A Descriptive study on Thrombocytopenia, Microangiopathy and End Organ Damage in Snakebites

A dissertation submitted in partial fulfillment of the rules and regulations for MD Branch I (General Medicine) examination of the Tamil Nadu Dr. M. G. R Medical University, Chennai, to be held in May 2019

CERTIFICATE

This is to certify that the dissertation titled **'A Descriptive Thrombocytopenia, Microangiopathy and End Organ Damage in Snakebites'**, is the bona fide original work of Dr. Anil Mathew Philip, in fulfillment of the rules and regulations for the M.D., Branch I, General Medicine degree Examination of the Tamil Nadu Dr. M.G.R University, Chennai to be held in 2019.

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DECLARATION

This is to declare that the dissertation titled **'A Descriptive Thrombocytopenia, Microangiopathy and End Organ Damage in Snakebites'**, which is submitted by me in partial fulfillment of the rules and regulations for the M.D., Branch I, General Medicine degree Examination of the Tamil Nadu Dr. M.G.R University, Chennai to be held in 2019, comprises of my original research work and information taken from secondary sources has been given due acknowledgment and citation.

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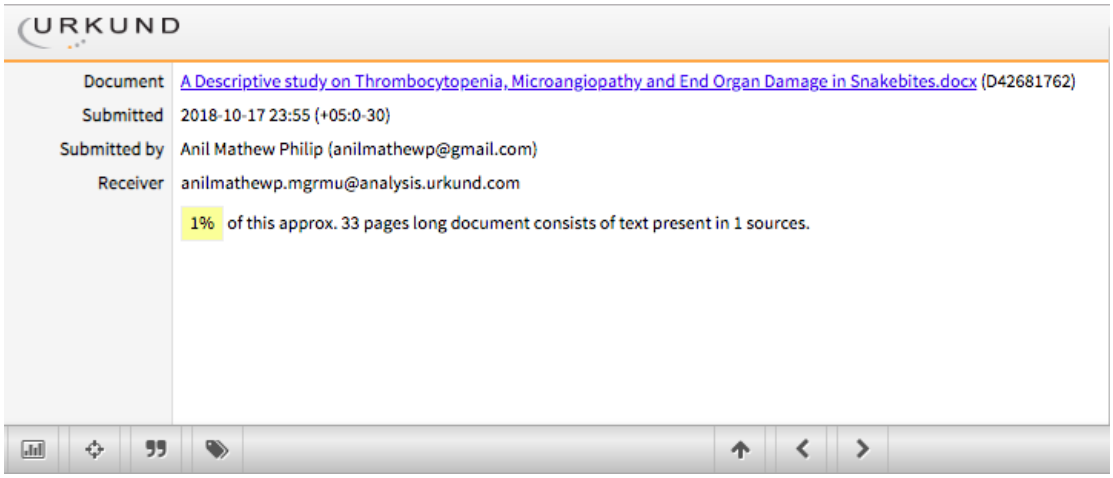

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ABBREVATIONS

TMA	·	Thrombotic Microangiopathy
HUS	·	Hemolytic Uremic Syndrome
TTP	·	Thrombotic Thrombocytopenic Purpura
WBCT	·	Whole Blood Clotting Time
ASV	·	Anti Snake Venom
AKI	·	Acute Kidney Injury
WHO	·	World Health Organization
LDH	·	Lactate dehydrogenase
VICC	·	Venom Induced Consumption Coagulopathy
PP	·	Plasmapheresis
PE	·	Plasma Exchange

INTRODUCTION

Snakebites are a neglected group of diseases in the tropics. There is significant variation in geographical distribution of various snake species in India. Hence it is essential to be able to identify envenomation syndromes in snakebites based on the envenomation pattern, hence making it possible to predict the ASV requirements, and expected complications in each syndrome.

Thrombotic Microangiopathy is a phenomenon that has not been well described in snake envenomation, and is one of the mechanisms responsible for end organ damage in snakebites and implicates serious morbidity and in some cases mortality and is grossly under recognized.

Hypothesis and Problem statement

We postulate that thrombotic Microangiopathy is a spectrum ranging from isolated thrombocytopenia to thrombocytopenia, schistoytes, MAHA and end organ damage.

In cases where there is a TMA there is a prolonged hospital stay and higher degree of morbidity and mortality.

AIM AND OBJECTIVES

Aim

To describe the clinical profile of patients with Thrombotic Microangiopathy in snakebites.

Objectives

1. To find the incidence of TMA spectrum in snake envenomation
2. To describe the frequency of the TMA spectrum disorder (isolated thrombocytopenia, thrombocytopenia with schistocytes, microangiopathic hemolytic anemia and HUS/TTP) in syndromes of snake envenomation
3. To describe the relationship between TMA spectrum and Venom Induced Consumption Coagulopathy
4. To describe the clinical course and the outcomes of patients with TMA spectrum disorders in snake envenomation

REVIEW OF LITERATURE

Snakebites are a major occupational hazard for farmers and daily wage laborers in rural India.(1) According to the World Health Organization (WHO) the estimated annual mortality which has been attributed to snake bites has been projected to be between 35,000 and 50,000 per year; there is likely a gross under reporting of snake envenomation, in terms of mortality and late presentation to medical facilities. Hence the actual estimated incidence and mortality of snakebites may be much higher.(2)

Therefore snakebites are a major health issue in rural India today, which is neglected.

Epidemiology

According to the WHO, incidence of snakebites worldwide is about 421,00 to 1,841,000 and mortality is between 20,000 and 94,000 deaths per annum.(3) South East Asia is the most heavily affected, which is multifactorial (population density, increased farming practices and a large number of venomous species of snakes in the regions).

In India, mortality rates are due to snakebites are the highest in the world, estimated to be around 35,000 to 50,000 per anum.(4) In Sri Lanka snakebites as a public health problem are of a similar magnitude to India, and studies from

these regions have shown that there is a gross misreporting of deaths due to snake envenomation.

Snakebites are an important occupational injury, which affect a multitude of workers including farmers, fisherman, herders and plantation workers. Another common practice in rural India is open style habitation and sleeping on the floor.

It has been noted that there are spikes of snakebites during rainy seasons and during harvesting seasons.(1) There is also increased mortality associated with snakebites during natural calamities like floods. There is a clear male preponderance of 2:1, seen most commonly in farmers and bites are usually noted on the lower limbs.

Venomous Snakes Species in India

There are roughly 236 species of snakes in India of which 13 are venomous. In India we have the big four, which includes 2 hemotoxic snakes - Russell's viper (*Daboia russelii*) and Saw scaled Viper (*Echis carinatus*) and 2 neurotoxic snakes – Krait (*Bangareus caeruleus*) and the Indian Cobra (*Naja naja*).(5) However there is a need to broaden this concept, as there are several highly venomous snakes, which are widely distributed and many geographically distributions which are relevant. An example of this Hump nosed viper (*Hypnale hypnale)* which is seen commonly in Kerala and the Monocellate Cobra (*Naja kouthia*) which is seen predominantly in the North East. Similarly there are several more species of venomous snakes belonging

mostly to the Elapidae, Viperidae and other Crotalinae, sea snakes (rarely seen in India, but few reported cases in coastal regions) all of which we have not accounted for with polyvalent ASV. There is inefficiency of polyvalent Anti Snake Venom to neutralize the same.(6)

In a prospective cohort done in Karnataka, which included 76 venomous snake bites Saravu et al showed that there was about 73.6% hemotoxic snake bites and 19.7% neurotoxic snake bites.(7)

In retrospective cohort of 200 patients done in Himachal Pradesh, Raina et al 46% had neurotoxicity and 31% hemotoxicity, hence this shows that in a diverse topography like India, it is important to note the difference of distribution of envenomation syndromes.(8)

Pathophysiology of Snake Envenomation

Snake venoms are varied mixture of different proteins and peptides, which vary from one species to another and even within species. These toxins are adapted to interact with a variety of cellular targets, affecting different organ systems, depending on which can cause hemorrhage, disruption of hemostasis, necrosis, myolysis, myocarditis, acute kidney injury, neuromuscular paralysis, thrombosis and hypovolemic shock.(9)

The toxic components of venom are classified as enzymes, glycoproteins, polypeptides and other compounds with low molecular weight. There are more

than 26 different enzymes that are detected in snake venom, 12 of which are common to all snake species.

The different toxins are broadly classified into different components:

1. Enzymes that clot fibrinogen
2. Enzymes that degrade fibrinogen
3. Plasminogen activators
4. Prothrombin activators
5. Factor V activators
6. Factor X activators
7. Protein C activators
8. Platelet aggregation inhibitors
9. Inhibitors of prothrombinase complex, thrombin, phospholipases. (9)

Different enzymes detected are fibrinogenolytic enzymes, which are of three types- alpha/beta/gamma fibrinogenases. Other enzymes include plasminogen activator releasers such as Echarin, prothrombin activator, prothrombinase complex formation inhibitors such as phosholipase A2, B, C and D, Factor X activators, Factor V activators, Factor XI activators, fibrinogenolysin, platelet aggregation inducers, either with or without coagulant activity.(10)

Platelet aggregation inhibitors, such as alpha fibrinogenases or 5-Nucleotidase, or ADPase, or fibrinogen receptor antagonists, Von Willebrand factor-dependent platelet aggregation inducers. Zinc metalloproteases, which disrupt the endothelial lining of blood vessels causing spontaneous bleeding, hyaluronidases (spreading factor), arginine esterases and, L-amino acid

oxidases which is widely found in snake venoms, and is responsible for the yellow colouration of snake venom due to the presence of riboflavin as a prosthetic group.(11)

Table 1 showing the Various Venom Proteins and their Mechanism of Action

Type of compound	**Action on body**	**Snake family**
Acetyl choline esterases AchE	Tetanic paralysis	Colubridae, Elapidae
Arginine esterases	Believed to predigest prey	Viperidae
Bradykinin potentiating peptides	Pain, hypotension, immobilize prey	Viperidae
C- type lectins	Modulate platelet activity, prevent clotting	Viperidae
Cysteine rich secretory proteins	Believed to induce hypothermia and immobilize prey	Colubridae, Elapidae,Viperidae

Disintegrins	Inhibit platelet activity and promote hemorrhaging	Viperidae
Hyaluronidases	Increase interstitial fluidity aiding in the dissemination of venom proteins	Elapidae, Viperidae

L-Amino acid oxidases	Cell damage, apoptosis	Elapidae, Viperidae
Metalloproteinases	Hemorrhage, myonecrosis, believed to predigest prey	Colubridae, Elapidae, Viperidae
Myotoxins	Myonecrosis, analgesia, immobilise prey	Viperidae
Phosphodiesterases	Causes hypotension and shock	Colubridae, Elapidae, Viperidae
Phospholipases	Causes myotoxicity,	Colubridae, Elapidae,

A2(PLA2)	myonecrosis, damage to call membranes	Viperidae
PLA2 based presynaptic neurotoxins	Immobilises prey	Elapidae, Viperidae
Prothrombin activators	Disseminated intravascular coagulation (DIC)	Elapidae, Viperidae
Purines and pyrimidines	Hypotension, paralysis, apoptosis, necrosis, immobilisation of prey	Elapidae, Viperidae
Serine proteases	Disrupts hemostasis, hypotension, immobilize prey	Colubridae, Viperidae
Three finger toxins (3FTx)	Rapid immobilization of prey, paralysis and death	Colubridae, Elapidae

Signs and Symptoms of Snake Bites

Snake venom are complex substances which have protiec and non-protiec parts, which produce local and systemic changes. Local changes being part of an acute inflammation causing edema, ecchymosis, blistering and skin necrosis and may lead on to infection and cellulitis. Systemic changes include hemotoxicity, neurotoxicity, rhabdomyolysis and acute kidney injury (AKI).(12)

Local symptoms include:

- Fang marks
- Local pain
- Local bleeding
- Bruising
- Lymphangitis
- Blistering
- Lymph node enlargement
- Soft tissue infections – these are a major complication of snakebites which have local envenomation. The enzymatic degradation of tissue caused by the snake venom causes extensive destruction and devitalization, predisposing it to infection with bacteria indigenous to the snake's oral flora. Atul et al found that the gram positive bacteria was more common than gram negative bacteria. Staphylococcus aureus followed by coagulase negative Staphylococcus and Streptococcus species.(13)

Systemic symptoms and signs:

General Nausea, vomiting, abdominal pain generalized weakness drowsiness and prostration

Cardiovascular visual disturbances, giddiness, collapse, shock, hypotension, pulmonary edema, cardiac arrhythmias, myocarditis

Hemotoxicity excessive bleeding from wounds, spontaneous systemic which include minor bleeding like bleeding from gums or epistaxis or could be a major bleed such as hematuria, hematemesis, melena, hematochezia, hemoptysis, intracranial or intra abdominal bleeds.(14)

Neurotoxicity Altered sensorium, drowsiness, ptosis, external opthalmoplegia, bulbar involvement, diaphragmatic paralysis or generalized flaccid paralysis.(15)

Rhabdomyolysis generalized pain in muscles, stiffness and tenderness of the muscles, trismus, dark coloured urine – myoglobinuria/hemoglobinuria, acute renal failure, hyperkalemia and cardiac arrest.

