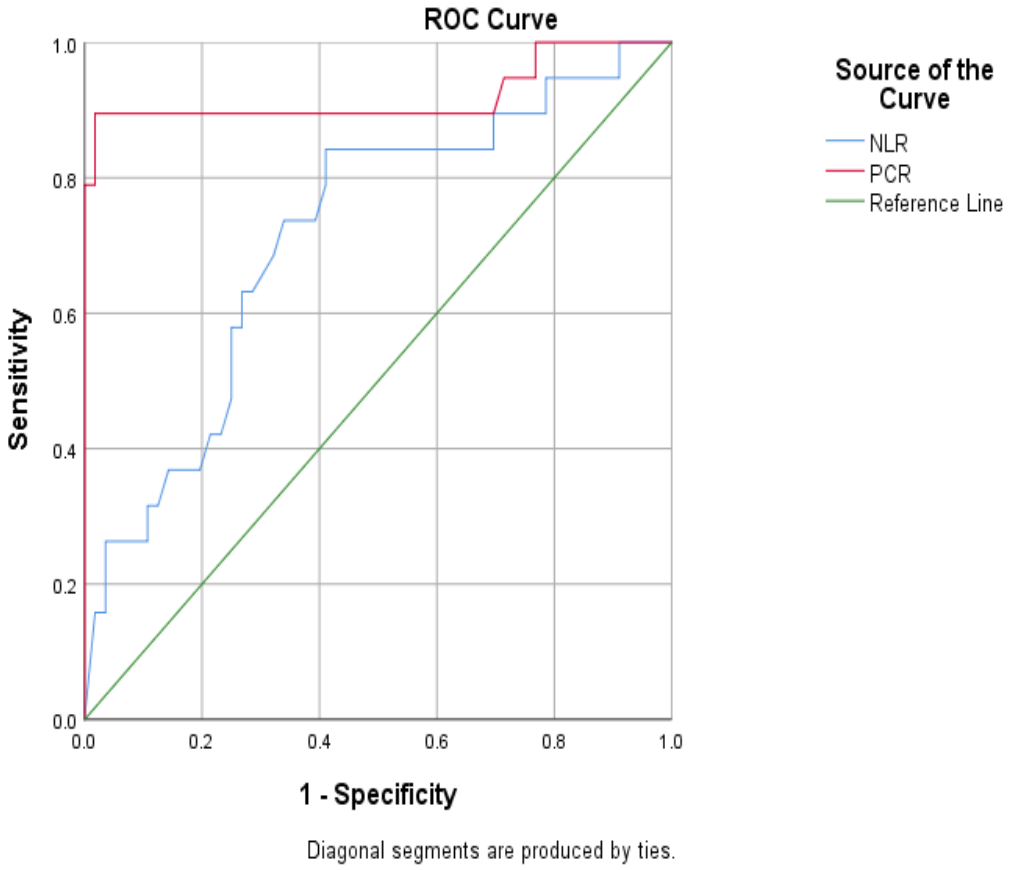
Pairwise Comparisons					
Sample 1-Sample 2	Test Statistic	Std. Error	Std. Test Statistic	P value	Adj. p value
AKI_S_CREATININE_DAY1-AKI_S_CREATININE_DAY_2	-1.000	.324	-3.082	.002	.006**
AKI_S_CREATININE_DAY1-AKI_S_CREATININE_D_3	-2.000	.324	-6.164	.000	.001**
AKI_S_CREATININE_DAY_2-AKI_S_CREATININE_D_3	-1.000	.324	-3.082	.002	.006**

Significance values have been adjusted by the Bonferroni correction for multiple tests; significant level set at (**p< 0.016)



Graph : Raise in Serum creatinine levels in AKI patients from day 1 to day 3

ROC curve for early prediction of markers for AKI



Area Under the Curve

Test Result Variable(s)	Area	Std. Error	P value	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
NLR	.716	.069	.005	.581	.851
PCR	.921	.052	.000	.818	1.000

Prediction marker

Predictor marker	Cut Off value	Sensitivity (%)	Specificity (%)
NLR	≥11.18	73	64
PCR	≥0.26	94	70

NLR equal to or greater than 11.18 was considered as a predictor factor for AKI (P<0.001**) with sensitivity of 73 and specificity of 64, and area under the ROC curve (AUC) of 0.716. PCR equal to or greater than 0.26 was considered as a predictor factor for AKI (P<0.001**) with sensitivity of 94 and specificity of 70, and area under the ROC curve (AUC) of 0.921.