Acute Kidney Injury Loin pain, hematuria, hemoglobinuria/myoglobinuria, decreased urine output, and worsening creatinine, pedal edema, anasarca and pulmonary edema.(16)

Envenomation Syndrome

The different clinical syndromes associated with snakebites are as follows:

1. No envenomation
2. Local swelling

3. Hemotoxicity with/without local swelling
4. Pure neurotoxicity
5. Neurotoxicity with local swelling
6. Hemotoxicity with neurotoxicity
7. Hemotoxicity/neurotoxicity and renal failure

The use of clinical envenomation syndrome, helps to identify the species in the snake bite, which would give a more reasonable idea of what complications to expect and how to manage them.

Species, which are relevant to South India, are:

Viperidae Bites

Russell's Viper(*Daboia russelii russelii*) bites present with local reaction at the bite site with swelling, blistering and necrosis along with coagulopathy. Other features frequently encountered are acute kidney injury and neurotoxicity in the form of ptosis. (17) Saw scaled viper (*Echis carinatus*) bites present with local reaction and coagulopathy/hemotoxicity.(14) Pit vipers like the hump nosed pit viper present with a local reaction, hemotoxicity and can have an acute kidney injury.(16)

Elapidae Bites

Species like the Indian Cobra (*Naja naja*) have extensive local reaction in the form of swelling, cellulitis, tissue necrosis and gangrene, with a descending paralysis which is progressive in nature.(18)

Krait Bites

The common krait (*Bungarus caeruleus*) is classically a painless bite followed by ophthalmoplegia, bulbar weakness and then respiratory distress due to the involvement of the diaphragmatic muscles.(19)

According to the WHO algorithm for South East Asia the following syndromes were defined to correlate with snake species.

Syndrome 1: local envenomation with coagulopathy associated with Viperidae

Syndrome 2: local envenomation with coagulopathy with/without acute kidney injury along with neurotoxicity is described with Russell's viper

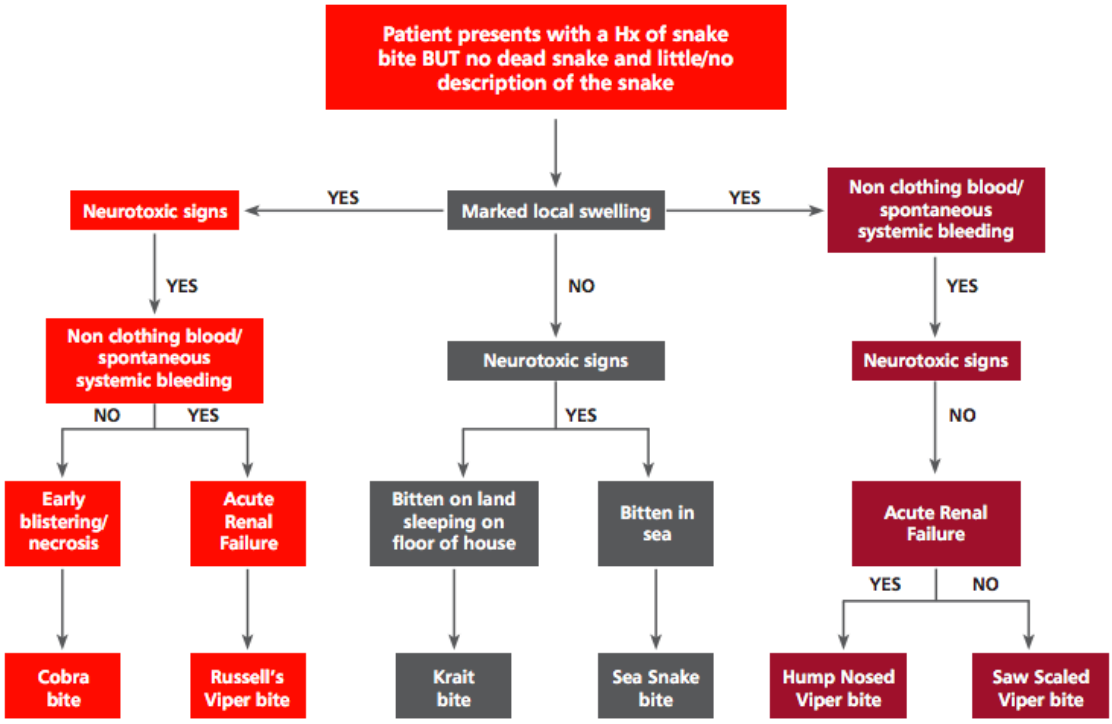
Syndrome 3: local envenomation with paralysis seen with cobra bites

Syndrome 4: paralysis with minimal or no local envenomation is seen with Krait bites

Syndrome 5: paralysis with acute kidney injury seen with Russell's viper bites

The algorithm was adapted from data published by Ariaratnam et al as seen in the figure below(20):

Figure 1 Algorithm for identification of snake responsible for bite



Arirathnam et al in a prospective cohort proposed the algorithm to identifying the snake bites in Sri Lanka(between August 1993- July 1997). It was noted that there was a high specificity in identifying the species with the envenomation syndrome as shown in Table 2. (20)

Table 2 Sensitivity and specificity of species identification with Envenomation Syndrome

Snake	Sensitivity (%)	Specificity (%)
Russell's viper	14	100
Cobra	78	96
Common Krait	66	100
Hump- nosed viper	10	97

Snake is brought as definitive evidence in only 25% of cases and once patient is transferred to higher centers often the snake is missed out, hence with a syndromic approach we are able to identify the culprit snake.

Management of Snake bites

First Aid

In a systematic review of first aid in snake bites, the authors looked at evidence from 14 studies, and concluded that a practical recommendation is pressure immobilization of the limb, as the spread of venom is mostly through the venous and lymphatic channels.(21)

Unnecessary searching for snake, handling and killing of the snake and traditional remedies and concoctions are not recommended as it increases risk for further envenomation and delay in initiation of ASV. (22) Incision of the wound and application of tight tourniquet showed increased incidence of local swelling and inflammation.(23)

Diagnosis

Importance to the timing and location of the bite, early and intense pain often implies significant envenomation.

Diagnostic Tests include:

- 20 minute whole blood clotting time, PT/APTT and Fibrinogen
- Hemoglobin, PCV, platelet counts, peripheral smear
- Urine test for proteinuria, RBC's, hemoglobinurua, myoglobinuria

- Serum Creatinine, urea, serum electrolytes

20 Minute Whole Blood Clotting Test(20WBCT)

This is an informative, easy to perform beside test, which does not require any training to perform. Here about 2ml of fresh venous blood is placed in a new clean and dry glass test tube and is left at ambient temperature for 20 minutes. The mechanism tested here is contact clotting. Use of plastic, polypropelene, polystyrene, syringes or glass washed in detergent, which prevents activation of Hageman factor, may give rise to false readings.

Non clotting 20WBCT is predictive of a fibrinogen concentration <0.5g/L with a >90% sensitivity and specificity.(24) Hence this is the simplest test that can be performed in primary health care facilities and rural areas to distinguish Viperidae from Elapid bites.

Anti Snake Venom (ASV)

In India, available ASV is polyvalent antisnake venom, which contains antibodies against the Russell's viper; saw scaled viper, common krait and the Indian cobra, which is isolated from horse serum after injecting snake venom by fractionation of plasma.

Monovalent Antivenom is considered the more efficacious, identification of the species may not be possible, hence across the country the polyvalent ASV is being used.

Dosing of ASV

There is no consensus on the number of vials of ASV which is to be initiated. Usual practice is a high dose initial dose of 10 vials with monitoring for anaphylaxis and hypersensitivity. (25) The patients should be monitored for resolution of coagulopathy and other manifestations every 4-6 hours and dose to be repeated if necessary. There have been multiple trials comparing low dose to high dose ASV (6 vials vs. 12 vials), which did not show any statistical difference in the resolution of envenomation in the two groups.(26) However these results are limited by small sample size and had not taken into consideration the species. A larger trial done in Nepal compared slow administration of ASV over 12 hours to initial 10 vial dosing at initial presentation. Here also there was no difference in both arms of the trial with regard to envenomation resolution and ASV anaphylaxis.(27)

A systematic review published in 2015 on low and high dose ASV concluded that there were no differences in resolution of envenomation syndromes and incidence of adverse reactions with ASV. However there was significant cost effectiveness of low dose regimens.(28)

There is stillroom for well conducted studies to get establish a standard protocol for ASV administration in India.

There are still several limitations to the polyvalent ASV available in India. There is an insufficient supply of ASV and costs are also high. In the Indian setting most snakebite victims are from a low socioeconomic strata.

There is a geographical variation in the distribution of the snakebites seen in India, several venomous species are not accounted for with the polyvalent ASV, and example of this is the Hump nosed viper, where the polyvalent ASV is inefficient.

Specific Management:

Local Envenomation

According to the WHO guidelines, immobilization of the limbs should be done early. ASV should be administered if there is increase in swelling and pain of more than half the limb in 48 hours or rapid increase in swelling. Antibiotics should be administered for cellulitis/necrotizing fasciitis. Surgical debridement should be offered early for source control.

Hemotoxicity

The indication for ASV administration include spontaneous systemic bleeding manifestations, coagulopathy defined as positive non clotting whole blood clotting time more than 20 minutes or INR >1.2 or prothrombin time 4-5 seconds longer than the control time. The parameters are repeated every 6 hours and if there is persistence of coagulopathy or systemic bleeding, then ASV further dose of ASV is given.

Neurotoxicity

Any neurotoxic manifestation at admission, bilateral ptosis, external ophthalmoplegia and paralysis requires ASV at admission and the patient has to be reassessed every 6 hours for resolution of signs and symptoms. Evidence

of respiratory muscle weakness like diaphragmatic and intercostal muscle weakness will require mechanical ventilation.

Acute Kidney injury

The patient may have oliguria, anuria, hemoglobinuria, myoglobinuria, rising creatinine/urea levels, evidence of rhabdomyolysis and intravascular haemolysis. ASV has to be administered for these situations and the patient needs to be monitored for the need for renal replacement therapy.

Venom Induced Consumption Coagulopathy

VICC- pathogenesis and clinical features:

Venom-induced consumption coagulopathy is the most common entity in haemotoxic snake bites, notably Russell's viper, Saw-scaled viper and Hump-nosed pit viper.

The most common derangements seen are prolonged INR, prolonged aPTT, low fibrinogen and low factor V, VIII and X levels.

Venom contains Factor V and X activators, which leads to formation of Prothrombinase complex (Xa/Va complex) thereby subsequently activating the coagulation cascade and leading to consumptive coagulopathy. It also contains thrombin-like enzymes, which lyse either alpha or beta chain of fibrinogen, giving rise to fibrinopeptide A or B causing consumption of fibrinogen without the formation of fibrin. The risk of bleeding in VICC appears to be associated with presence of Prothrombin activators- metalloproteinases in snake venom

which not only activate the coagulation cascade but also damage vessel wall integrity predisposing to bleeding. VICC can co-exist with HUS-TMA, leading to the popular mistaken belief that VICC is a form of DIC.

VICC usually presents with local bleeding manifestations- from the bite site/ cannula site. However, gum bleeding, gastrointestinal or genitourinary bleeding and intracerebral haemorrhage are also seen. The more serious bleeding manifestations are seen in bites with *Echis* spp – due to substances called haemorrhagins.

A cohort study involving 146 patients with Russell's viper envenomation done in a tertiary care hospital at Sri Lanka using Enzyme immunoabsorbent assay for venom detection to assess dynamic relationship between Russell's viper antivenom and clotting factor levels showed that haemotoxic envenomation by Russell's Viper is associated with an elevated PT/INR and aPTT, low fibrinogen, Factor V, VIII and X levels. Coagulation profile trends showed that aPTT normalized by 24 hours; PT/INR, Fibrinogen, Factors V and X normalized by 48 hours. There was a non-significant statistical association between pre-ASV venom concentration and INR ($p=0.02$), aPTT ($p=0.03$). This study also showed that PT/ INR was still elevated at 6 hours post-ASV administration, stating that 6 hours maybe early for reassessment of coagulation status.(29)

Are VICC and DIC the same?

Recent studies have shown that pathogenesis of Venom-induced consumption coagulopathy is unique and dissimilar to DIC. Isbister *et al*, in 2010 showed that VICC is not the same as DIC. VICC is not characterized by systemic microthrombi and end-organ damage due to the thrombi. DIC is mediated via the tissue factor/ VIIa pathway. Initiation of VICC is at any point in the coagulation cascade upstream from thrombin. The time course in VICC is rapid- occurring within a few hours of envenomation and resolution within 24-48 hours.(30)

Diagnostic criteria proposed by Isbister et al.

Thrombotic Microangiopathy

Thrombotic Microangiopathy (TMA) is a set of diverse syndromes. Clinical features include microangiopathic hemolytic anemia, thrombocytopenia and end organ damage. They have characteristic pathological features of vascular damage, which is manifested by arteriolar and capillary thrombosis, with abnormalities of the endothelium and the vessel wall.(31)

Thrombotic microangiopathies were previously categorized as Hemolytic Uremic Syndrome (HUS) and Thrombotic Thrombocytopenic Purpura (TTP). HUS being characterized by thrombocytopenia, microangiopathic hemolytic

anemia and renal failure. TTP classically described as a pentad of thrombocytopenia, microangiopathic hemolytic anemia, neurological deficits, renal dysfunction and fever. However, about 60% of patients diagnosed with TTP lack one or more of these criteria, while 30% of those receiving a diagnosis of HUS exhibit subtle neurological symptoms and fever, this shows the difficulty to differentiate the two. Hence have been broadly classified as Thrombotic Microangiopathies.(32)

A recent revision has been made in the classification of TM, due to this difficulty in differentiating the syndromes and the pathophysiology. Currently being classified as Hereditary and Acquired Thrombotic Microangiopathies.

Primary TMA syndromes are:

- Thrombotic Thrombocytopenic purpura (TTP)
- Shiga Toxin Mediated Hemolytic Uremic syndrome (ST-HUS)
- Complement Mediated TMA
- Drug Induced TMA
- Metabolism Mediated TMA
- Coagulation mediated TMA

Acute episodes of thrombotic microangiopathies have been observed in association with viral and bacterial infections, toxins, pregnancy, HELLP syndrome, bone marrow transplantation, drug (mitomycin, cyclosporin A, ticlopidine) therapy, and cancer, and have been variously referred to as TTP,

HUS, TTP/HUS, TTP-like disease or secondary TTP. (31)

Classification and Pathophysiology:

Thrombotic thrombocytopenic purpura (TTP)

This is a severe deficiency of ADAMTS13 (activity <10%), but the diagnosis of TTP is based on clinical judgment, as ADAMTS level measurement results are usually not available for several days.

ADAMTS is a metalloprotease, which cleaves von Willebrand factor multimers, which are secreted from the vascular endothelium. Deficiency of ADAMTS13 results in the unusually large multimers to cause platelet thrombi in the small vessel causing TTP. Hereditary TTP (Upshaw-Schulman syndrome) is a homo/heterozygous mutation of ADAMTS13. Antibodies directed against ADAMTS13 cause acquired TTP. (32)(33)

Treatment of TTP is ADAMTS13 replacement with plasma infusion/plasma exchange. Before the use of plasma exchange for TTP, survival was only 10%. Glucocorticoids are considered the standard treatment in conjunction with Plasma exchange. Other treatment options are Rituximab and IVIG.(31)

Complement- Mediated TMA(Acquired and Hereditary)

These are syndromes with predominant renal failure. This results due to uncontrolled activation of the alternative complement pathway on the cell membranes including the vascular endothelium and kidneys. This can be due to hereditary deficiency of regulatory proteins like complement factor H [CFH],

complement factor H related proteins [CFHRs] CFI, membrane cofactor protein [MCP, CD46]), or a hereditary abnormality of proteins that accelerate activation of this pathway (eg, CFB, C3).

Deficiency of complement factor H (CFH) or complement factor I (CFI) can also be acquired caused by an autoantibody that inhibits CFH or CFI activity.(34)

The only available anticomplement agent available is ecluzimab, the high cost and limited availability limit its use.(31)

Drug-induced TMA

Some agents can cause immune-mediated TMA due to drug-dependent antibodies that react with platelets, neutrophils, endothelial cells, and/or other cells. (29) is the most common and best-described etiology of immune-mediated DITMA. Gemcitabine, oxaliplatin, and quetiapine may also cause acute episodes of TMA that appear to be immune-mediated. Acute kidney injury in quinine-induced, immune-mediated TMA is typically severe.(31)

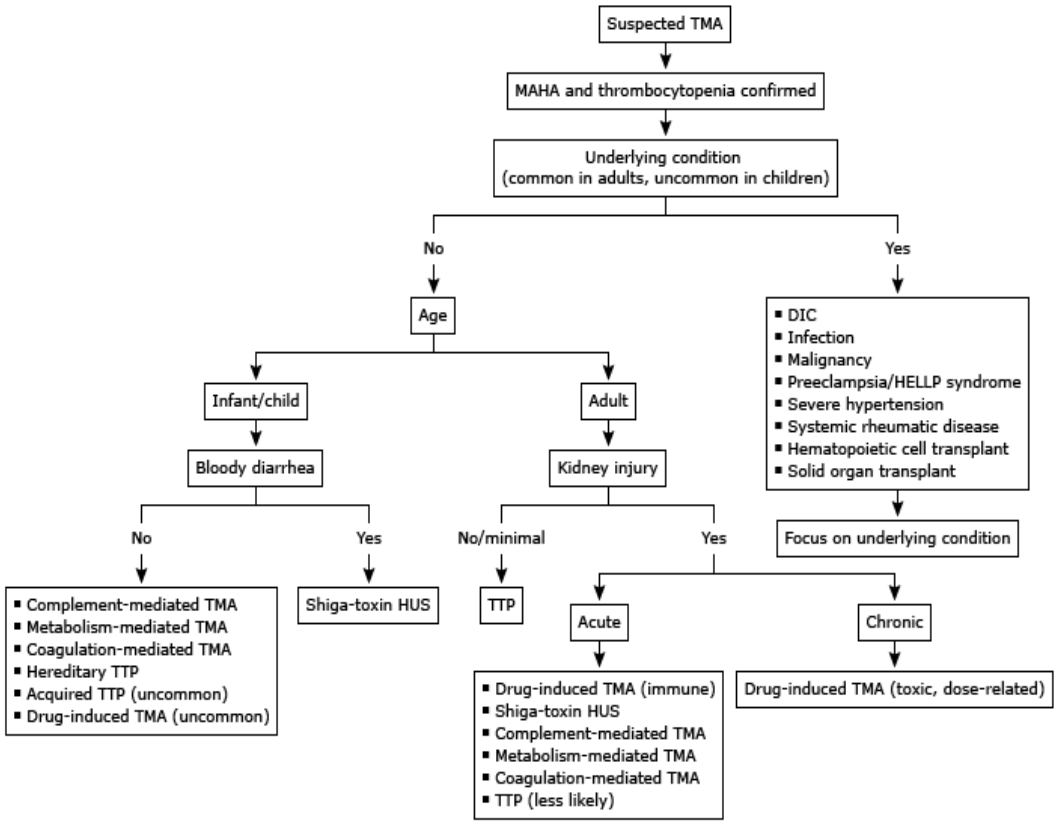
Metabolism mediated TMAs:

Hereditary metabolism-mediated or coagulation-mediated TMAs typically occur in infants but can occur in adults; these disorders do not have specific presenting symptoms. Patients may describe symptoms related to progressive kidney failure, such as weakness and fatigue.(31)

Coagulation-mediated TMA:

Hereditary deficiency of proteins involved in coagulation can cause TMA. These syndromes differ from the abnormalities associated with hereditary thrombophilia, which cause thromboembolism in large vessels rather than systemic microvascular thrombosis. Mutations in genes encoding thrombomodulin (TM), plasminogen, and diacylglycerol kinase epsilon (*DGKE*) have been reported to be associated with TMA.(31)

Figure 2 Approach to Thrombotic Microangiopathies(35)



Thrombotic Microangiopathy in Snake Envenomation

Multiple publications from Australia and Sri Lanka have shown case reports of TMA in snakebites with the Brown Snake, Russell's viper and Humped nose viper bites.(30,36,37) Many of these studies have limitations of ADAMTS13 and complements not being included in the study.

Venom induced consumptive coagulation (VICC) is a well-known consequence of viper bites. It is also known that some viper venoms, such as those of hump nosed viper and Russell's viper, can precipitate renal failure. The common tendency is to view both these manifestations as a part of a same syndrome. VICC is characterized by rapid onset coagulopathy within hours after the snake bite with elevated D-dimer levels, prolonged prothrombin time, and low fibrinogen levels which at times is associated with thrombocytopenia. This resolves within 24 to 48 hours. It is not associated with systemic microthrombi and end organ failure. (30,38) Hence the pathophysiology of the end organ damage remains a question and is likely contributed to Thrombotic Microangiopathy which is an under recognized entity.

Hence it has been postulated that the end organ damage is due to a venom induced thrombotic Microangiopathy, and that VICC and TMA are exclusive. Most case reports have shown an HUS like syndrome, and not shown much of a TTP spectrum, which is likely due to TTP being so rare.

Hence TMA could present as TTP or a complement mediated Thrombotic Microangiopathy in Snake envenomation. In all of these case reports the investigators have not been able to substantiate findings with investigations like complements or ADAMTS13.

Myint / Warrel et al showed that out of 123 Russell's viper bites they had an almost 26% subset who had thrombocytopenia and about 44% had oliguria and these patients had a prolonged hospital stay. (39)

In a study done in Kerala, Joseph K Joseph et al showed that low platelets, drop in Hemoglobin, rising creatinine and proteinuria showed a poor outcome and prolonged hospitalization. (40) Which shows that patients with thrombocytopenia may fall into a spectrum of TMA, which would explain the poorer prognosis in this subset.

Hence it could be postulated that the spectrum of Thrombotic Microangiopathy extends from thrombocytopenia only to thrombocytopenia, MAHA, and end – organ damage. There is also a significant overlap of TMA and VICC, and these patients often have a poorer prognosis.

Role of Plasma Exchange in TMA secondary to Snakebite

The proposed mechanism is that the venom or endothelial toxins act on von Willebrand factor activators and initiate TMA by inducing endothelial damage. (41)The role of ADAMTS 13 in still unclear as there is no studies, which have

evaluated ADAMTS13. Hence it is unclear if these patients would improve with plasma exchange, as this is a secondary TMA, which should resolve without replacement of factors. Data on plasma exchange in snakebites is limited as shown below in figure 3. Most citations have shown good/modest improvement in hospital stay and outcome.