DISCUSSION

DISCUSSION AND SUMMARY

This study was conducted in Government Rajaji Hospital and Madurai medical college, Madurai. It is a longitudinal prospective study of total of 75 haemotoxic venomous snake bite cases.

Each patient is selected according to inclusion, exclusion and defining criteria and they were examined for signs of local and systemic envenomation. Every patient was subjected to following investigations, WBCT, Total Count, Differential count, hemoglobin, Platelet count, Blood Peripheral smear, Renal function test, Spot PCR and other investigations whenever required.

After the admission all patients were treated with ASV and other supportive measures.

The following features were noted in this study,

1. Out of 75 patients, 58 (77%) were males and 17(23%) were females
2. Highest incidence of snakebite was seen in age group of 20-40 years
3. Majority of snakebite patients were from rural areas, they are agricultural workers and daily wagers, most of the patients were the breadwinner of their family.
4. Russel viper and Saw scaled viper are only hemotoxic venomous snakes identifiable in this study
5. Almost all patients in this study, who were hemotoxic invariably positive whole blood clotting time test.

6. Rarely hemotoxic and bleeding gums were present in few patients
7. Among the 75 patients, 19 patients went into AKI. Majority of them required hemodialysis.
8. As the study includes only the patient admitted within 24 hours of bite.so, early administration of ASV, might have prevented the patients going for severe AKI.
9. Patients with toxicity have invariably elevated levels of NLR (In AKI PCR cut off ≥13.87 and P-value) with sensitivity 73% and specificity 64% for AKI.
10. Spot PCR has significant correlation with patients progressed to AKI (PCR cut off ≥ 4.46, P value 0.001) with a sensitivity of 94% and specificity of 70%
11. While comparing the study Aye, Kyi-Phyu et al. there is significant correlation between increased PCR and Progression to AKI

Study	Urine Spot PCR	
	NON- AKI	AKI
Aye, Kyi-Phyu et al	0.14	2.47
In present study	0.37	4.46

LIMITATION OF THIS STUDY

- The study was conducted at a government medical college hospital which is a tertiary centre and southern Tamil Nadu zone referral centre and the cases may not be representative of the population of the region.
- NLR and PCR levels are studies only in hemotoxic snake patients, more details can be obtained if this study is compared with neurotoxic and non-venomous snakebite patients
- Short number of cases and short duration of the study are the limitations of this study.
- The species of snake found in south Tamil Nadu region and Madurai region may vary as compared to other areas.

CONCLUSION

CONCLUSION

- In the present study it is evident that NLR is elevated proportionately in patient with hemotoxic envenomation
- In patients with hemotoxic systemic envenomation, NLR is elevated in all the patients. And its value significantly increased in patients going for AKI.
- In the present study it is observed that spot PCR is elevated to a significant level in patients going for AKI.
- In this study, NLR is elevated all hemotoxic patients, their level is elevated in AKI patients, but its sensitivity is less than PCR.
- Hence it would be paramount importance to consider Spot PCR as an early predictor of AKI in hemotoxic snake bite.

ANNEXURES

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PROFORMA

Name:

Age/Sex:

Occupation:

Presenting Complaints:

Past History: Previous history of snake bite
T2DM/SHT/CAD/CKD/Thyroid disorders

Clinical Examination:

General Examination:

Consciousness

Febrile/Afebrile

Pallor

Icterus

Cyanosis

Clubbing

Generalized Lymphadenopathy

Pedal edema

VITALS:

PR:
BP:
RR:
SPO2:

SYSTEMIC EXAMINATION:

CVS:
RS:
ABDOMEN:
CNS:

LOCAL EXAMINATION:

LAB INVESTIGATIONS:

Complete Blood Count

Peripheral Smear

Renal Function Test

RBS

Urine R/E

ECG

Spot PCR

ஆராய்ச்சிஒப்புதல்படிவம்:

பெயர்:

வயது:

தேதி:

நோயாளிஎண்:

ஆராய்ச்சிசேர்க்கைஎண்:

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கங்களும் முழுமையாக எனக்கு விளக்கபட்டது. எனக்கு விளக்கபட்ட விஷயங்களை நான்புரிந்து கொண்டு எனது முழுமனதுடன் சம்மதிக்கிறேன். இந்த ஆராய்ச்சியில் பிறரின் நிர்பந்தமின்றி என் சொந்தவிருப்பத்தின் பேரில்தான் பங்கு பெறுகிறேன் மற்றும் நான் இந்த ஆராய்ச்சியில் இருந்து எந்தநேரமும் பின்வாங்கலாம் என்றும் அதனால் எந்தபாதிப்பும் எனக்குஏற்படாது என்பதையும் புரிந்து கொண்டேன். நான் என்னுடைய சுயநினைவுடன் மற்றும் முழு சுதந்திரத்துடன் இந்த மருத்துவ ஆராய்ச்சியில் பங்குகொள்ள சம்மதிக்கிறேன்.

ஒப்பம்

MASTER CHART

S.NO	PATIENT	SEX	AGE	SNAKE IDENTIFIED	BLEEDING MANIFESTATIONS	WBCT>20 MIN	VIALS OF ASV	TC	NEUTROPHILS	LYMPHOCYTES	NLR	URINE PROTEIN	URINE CREATININE	PCR	UREA DAY 1	S.CREATININE DAY1	UREA DAY 2	S.CREATININE DAY 2	UREA DAY 3	S.CREATININE D 3
1	Patient 1	Male	19	S.S.V	Nil	Yes	16	10600	52	28	1.9	5	12	0.4	22	1.1	23	1	21	0.8
2	Patient 2	Male	27	R.V	Nil	Yes	10	15000	90	8	11.3	20	30	0.7	27	0.8	23	1	24	0.9
3	patient 3	Male	25	R.V	Nil	Yes	20	22900	87	9	9.7	125	40	3.1	30	1.1	112	2.4	147	3
4	Patient 4	Female	45	S.S.V	hematuria	Yes	18	16600	88	10	8.8	18	32	0.6	32	1	28	0.8	24	0.7
5	Patient 5	Male	52	unknown	Nil	Yes	18	11000	83	15	5.5	6	15	0.4	28	1	24	0.8	25	1.1
6	Patient 6	Male	33	unknown	Nil	Yes	22	13300	80	26	3.1	5	17	0.3	31	1.1	27	1.1	23	1.2
7	Patient 7	Male	32	S.S.V	Nil	Yes	20	11000	70	22	3.2	12	31	0.4	18	0.7	20	0.8	19	0.8
8	Patient 8	Male	28	S.S.V	Nil	Yes	18	9600	77	20	3.9	6	21	0.3	23	0.9	29	1.2	25	0.9
9	Patient 9	Male	24	R.V	Nil	Yes	16	10800	87	10	8.7	8	19	0.4	34	1.2	29	1.1	27	1.1
10	Patient 10	Male	31	unknown	Nil	Yes	10	12300	93	6	15.5	7	18	0.4	28	1.2	25	1	26	1.1
11	Patient 11	Female	43	unknown	Nil	Yes	15	10600	89	11	8.1	112	65	1.7	32	0.9	34	1.1	41	1.2
12	Patient 12	Male	40	unknown	Nil	Yes	8	14700	95	4	23.8	13	38	0.3	26	1.2	29	1.4	30	1
13	Patient 13	Male	19	R.V	Nil	Yes	8	11250	86	14	6.1	7	27	0.3	25	0.9	32	1.1	33	1.3
14	Patient 14	Female	52	unknown	Nil	Yes	16	10350	92	7	13.1	5	16	0.3	31	1.1	25	1.2	28	0.9
15	Patient 15	Male	32	unknown	Nil	Yes	21	7950	82	15	5.5	9	25	0.4	26	1	24	1	23	0.8
16	Patient 16	Male	26	unknown	Nil	Yes	5	13200	90	10	9.0	5	31	0.2	22	0.9	20	1	22	0.9
17	Patient 17	Female	27	unknown	Nil	Yes	15	14100	92	8	11.5	8	35	0.2	24	0.8	25	1.1	23	1
18	Patient 18	Male	45	unknown	Nil	Yes	8	9700	83	7	11.9	5	18	0.3	42	1.2	35	0.9	31	0.9
19	Patient 19	Male	33	S.S.V	Nil	Yes	15	16600	92	5	18.4	7	21	0.3	23	0.8	20	0.9	16	0.7
20	Patient 20	Male	37	unknown	Nil	Yes	16	17300	90	6	15.0	6	25	0.2	26	1.1	24	1.2	21	0.7
21	Patient 21	Female	46	R.V	Nil	Yes	8	6550	74	19	3.9	12	53	0.2	33	1.4	42	0.9	34	1.1