The clinical efficacy of plasma exchange in snake envenomation is not clear, even though immune complex and toxin removal may be augmented, studies have not shown difference in renal recovery, anemia or platelet count with or without plasma exchange.(41)

American society for Apharesis has put role of plasma exchange in envenomation as Grade 2C, Category 3, which is a weak recommendation.(42)

Figure 3 Thrombotic Microangiopathy in snakebites and Plasma Exchange/Hemodialysis(37)

Author (year)	Number of patients	Age	Sex	Snake species	Clinical presentation	Renal biopsy	Treatment	Outcome
Date *et al.* - India (1986)[6]	16	NA	NA	Russell's viper	HUS	Fibrin thrombi in glomeruli in 5 patients	HD/PD	NA
Cobcroft *et al.*- Australia (1997)[7]	1	33	Male	Taipan	HUS	Fibrin thrombi of interlobular artery	HD/PE	Died
Isbister *et al.* - Australia (2007)[8]	6	NA	NA	Brown snake	HUS	Fibrin thrombi in glomeruli	HD/PE	All recovered
Casamento *et al.* - Australia (2011)[9]	2	55,46	Female-1, male-1	Tiger snake	HUS	Not done	HD/PE	Partial recovery
Karunatilake *et al.* - Sri Lanka (2012)[10]	1	35	Male	Hump-nosed viper	HUS	Not done	HD	NA
Herath *et al.* – Sri Lanka (2012)[11]	7		Female-4, male-3	Hump-nosed viper	HUS	Fibrin thrombi in glomeruli	HD	Complete recovery-3 chronic kidney disease 2, died-2
Mitrakrishnan *et al.* – Sri Lanka (2013)[12]	1	70	Male	Hump-nosed viper	HUS	Not done	HD/PE	Complete recovery
Withana *et al.* – Sri Lanka (2014)[13]	1	55	Female	Hump-nosed viper	TTP	Not done	HD/PE	Complete recovery

NA: Not available, HUS: Hemolytic-uremic syndrome, TTP: Thrombotic thrombocytopenic purpura, PE: Plasma exchange, HD: Hemodialysis, PD: Peritoneal dialysis

There are no well-conducted studies, which have been done looking at Thrombotic Microangiopathy looking at diagnostic methods like ADAMTS13/ von Willebrand factor assays or therapeutic role of plasma exchange. Hence there is an urgent need for such studies for optimizing therapy in such patients.

MATERIALS AND METHODS

Setting

All patients admitted to Christian Medical College, Hospital, Vellore with suspected/ confirmed snakebite from April 2017 to July 2018, would receive standard-of-care treatment. During hospital admission patients will be observed both clinically and with appropriate investigations daily till discharge. Observations seen within the groups will be recorded for comparison.
In addition data will be retrieved from past records of the last 5 years to add a retrospective analysis for the last 5 years (5 years retrospective and 1 year prospective).

Participants

All patients above the age of 18 years, admitted with suspected or confirmed snake envenomation from April 2017 to July 2018 were recruited to the study with informed consent, which was be taken in the Department of Emergency Medicine, prior to admission for prospective analysis, if patients had a platelet count less than 1, 50,000 they were closely monitored for features suggestive of Thrombotic Microangiopathy and were included in the study population.

For the retrospective analysis all patients above the age of 18 years, admitted with suspected or confirmed snake envenomation from April 2012 to March 2017 was recruited.

Inclusion criteria

- All consenting adult patients presenting to CMC Hospital with suspected snake bite within 24 hours
- Patients with a thrombocytopenia of less than 1,50,000 (in the first 3 days of hospitalization).
- Patients that have presented with snakebites with a thrombocytopenia less than 1,50,000, during a hospital admission in Christian Medical College over the last 5 years (Information obtained through Clinical workstation and hospital records of the same).

Case definitions

Thrombotic Microangiopathy – Thrombocytopenia (platelets<1,50,000), Microangiopathic haemolytic anemia(drop in Hemoglobin/fragmented red cells evidenced by schistocytes, elevated LDH) with :

Acute renal impairment, including oliguria/anuria, elevated creatinine (>1.5mg/dl)

And/or

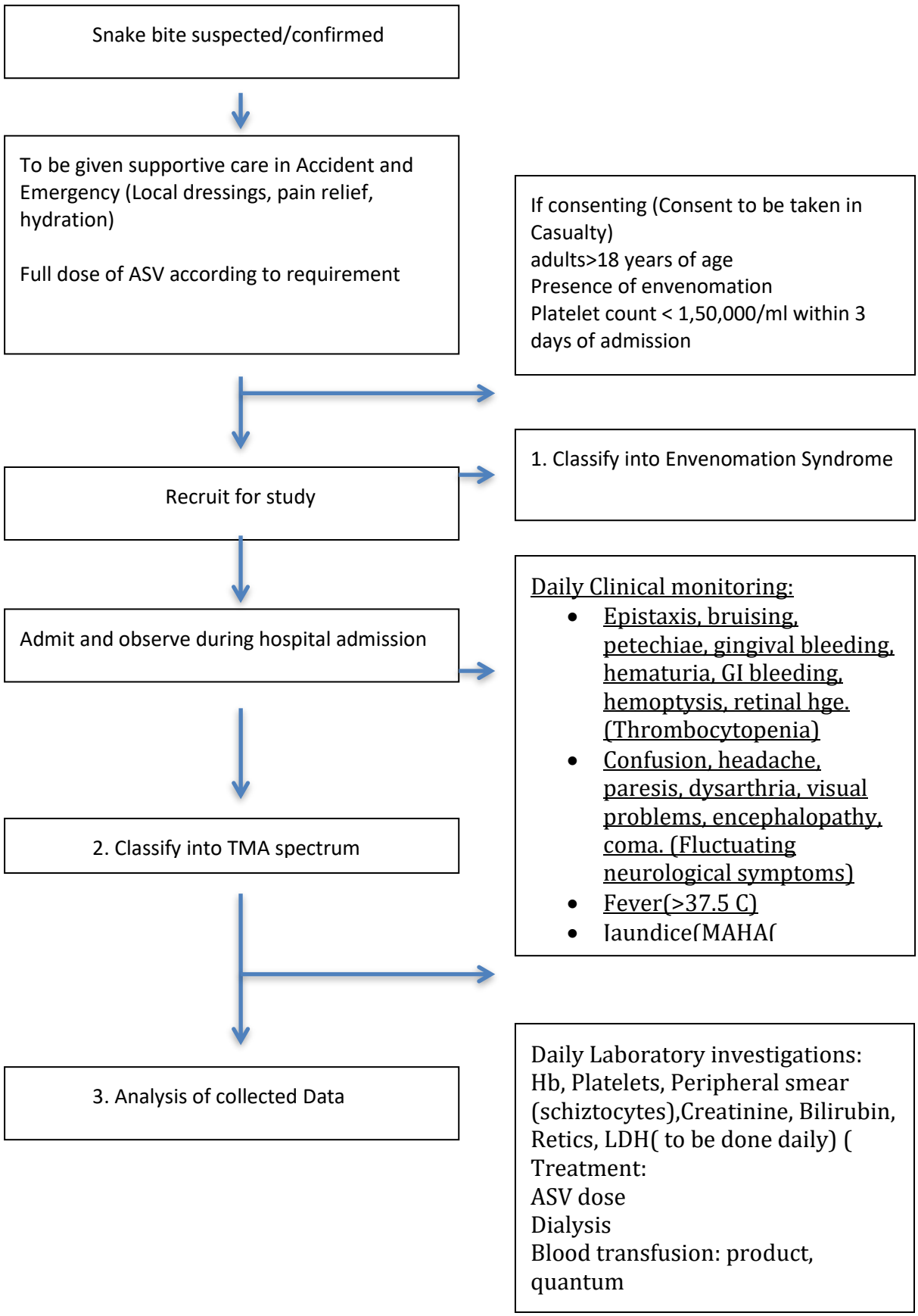
Acute neurological features (reduced consciousness, seizures, cerebrovascular accident, and coma)

Cases are categorized as follows:

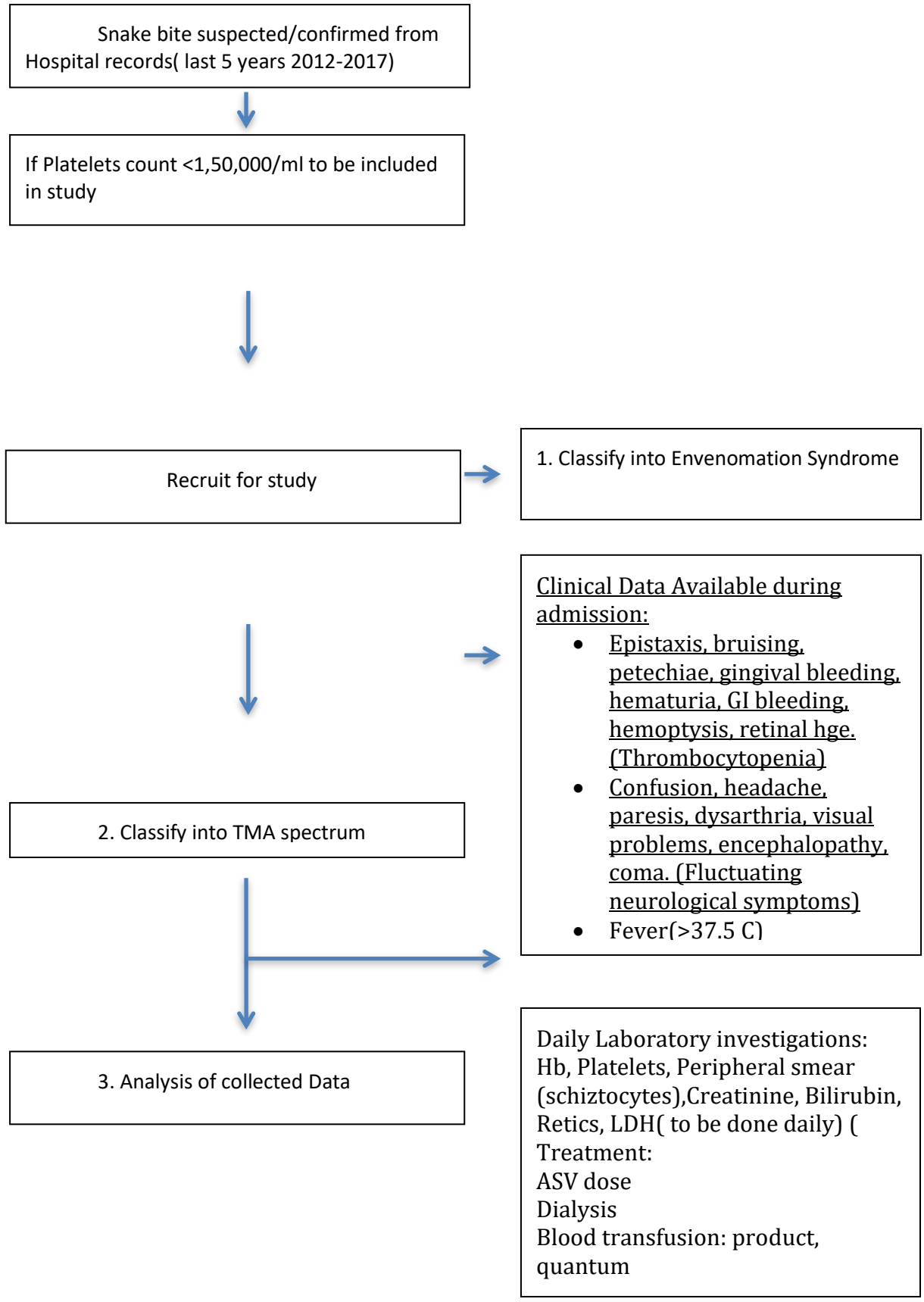
1. Thrombocytopenia only

2. Thrombocytopenia with evidence of schistocytes
3. Thrombocytopenia with evidence of schistocytes and microangiopathic haemolytic anaemia (anaemia, retriculocytosis, indirect hyperbilirubinemia and elevated LDH)
4. Thrombocytopenia with evidence of schistocytes and Neurological dysfunction: altered sensorium, focal neurological with or without Renal dysfunction: elevated creatinine

Detailed diagrammatic Algorithm of the Prospective Part of the study



Detailed Diagrammatic Algorithm of Retrospective Part of Study



Variables

Admission characteristics: Characteristics of bite, symptoms and signs, pre hospital management

Clinical syndrome (envenomation) : local swelling only, pure haemotoxicity, haemotoxicity and neurotoxicity and/or AKI, neurotoxicity with or without local swelling, pure AKI

Clinical findings:

- Epistaxis, bruising, petechiae, gingival bleeding, hematuria, gastrointestinal bleeding, hemoptysis, retinal bleeding. (Thrombocytopenia)

- Confusion, headache, paresis, aphasia, dysarthria, visual problems, encephalopathy, coma.
- Fever >37.5 C
- Jaundice. (Microangiopathic haemolytic anemia)
- Frothy urine, hematuria. (Renal Impairment)
- Respiratory distress, single breath count, ptosis, neck holding time.

Laboratory abnormalities: CBC, clotting screen (PT/aPTT, Fibrinogen), platelets, Peripheral smear for schistoytes, reticulocyte count, LDH, bilirubin (Total/Direct), creatinine.

Treatment

ICU care, mechanical ventilation, dialysis, plasma exchange, surgical treatment, antibiotics, anti snake venom dose, allergy and anaphylaxis, blood transfusion

Time course of TMA

Temporal profile of platelet count, schistoytes, hemoglobin and organ dysfunction.

Outcomes

Clinical outcome of snake bite in different snake bite syndromes in patients with TMA and without TMA, in relation to death, duration of hospitalization, need for dialysis and blood products

Data Sources/measurement

Admission characteristics, clinical syndromes and outcomes- From Patient Emergency and IP records, Clinical workstation

a. Progress notes, transfusion records, treatment records- dialysis/plasma exchange, surgical intervention, antibiotics based on ward and ICU records and details from Clinical workstation.

b. Comparability of assessment: association between envenomation syndromes and TMA spectrum, Association of VICC and TMA, clinical outcomes in patients with TMA and without.

Follow up

Follow up of the patients was done during hospital stay, from admission to discharge. Patients were monitored daily both clinically and with investigations. Information was obtained from progress notes, transfusion records, treatment records from Wards/ICU and the Clinical workstation.

Bias

All consecutive patients with snake envenomation were included in the study to avoid any form of bias.

Sample size

Using the data from the thesis published in the previous year, the prevalence was about 66% (Dr. George's thesis) and another article from Lancet (both references given below), the required sample size to show an incidence of

spectrum of TMA among snake bites was found to be 61 subjects with 12.5% precision and 95% confidence limit with an anticipated prevalence of about 46% (obtained as an average of 66 and 26 from the quoted studies below).

References:

A Descriptive study on the Clinical Profile of Snake Envenomation in a Tertiary Care Center in Tamil Nadu and the Diagnostic and Prognostic Utility of Serum Phospholipase A2 in Various Envenomation Syndromes

Lancet. 1985 Dec 7;2(8467):1259-64. Bites by Russell's viper (Viperarussellisiamensis) in Burma: haemostatic, vascular, and renal disturbances and response to treatment. Myint-Lwin, Warrell DA, Phillips RE, Tin-Nu-Swe, Tun-Pe, Maung-Maung-Lay.

Formula:

$$n = \frac{Z^2_{1-\alpha/2}\, p(1-p)}{d^2}$$

Where,

p : Expected proportion

d : Absolute precision

1- α/2 : Desired Confidence level

Reference for the above formula: Lemeshow S, Hosmer DW, Klar J, Lwanga SK. Adequacy of Sample Size in Health Studies. John Wiley and Sons, 1990.

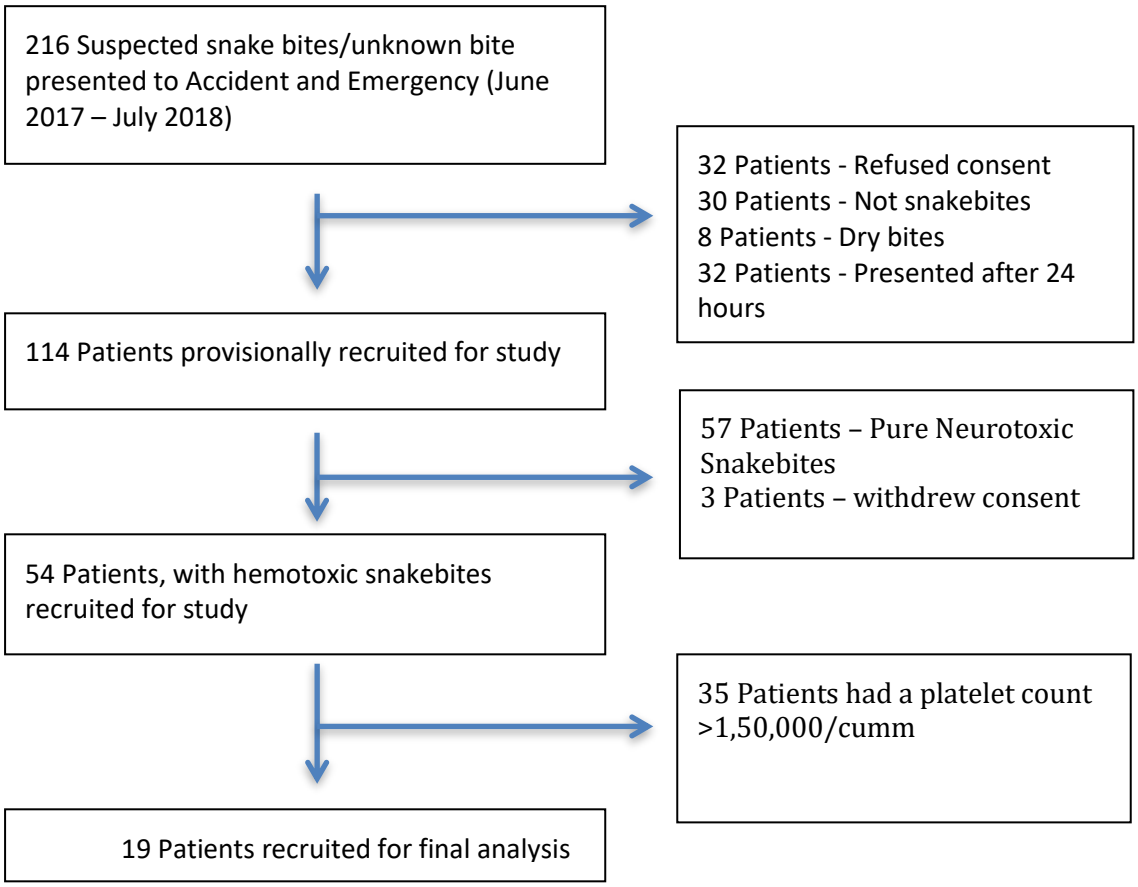
Single Proportion - Absolute Precision

Expected incidence (proportion)	0.46	0.26	0.66	0.46	0.46	0.46
Precision (%)	5	5	5	10	12.5	15
Desired confidence level (1- alpha) %	95	95	95	95	95	95
Required sample size	382	296	345	95	61	42

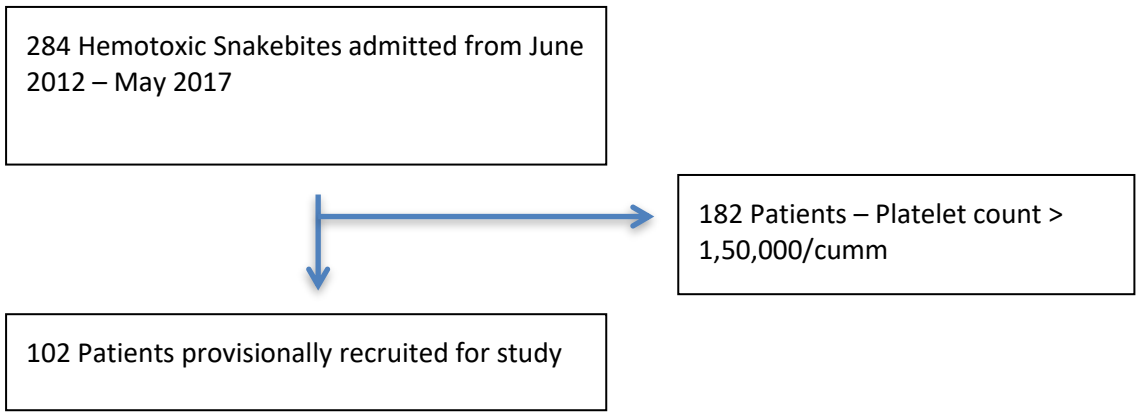
Statistical methods

Descriptive statistics were used such as mean, standard deviation, Median and Inter quartile range for the Haemoglobin level, Platelets, Creatinine and ASV total, ICU stay etc., Frequency and Percentage were reported for Gender, TMA spectrum, Dialysis, Plasmapharesis and VICC etc., If the TMA spectrum groups follows normal distribution across Haemoglobin level and Baseline creatinine. If across the group does not follows normal distribution, Kruskal Wallis test was used across the TMA spectrum with Platelets, Creatinine, ASV total, ICU stay, Duration of hospitalization etc.,. Categorical variables (such as clinical syndromes) and the outcomes such as death, VICC etc., was compared across the groups, Fisher's exact test was used. P value < 0.05 was considered as a statistical significance. The analysis was carried out using SPSS 21.0 version.

STROBE FIGURE: Prospective Cohort



STROBE FIGURE: Retrospective Cohort



RESULTS

Prevalence of TMA spectrum Disorder and Full Spectrum Disorder

121 patients were included in this study, 19 in the prospective cohort and 102 in the retrospective cohort.

The prevalence of TMA spectrum in hemotoxic snakebites in the prospective arm was 51.35% (19 cases out of 37 hemotoxic snake bites) and 21.6% with the full spectrum disorder (8 cases out of 37 hemotoxic snake bite). In the prospective and retrospective arms together, the prevalence of TMA spectrum was 35.9% (102 cases out of 284 hemotoxic snake bites) and 7.74 % with the full spectrum disorder (22 cases out of 284 hemotoxic snake bite).

Table 3 Baseline Characteristics

Variable	**Prospective(n=19)**	**Retrospective(n=102)**	**Total(n=121)**
	n(%)	**n(%)**	**n(%)**
Gender Male Female	 14(73.7) 5(26.3)	 75(73.5) 27(26.5)	 89(73.6) 32(26.4)
Age (Mean ± SD)	38.58 ± 12.10	46.46 ± 14.21	45.22 ± 14.15
Site of Bite Upper Limb Lower Limb Trunk Face	 4(21.1) 14(73.7) - 1(5.3)	 11(10.8) 89(87.3) 1(1.0) 1(1.0)	 15(12.4) 103(85.1) 1(0.8) 2(1.7)

Locality			
Chittoor	8(42.1)	23(23.5)	31(25.6)
Thiruvanmallai	2(10.5)	19(18.6)	21(17.4)
Vellore	7(36.8)	58(56.9)	65(53.7)
Others	2(10.6)	2(2.0)	4(3.3)

Baseline Characteristics (Refer to Table 1)

Baseline characteristics of the prospective and retrospective arm were matched. The majority of the patients was male (73.6%), with a mean age of 45.22 years of age and had a lower limb bite (85.1%).

In the retrospective cohort it was noted that patient geographical distribution was mainly from Vellore, Tamil Nadu (56.9%) whereas in the prospective cohort the population was mostly from Chittoor, Andhra Pradesh (42.1%).