22	Patient 22	Male	22	unknown	Nil	Yes	21	11200	82	11	7.5	9	34	0.3	42	0.7	38	0.7	32	0.8
23	Patient 23	Male	29	unknown	Nil	Yes	16	18300	93	5	18.6	11	43	0.3	17	0.9	36	1	29	0.9
24	Patient 24	Male	36	S.S.V	Nil	Yes	10	12650	92	8	11.5	5	54	0.1	32	1.1	28	0.9	30	1
25	Patient 25	female	41	unknown	Nil	Yes	20	26290	95	4	23.8	142	34	4.2	31	1.1	62	2.8	114	3.5
26	Patient 26	Female	38	unknown	Nil	Yes	10	16700	85	8	10.6	23	67	0.3	19	0.7	25	0.8	27	0.7
27	Patient 27	Male	34	S.S.V	Nil	Yes	21	11140	94	5	18.8	97	19	5.1	25	0.9	69	2.3	108	3.4
28	Patient 28	Female	29	unknown	Nil	Yes	10	15400	93	5	18.6	25	76	0.3	19	0.6	23	0.8	33	1
29	Patient 29	Male	25	unknown	Nil	Yes	8	14100	93	6	15.5	6	25	0.2	14	1	17	0.7	18	0.9
30	Patient 30	Male	34	unknown	Nil	Yes	15	16300	58	23	2.5	8	31	0.3	17	1	71	2.3	87	2.7
31	Patient 31	Female	41	R.V	Nil	Yes	18	12900	88	7	12.6	142	26	5.5	38	1.1	62	1.8	93	2.4
32	Patient 32	Female	32	unknown	Nil	Yes	16	18100	86	10	8.6	7	32	0.2	27	0.9	20	0.9	23	0.8
33	Patient 33	Male	24	R.V	Nil	Yes	8	11900	82	13	6.3	50	64	0.8	27	1.1	24	1	25	1.1
34	Patient 34	Male	27	unknown	Nil	Yes	18	13100	91	6	15.2	7	24	0.3	16	0.8	25	1.1	19	0.8
35	Patient 35	Male	44	unknown	Nil	Yes	15	9950	78	20	3.9	6	17	0.4	19	0.8	32	1.1	27	0.9
36	Patient 36	Male	35	unknown	Nil	Yes	10	12100	89	8	11.1	13	52	0.3	17	0.9	20	1	23	0.9
37	Patient 37	Male	18	S.SV	Nil	Yes	20	26290	95	4	23.8	176	22	8.0	19	0.7	72	1.9	109	3.8
38	Patient 38	Male	47	unknown	Nil	Yes	10	17400	92	5	18.4	5	21	0.2	39	1	21	0.8	22	0.7
39	Patient 39	Male	54	unknown	Nil	Yes	8	11600	76	21	3.6	9	18	0.5	32	1.2	27	1	29	1.1
40	Patient 40	Female	37	S.S.V	Nil	Yes	20	7200	33	57	0.6	8	17	0.5	21	1.3	31	1.4	30	1.1
41	Patient 41	Male	31	R.V	Nil	Yes	8	16500	65	24	2.7	7	15	0.5	35	0.9	28	1.2	25	1.2
42	Patient 42	Male	21	unknown	Nil	Yes	10	12600	67	31	2.2	6	19	0.3	23	0.6	27	0.9	25	0.8
43	Patient 43	Male	27	unknown	Nil	Yes	16	12400	92	7	13.1	115	34	3.4	28	1.1	49	1.7	88	2.5
44	Patient 44	Male	47	unknown	Nil	Yes	10	8900	65	27	2.4	12	44	0.3	16	0.8	20	0.9	24	0.9
45	Patient 45	Male	38	R.V	Nil	Yes	16	11500	90	4	22.5	5	18	0.3	24	1.4	34	1.2	22	1.2
46	Patient 46	Female	29	unknown	Nil	Yes	15	24100	89	7	12.7	64	32	2.0	36	1.1	69	2.8	97	3.3
47	Patient 47	Male	26	unknown	Nil	Yes	18	10900	75	16	4.7	25	17	1.5	30	1	38	1.6	67	2.4
48	Patient 48	Male	36	unknown	Nil	Yes	8	10450	83	15	5.5	6	19	0.3	23	1	17	0.9	18	0.9
49	Patient 49	Male	53	unknown	Nil	Yes	20	14400	92	8	11.5	165	21	7.9	40	1.2	74	2.5	106	4.1
50	Patient 50	Male	48	unknown	Nil	Yes	18	15800	89	9	9.9	20	47	0.4	19	0.8	20	0.9	18	0.7