Table 4 Laboratory Parameters

Variable	Prospective(n=19)	Retrospective(n=102)	Total(n=121)
	n(%)	n(%)	n(%)
WBCT <20 min >20 min	 6(31.6) 13(68.4)	 5(4.9) 97(95.1)	 11(9.1) 110(90.9)
Hemoglobin (g/dL) (Mean ± SD)	13.18 ± 2.63	13.51 ± 2.45	13.45 ± 2.47
Total Counts (/dL) (Mean ± SD)	16852.06 ± 7124.71	19110.87 ± 10352.06	18756.27 ± 9924.32
Platelets (/cumm) (Mean ± SD) Mild (>1,00,000) Moderate (50,000 – 1,00,000) Severe (<50,000)	 14(73.7) 2(10.5) 3(15.7)	 52(51.0) 23(22.5) 27(26.5)	 66(54.5) 25(20.7) 30(24.8)
Creatinine (mg/dL) (Mean ± SD)	2.03 ± 1.66s	1.44 ± 0.82	1.53 ± 1.01
INR (Mean ± SD)	2.96 ± 2.64	4.81 ± 3.73	4.52 ± 3.64
APTT(s) (Mean ± SD)	48.54 ± 35.08	86.22 ± 66.57	80.30 ± 64.06
CPK(IU/dL) (Mean ± SD)	2060.79 ± 3068.09	3258.63 ± 7550.14	2478.06 ± 4588.46

Laboratory Parameters (refer to Table 2)

The degree of VICC was more severe in the retrospective arm. WBCT was prolonged in 68.4% of patient's in the prospective cohort as compared to 95.1% in the retrospective cohort. The mean INR in the prospective cohort was 2.96 as compared to 4.81 in the retrospective cohort. The mean aPTT in the prospective cohort was 48.54 as compared to 86.22 in the retrospective cohort. 24.8% of the

retrospective cohort and 15.7% of the prospective cohort had severe thrombocytopenia (<50,000/cumm). There was elevation of CPK in both the prospective and retrospective cohorts.

Table 5 Thrombotic microangiopathy spectrum

TMA Spectrum	**Prospective(n=19)**	**Retrospective(n=102)**	**Total(n=121)**
	n(%)	**n(%)**	**n(%)**
Thrombocytopenia only	**6(31.6)**	**57(55.9)**	**63(52.1)**
Thrombocytopenia + MAHA	1(5.3)	4(3.9)	5(4.1)
Thrombocytopenia + MAHA + Schistocytes	1(5.3)	3(2.9)	4(3.3)
Total MAHA	**2(10.6)**	**7(6.8)**	**9(7.4)**
Thrombocytopenia + MAHA + Schistocytes +Renal Failure	8(42.1)	22(21.6)	30(24.8)
Thrombocytopenia + Renal Failure	3(15.8)	16(15.7)	19(15.7)
Total Renal Failure + Thrombocytopenia	**11(57.9)**	**38(37.3)**	**49(40.5)**

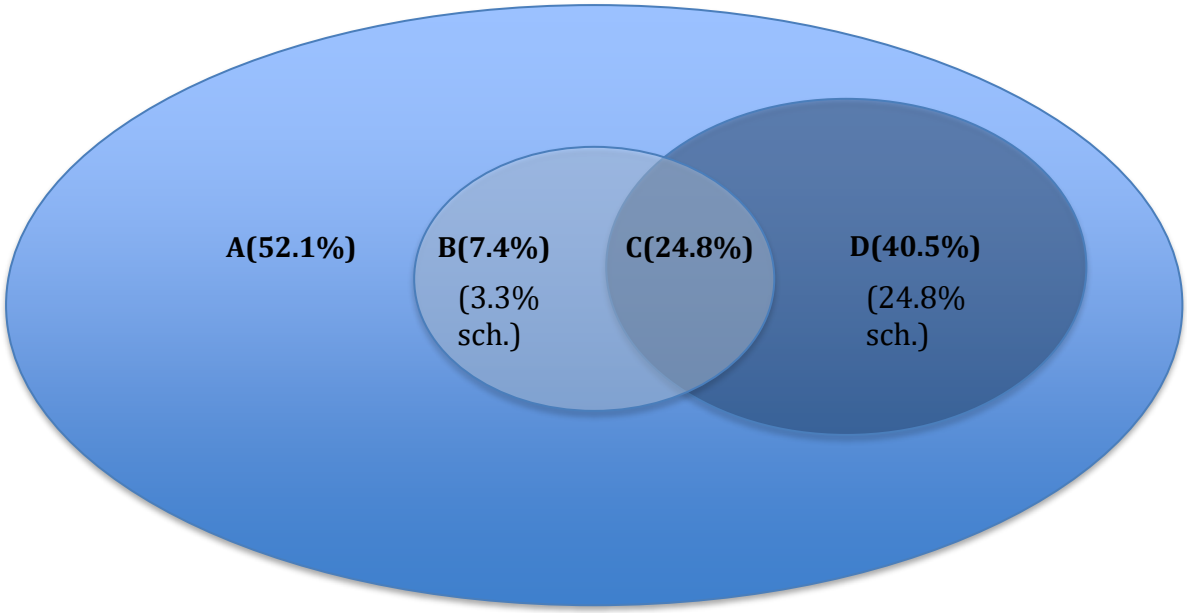
Thrombotic microangiopathy spectrum (refer to Table 3)

In the prospective cohort, 31.6 % had isolated thrombocytopenia, 10.6 % had thrombocytopenia and MAHA and 57.9 % had thrombocytopenia with renal failure. 42.1 % had thrombocytopenia, MAHA, renal failure and schistocytes.
In the retrospective arm, 55.9% had isolated thrombocytopenia, 6.8% had thrombocytopenia and MAHA and 37.3% had thrombocytopenia with renal failure. 21.6% had thrombocytopenia, MAHA, renal failure and schistocytes.

In the prospective arm, 47.4% had schistocytes compared to 24.5% in the retrospective arm. Recently the Department of Transfusion Medicine has included microspherocytes in the reporting of schistocytes. This is likely to have increased the schistocytes percentage in the prospective arm as compared to the retrospective arm.

Overall of the 121 cases, 52.1% had isolated thrombocytopenia, 40.5% had thrombocytopenia with renal failure, 7.4% had thrombocytopenia with MAHA and 24.8% had thrombocytopenia, renal failure and MAHA (see Figure 3) 61.2% of patients with renal failure had schistocytes.

Figure 3 Broad Classification of TMA



A: Isolated Thrombocytopenia

B: Thrombocytopenia +Microangiopathic Hemolytic Anemia

C: Thrombocytopenia + MAHA + Renal Failure

D: Thrombocytopenia and Renal Failure

Table 6 Envenomation Syndrome

Envenomation Syndrome	**Prospective(n=19)**	**Retrospective(n=102)**	**Total(n=121)**
	n(%)	**n(%)**	**n(%)**
Local Reaction + Hemotoxicity	5(26.3)	27(26.4)	32(26.5)
Pure Hemotoxicity	1(5.3)	4(3.9)	5(4.1)
Total isolated hemotoxicity	**6(31.6)**	**31(30.3)**	**37(30.6)**
Hemotoxicity + AKI	4(21.1)	5(4.9)	9(7.4)
Hemotoxicity + Neurotoxicity	6(31.6)	45(44.1)	51(42.1)
Hemotoxicity + Neurotoxicity + AKI	3(15.8)	21(20.6)	24(19.8)
Total Hemotoxicity ± Neurotoxicity ± AKI	**13(68.5)**	**71(69.7)**	**84(69.3)**

Envenomation syndrome (refer to Table 4)

Majority of the patient population in both the prospective and retrospective cohorts presented with an envenomation syndrome of hemotoxicity with neurotoxicity and/or AKI suggestive of Russell's viper like syndrome in 84(69.4%) of the patients and 37(30.6%) presented with a pure hemotoxic envenomation syndrome (see figure 2)

Figure 4 Envenomation Syndrome

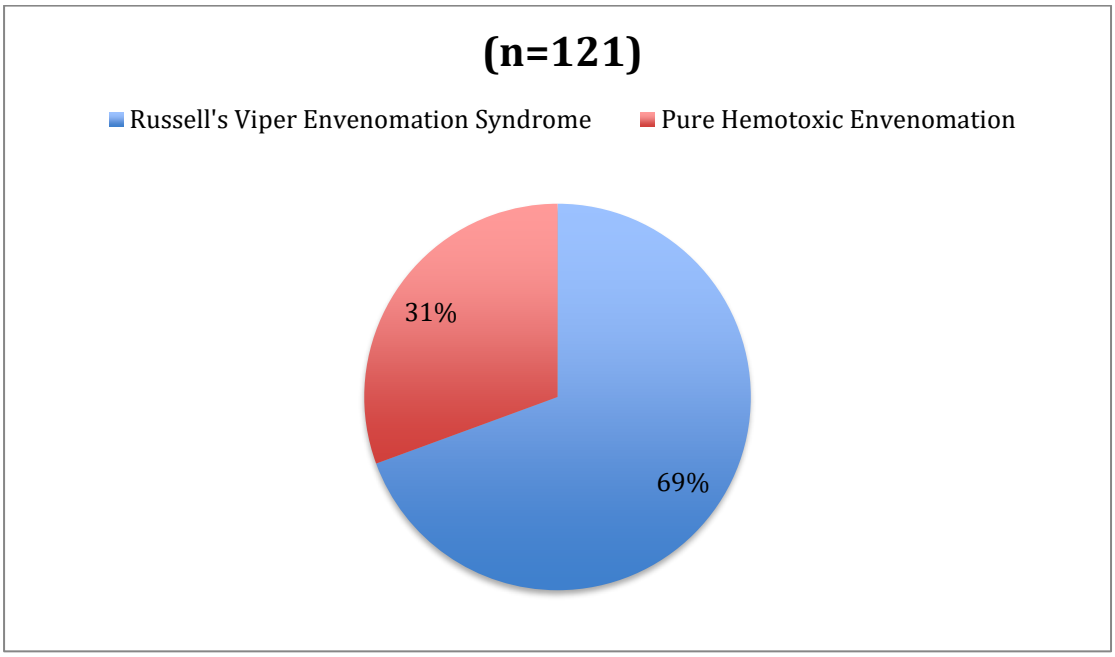


Table 7 VICC

VICC	**Prospective(n=19)**	**Retrospective(n=102)**	**Total(n=121)**
	n(%)	**n(%)**	**n(%)**
Yes	12(63.2)	86(84.3)	98(81)
No	7(36.8)	16(15.7)	23(19)

Table 8 TMA, VICC and Baseline Platelets

VICC	Platelets Baseline n(%)			
	Mild (>1,00,00/cumm)	Moderate (50,000-1,00,00/cumm)	Severe (<50,000/cumm)	P value
Yes (n=98)	55(56.1)	20(20.4)	23(23.5)	0.258
No (n=23)	11(47.1)	5(21.7)	7(30.4)	
Total (n=121)	66(54.5)	25(20.7)	30(24.8)	

VICC, TMA and correlation with platelets (refer to Table 5 and 6)

VICC was seen in 63.2% of the prospective cohort as compared to 84.3% of subjects in the retrospective cohort.It was noted that 30.4% patients without VICC, had a severe thrombocytopenia as compared to 23.5% with VICC. Overall 54.5% of TMA spectrum had mild thrombocytopenia, 20.7% moderate and 24.8% severe thrombocytopenia.

Figure 5 VICC (Prospective and Retrospective)

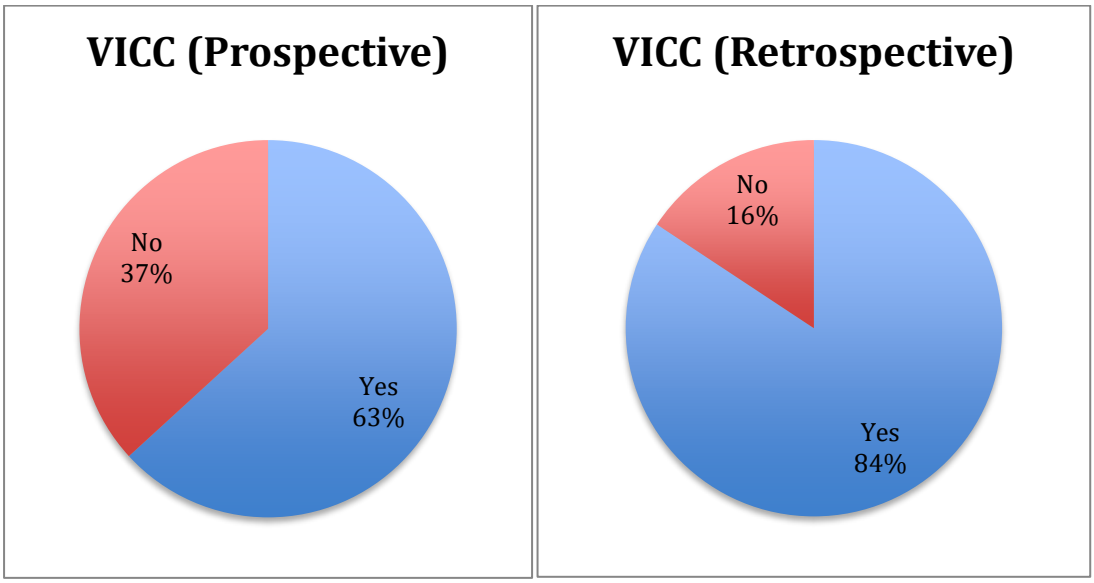
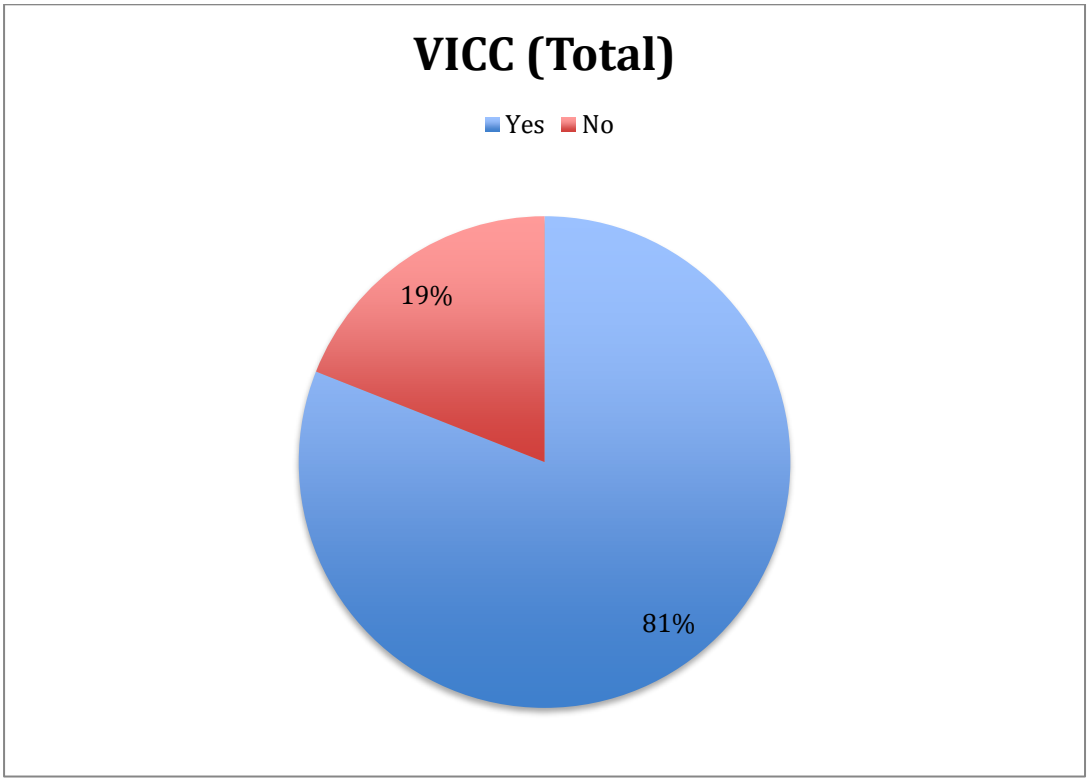


Figure 6 VICC(Total)



In about 19% patient population, there is thrombocytopenia without VICC, which shows that there is isolated microangiopathy occurring without VICC

Table 9 Envenomation syndrome with stratified TMA groups

Envenomation Syndrome	**Stratified groups**			
	Isolated Thrombocytopenia n(%)	**Thrombocytopenia with Schistocytes and Renal Failure n(%)**	**Thrombocytopenia with Renal Failure n(%)**	**P Value**
Pure Hemotoxic Envenomation (n=35)	31(88.6)	0(0)	4(11.4))	<0.001*
Russell's Viper like Envenomation (n=76)	34(44.7)	30(39.5)	12(15.8)	

Envenomation Syndrome and TMA (refer to Table 7)

In patients with an a pure hemotoxic envenomation syndrome, it was noted that they had less severe manifestations, with isolated thrombocytopenia which was seen in 88.6 %, thrombocytopenia with MAHA and renal failure was 0% and thrombocytopenia with renal failure in 11.4%. In contrast in the Russell's viper envenomation syndrome isolated thrombocytopenia occurred in 44.7%, Thrombocytopenia with MAHA and renal failure 39.5% and thrombocytopenia with renal failure in 15.8%. (See Figure 5, detailed Table of Envenomation Syndrome and TMA, Table 17 given in Annexure 6). The difference in TMA spectrum according to envenomation syndrome was statistically significant (p=0.001)

Figure 7 Snake Envenomation Syndrome and TMA Spectrum

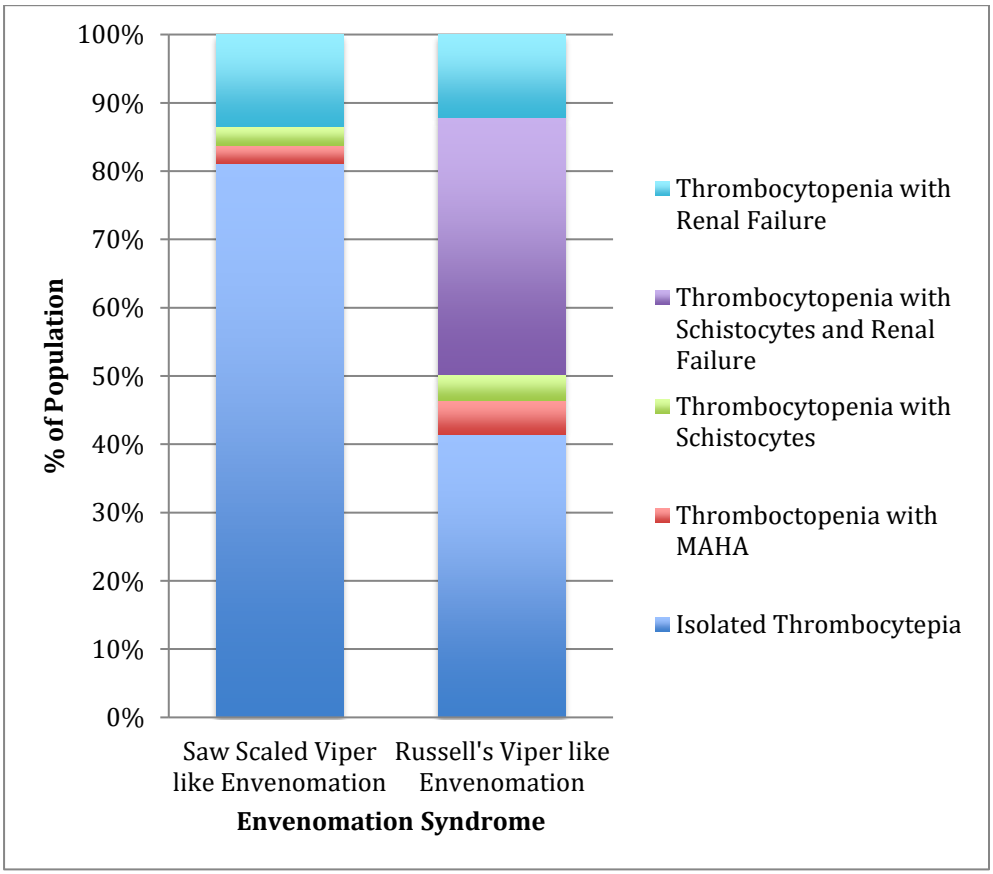


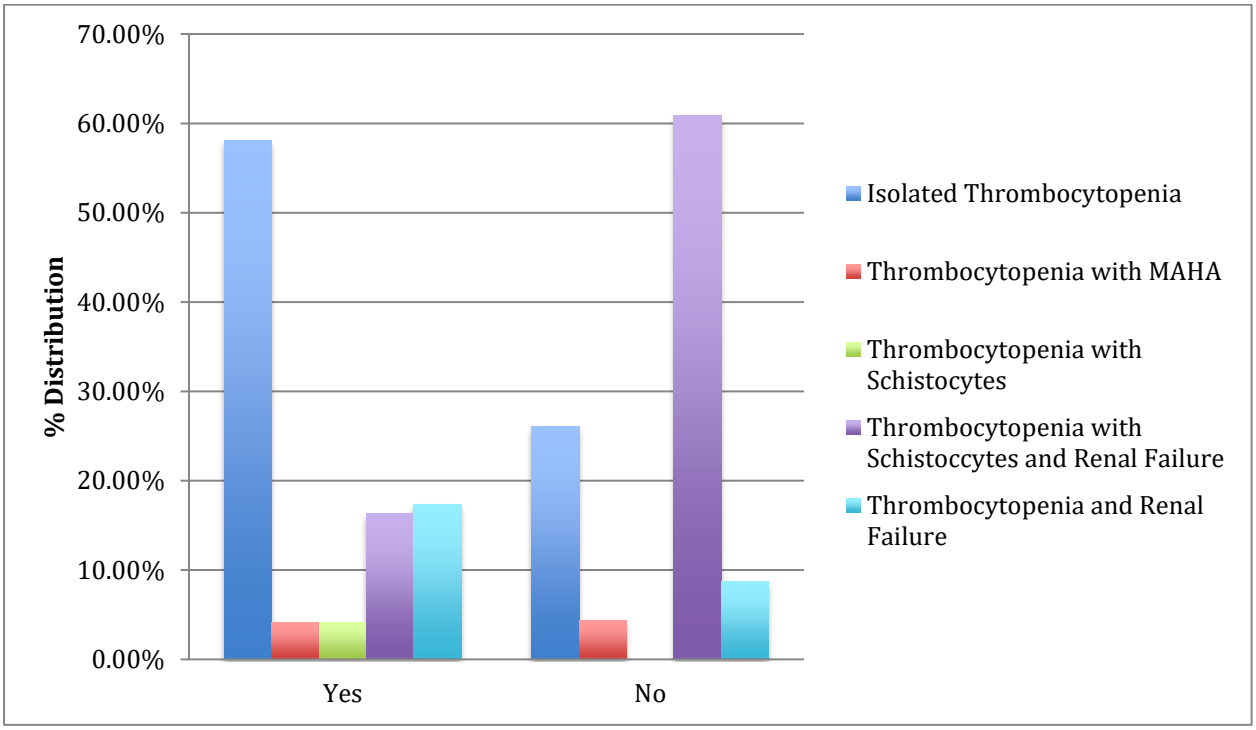
Table 10 VICC correlation with TMA Spectrum

VICC	TMA Spectrum (Prospective n=19, Retrospective n=102, Total n=121)														
	Thrombocytopenia only			Thrombocytopenia + MAHA			Thrombocytopenia + MAHA + Scistocytes			Thrombocytopenia + MAHA + Scistocytes +Renal Failure			Thrombocytopenia + Renal Failure		
	P(n=8) n(%)	R(n=57) n(%)	T(n=65) n(%)	P(n=1) n(%)	R(n=4) n(%)	T(n=5) n(%)	P(n=1) n(%)	R(n=3) n(%)	T(n=4) n(%)	P(n=8) n(%)	R(n=22) n(%)	T(n=30) n(%)	P(n=3) n(%)	R(n=13) n(%)	T(n=16) n(%)
Yes (n=98)	8(100)	51(89.5)	59(90.5)	-	4(100)	4(80)	1(100)	3(100)	4(100)	2(25)	14(63.6)	16(53.3)	3(100)	11(84.6)	14(89.5)
No (n=23)	-	6(10.5)	6(9.5)	1(100)	-	1(20)	-	-	-	6(75)	8(36.4)	14(46.7)	-	2(18.18)	2(10.5)

Table 11 VICC in relation to TMA spectrum

VICC	**Stratified groups (n=111)**			
	Isolated Thrombocytopenia (n=65) n(%)	**Thrombocytopenia with Schistocytes and Renal Failure (n=30) n(%)**	**Thrombocytopenia with Renal Failure (n=16) n(%)**	**P Value**
Yes (n=89)	59(66.3)	16(18.0)	14(15.7)	<0.001
No (n=22)	6(27.3)	14(63.6)	2(9.1)	

Figure 8 VICC correlation with TMA Spectrum



From this data we are able to see that in patients that present with VICC (81.1%), most subjects had less severe manifestations, with isolated thrombocytopenia which was seen in 66.3%, thrombocytopenia with MAHA in 18% and thrombocytopenia with renal failure in 15.7%. In contrast to the patients without VICC, isolated thrombocytopenia occurred in 27.3%, Thrombocytopenia with MAHA and renal failure 63.6% and thrombocytopenia with renal failure in 9.1%.