51	Patient 51	Male	17	R.V	Nil	Yes	10	12600	88	5	17.6	23	63	0.4	25	0.9	23	0.9	27	0.8
52	Patient 52	Male	47	R.V	Gum bleeding	Yes	18	20400	91	5	18.2	100	60	1.7	39	1.1	47	1.4	62	3.1
52	Patient 52	Male	55	unknown	Nil	Yes	8	10850	80	18	4.4	11	28	0.4	16	0.8	20	1	23	0.9
54	Patient 54	Female	44	unknown	Nil	Yes	16	15800	95	5	19.0	154	24	6.4	32	1	59	1.9	93	3.4
55	Patient 55	Male	28	unknown	Nil	Yes	8	8400	74	22	3.4	12	46	0.3	29	1.1	28	1.1	26	1.2
56	Patient 56	Male	25	unknown	Nil	Yes	10	11450	84	16	5.3	6	24	0.3	34	0.7	32	0.8	28	1.1
57	Patient 57	Male	32	R.V	Nil	Yes	16	13500	90	8	11.3	9	34	0.3	31	1.1	47	1.4	56	1.8
58	Patient 58	Male	28	unknown	Nil	Yes	10	12100	85	11	7.7	11	42	0.3	44	1.2	36	1.3	34	1.1
59	Patient 59	Female	55	S.S.V	Nil	YES	18	23300	85	7	12.1	175	21	8.3	33	1.3	59	2.1	105	3.3
60	Patient 60	Female	29	R.V	Nil	Yes	10	6460	85	13	6.5	12	23	0.5	27	1.2	31	1.3	30	1.2
61	Patient 61	Male	43	unknown	Nil	Yes	23	10350	76	22	3.5	9	17	0.5	33	1.1	29	0.9	28	1
62	Patient 62	Male	16	R.V	Bleeding gums	YES	20	23900	95	4	23.8	169	27	6.3	17	0.8	54	2.1	87	3.9
63	Patient 63	Male	26	R.V	Nil	Yes	18	10600	84	23	3.7	127	22	5.8	39	0.9	82	2.1	115	3.9
64	Patient 64	Male	39	unknown	Nil	Yes	10	11250	89	10	8.9	11	25	0.4	21	0.8	26	1.1	23	0.9
65	Patient 65	Male	28	S.S.V	Nil	Yes	8	10200	80	18	4.4	5	22	0.2	25	0.7	27	0.8	24	1
66	Patient 66	Male	31	unknown	nil	yes	10	9800	87	6	14.5	9	17	0.5	24	0.9	23	1.1	27	1
67	Patient 67	Female	36	R.V	nl	Yes	8	14250	89	10	8.9	6	32	0.2	23	1.3	24	1.1	25	1.2
68	Patient 68	Male	32	unknown	nil	yes	15	13800	89	9	9.9	132	18	7.3	32	1.1	72	2.8	121	3.5
69	Patient 69	male	37	R.V	Nil	Yes	18	9500	73	24	3.0	12	37	0.3	35	1.2	32	1.1	34	1.1
70	Patient 70	Male	22	unknown	Nil	Yes	8	8650	70	28	2.5	5	17	0.3	22	0.7	25	1	20	0.9
71	patient 71	Male	45	R.V	Nil	Yes	20	13100	88	5	17.6	164	34	4.8	34	1.2	70	4.3	100	6.4
72	Patient 72	Male	51	R.V	Nil	Yes	10	9600	84	8	10.5	8	23	0.3	22	1.3	29	1.2	26	1.1
73	Patient 73	Male	42	S.S.V	Nil	YES	16	10300	90	5	18.0	15	37	0.4	29	1.2	27	1.2	23	0.8
74	Patient 74	Female	38	unknown	nil	yes	10	24100	90	6	15.0	84	27	3.1	36	1.1	69	2.8	97	3.3
75	Patient 75	Male	25	unknown	Nil	yes	15	16600	87	7	12.4	17	52	0.3	39	1	21	0.8	23	0.9

ETHICAL COMMITTEE

INSTITUTIONAL ETHICS COMMITTEE
MADURAI MEDICAL COLLEGE & GOVT. RAJAJI HOSPITAL, MADURAI
CDSCO:Reg.No.ECR/1365/Inst/TN/2020 &
DHR Reg.No.EC/NEW/INST/2020/484

Study Title	:	NLR (Neutrophil Lymphocyte Ratio) and SPOT PCR (Protein Creatinine Ratio) as early predictors of AKI in haemotoxic snakebite
Principle Investigator	:	Dr.PAVITHRAN.S
Designation	:	PG in MD., General Medicine (2019-2022)
Guide	:	Prof.Dr.SENTHAMARAI, M.D., Professor in General Medicine
Department	:	Department of General Medicine Government Rajaji Hospital & Madurai Medical College, Madurai

The request for an approval from the Institutional Ethics Committee (IEC) was considered on the IEC meeting held on **22.06.2021** GRH Auditorium, Government Rajaji Hospital, Madurai at 10.00 AM.

The Members of the committee, the Secretary and the Chairman are pleased to inform you that your proposed project mentioned above is **Approved.**

You should inform the IEC in case of any changes in study procedure, methodology, sample size investigation, Investigator or guide or any other changes.

1. You should not deviate from the area of work for which you had applied for ethical clearance.

2. You should inform the IEC immediately, in case of any adverse events or serious adverse reactions. If encountered during from study.

3. You should abide to the rules and regulations of the institution(s)

4. You should complete the work within the specific period and if any extension is required, you should apply for the permission again for extension period.

5. You should submit the summary of the work to the ethical committee on completion of the study.

MEMBER SECRETARY,
IEC, Madurai Medical College,
Madurai

Dr.K.RAADHIKA, M.D(Pharm)
Associate Professor
Member Secretary
IEC - Madurai Medical College
Madurai.

மதுரை மருத்துவக் கல்லூரி
25 JUN 2021
2020

CHAIRMAN,
IEC, Madurai Medical College,
Madurai

Prof. Dr. V. Nagaraajan
MD..MNAMS..DM..DSC(Neuro)..DSC(Hon)
CHAIRMAN
IEC Madurai Medical College
Madurai

ANTI PLAGIARISM CERTIFICATE

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ANTI PLAGIARISM CERTIFICATE - II

This is to certify that this dissertation titled **"NLR (NEUTROPHIL LYMPHOCYTE RATIO) AND SPOT PCR (PROTEIN CREATININE RATIO) AS EARLY PREDICTORS OF AKI IN HAEMOTOXIC SNAKEBITE"** of the candidate **Dr. PAVITHRAN.S** with **Registration Number 201911111** for the award of M.D degree in the branch of GENERAL MEDICINE. I personally verified the urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file containing from introduction to conclusion pages and result shows **3** percentage of plagiarism in the dissertation.

Prof. Dr. A. SENTHAMARAI M.D.,
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