Therefore there is a group of patients with snake bite induced TMA without VICC. This group of patients had more severe manifestations than TMA without VICC.

Table 12 Treatment Outcomes

Variable	Prospective (n=19)	Retrospective (n=102)	Total(n=121)	
	n(%)	n(%)	n(%)	P value
Time to ASV (Mean ± SD)	4:06:40 ± 3:40:20	3:48:17 ± 4:13:25	3:51:02 ± 4:07:58	0.407
ASV (Outside) (Mean ± SD)	7.53 ± 8.72	7.02 ± 10.30	7.10 ± 10.04	0.799
ASV (CMCH) (Mean ± SD)	9.58 ± 7.07	11.11 ± 5.10	10.87 ± 5.45	0.460
ASV (Total) (Mean ± SD)	17.11 ± 8.36	18.13 ± 9.94	17.97 ± 5.45	0.926
Need for Transfusion				
Yes	6(31.6)	18(17.6)	24(19.8)	0.208
No	13(68.4)	84(82.4)	97(80.2)	
Days of Admission (Mean ± SD)	7.79 ± 6.08	4.89 ± 4.39	5.35 ± 4.79	0.02
Need for ICU Admission				
Yes	5(26.3)	14(13.7)	19(15.7)	0.260
No	14(73.7)	88(86.3)	102(84.3)	
ICU Days (Mean ± SD)	1.21 ± 1.93	0.49 ± 1.57	0.60 ± 1.61	0.198
Dialysis				
Yes	6(31.6)	17(16.7)	23(19.0)	0.198
No	13(68.4)	85(83.3)	98(81.0)	
Plasmapharesis				
Yes	3(15.8)	3(2.9)	6(4.95)	0.049
No	16(84.2)	99(97.1)	115(95.05)	
Final Outcome	19(100)	92(90.2)	111(91.7)	-
Discharge	-	10(9.8)	10(8.2)	
DAMA/Death				

Treatment outcomes (refer to Table 10)

Subjects in the prospective and retrospective cohort both had similar treatment outcomes. The mean total ASV requirements in the prospective and retrospective cohort were 17.1 and 18.1 vials of ASV, respectively.

In the prospective cohort patients had a significantly longer duration hospital admission as compared to the retrospective cohort (7.79 days as compared to 4.89 days, p=0.02). 26.3% of patients in the prospective arm required ICU care, compared to 13.7% in the retrospective cohort. The mean ICU stay in the prospective cohort, was 1.21 days compared to 0.49 days in the retrospective arm. 31.6% of the prospective cohort patients required dialysis compared to 16.7% in the retrospective cohort. There was significantly higher requirement of plasmapharesis in prospective arm of 15.8% as compared to 2.9% in the retrospective arm (p=0.049) and may be attributed to a higher incidence of TMA with renal failure, thrombocytopenia and schistocytes in the prospective cohort as compared to retrospective cohort (42.1% versus 21.6%)

As treatment approaches have evolved, the use of plasmapharesis has increased and may have led to a longer hospital stay.

The final outcome of patients in both the prospective arm and retrospective arm both were good (91.7% of the patients were discharged) and death occurred in only 4.9% of patients, which was noted in the retrospective cohort. There were no deaths or discharge against medical advice in the prospective arm suggesting the outcome of patients with full spectrum of TMA had improved in the recent period.

Table 13 Severity of TMA Spectrum: Admission Laboratory Values

	TMA Spectrum(Stratified groups)									
	Thrombocytopenia only (n=65)			**Thrombocytopenia + MAHA + Scistocytes +Renal Failure (n=30)**			**Thrombocytopenia + Renal Failure (n=16)**			**P value**
	B	**D3**	**D6**	**B**	**D3**	**D6**	**B**	**D3**	**D6**	
Hemoglobin (g%) (Mean ± SD)	13.57 ± 2.51	11.18 ± 2.02	11.00 ± 2.44	12.83 ± 2.59	9.22 ± 1.70	7.75 ± 1.32	13.93 ± 2.44	11.68 ± 1.41	12.10 ± 1.55	<o.280
Platelets (/cumm) (Mean ± SD)	1,15,295.38 ± 1,20,424.18	1,52,795.38 ± 1,20,424.18	1,56,166.67 ± 62,496.13	85,446.67 ± 55,493.63	55,344.83 ± 46,121.94	86,772.73 ± 90,307.90	1,3612.50 ± 1,42,070.50	1,36,812.50 ± 1,42,070.5	1,66,000.00 ± 4,242.64	<0.239
Creatinine (mg/dL) (Mean ± SD)	1.03 ± 0.23	0.84 ± 0.27	0.80 ± 0.26	2.70 ± 1.38	4.64 ± 2.32	6.55 ± 2.17	1.58 ± 0.28	1.93 ± 1.76	3.60 ± 2.67	<0.001
LDH (IU/dL) (Mean ± SD)	997.1 ± 527.2	626.0 ± 527.3	589.3 ± 205.2	5,466.33 ± 11,777.1	3,194.0 ± 2,370.8	1830.5 ± 1,208.5	926.3 ± 94.7	1265 ± 430.6	-	0.002
INR (Mean ± SD)	5.03 ± 3.65			2.85 ± 2.97			5.24 ± 4.08			0.001
aPTT (s) (Mean ± SD)	82.42 ± 63.77			64.94 ± 56.34			89.21 ± 72.98			0.694

Table 14 Severity of TMA Spectrum: Treatment and Outcomes

	TMA Spectrum(Stratified groups)			
	Thrombocytopenia only (n=65)	**Thrombocytopenia + MAHA + Scistocytes +Renal Failure (n=30)**	**Thrombocytopenia + Renal Failure (n=16)**	**P Value**
ASV Total(Vials) (Mean ± SD)	16.41 ± 8.56	21.63 ± 8.56	16.62 ± 8.56	0.051
Hospital Stay (Days) (Median)	2(2,4)	12(7.75,13.25)	3(2,4.75)	<0.001
ICU Stay (Days) (Mean ± SD)	0(0,0)	1.83 ± 2.78	0.50 ± 1.15	<0.001
Dialysis Yes No	- 65(100)	22(73.3) 8(26.7)	1(6.25) 15(93.75)	<0.001
Plasmapharesis Yes No	- 65(100)	6(20) 24(80)	- 16(100)	-
Final Outcome Discharge DAMA/Death	63((96.9) 2(3.1)	24(80) 6(20)	14(87.5) 2(12.5)	0.015

Severity of TMA Spectrum: Admission Laboratory Values (Refer to Table 12)

Out of the TMA groups, the laboratory values at admission were comparable except in the TMA group with full spectrum, in which there were the lowest Hemoglobin (12.83 g/dL), platelets (85,446/cumm), with the highest creatinine (2.07 mg/dL) and LDH (5,466 IU/dL) values. Coagulopathy was least in this group with mean INR of 2.85 and aPTT of 64.85s.

Severity of TMA Spectrum: Treatment and Outcomes (Refer to Table 13)

In comparison of treatment of the TMA spectrum, the full TMA spectrum required more ASV (21.63 vials, $p=0.051$) and had longer hospital and ICU stay (11.3 days and 1.83 days respectively, $p<0.001$) and 73.3% of patients required dialysis ($p=<0.001$).

The final outcomes were significantly different in the groups. 6 patients (20%) of the full TMA spectrum had death/DAMA compared to 12.5% in the thrombocytopenia with renal failure group and 3.1% in the isolated thrombocytopenia group ($p=0.015$). There were 3(10%) deaths in the full spectrum TMA disorder and 2 deaths (12.5%) in the thrombocytopenia and renal failure group.

This data shows that patients who develop the full TMA spectrum have a more severe disease, as compared to isolated thrombocytopenia, which is a more benign disease process.

Detailed clinical case descriptions of full spectrum TMA disorder in prospective cohort (8 patients)

Patient 1:

18 year old male, student, from Chittoor, presented to CMCH, 18hours after snake bite. Initial symptoms developed within 30 minutes, with bleeding from site and some minimal gum bleeding, following which he developed ptosis.
He had received first aid from local hospital and first ASV was administered at approximately 4 hours and 30 minutes (10 vials).
He was referred to CMCH as he developed decreased urine output.

At time of admission he was noted to have a severe thrombocytopenia, falling hemoglobin with MAHA evidenced by high LDH, mild indirect bilirubinemia, and presence of schistocytes on a peripheral smear, also noted to have an oliguric renal failure.
During hospital stay he developed a cellulitis requiring fasciotomy, and was initiated on hemodialysis in view of worsening renal failure, requiring 8 sessions of hemodialysis.

Snake Envenomation syndrome: Hemotoxic with Neurotoxicity and Acute Kidney injury
TMA Spectrum: Thrombocytopenia, MAHA, schistocytes and End organ damage.

	0	3	6	Discharge	3 months
Hb (g%)	12.4	7.1	7.3	8.6	12.0
Platelets (cumm)	9,000	8,000	53,000	4,83,000	3,42,000
Creatinine (mg/dL)	7.46	5.9	9.5	4.99	2.54
Schistocytes (%)	1	4	3.2	nil	
LDH(IU/dL)	14749	9541	3462		
PT/INR	1.35				
aPTT(s)	51				

Treatment	Requirement
Hospital Stay (days)	26
ICU Stay (days)	-
Dialysis (sessions)	8
Plasmapharesis (sessions)	-
Surgical intervention	Fasciotomy
Transfusion	
Packed Red cells	4
Cryoprecipitate	-
Fresh Frozen Plasma	-
Platelets	-
Outcome	Discharged

Patient was discharged in a stable condition, persisted to have a non oliguric renal failure, not requiring further dialysis, follow up at 3 months showed that he

had a persistently elevated creatinine but had decreased significantly hence renal biopsy was done which showed:

Renal Biopsy(at 3 months): Mesangioproliferative glomerulonephritis with focal segmental and diffuse global glomerulosclerosis

Concomitant Interstitial nephritis with focal tubular injury

IF: Granular mesangial and focal capillary deposits of IgM, IgG and C3

End organ damage in this patient was likely due to Thrombotic Microangiopathy and Toxin related glomerulonephritis.

Patient 2:

36 year old house-wife, from Vellore, presented to CMCH, 36 hours after snake bite. She did not have any hemotoxic/neurotoxic snakebites at presentation and hence was discharged, told to have a dry bite. At 36 hours she developed oliguric renal failure and was noted to have pulmonary edema.

She did not receive ASV at presentation or at time of admission.

At time of admission he was noted to have a moderate thrombocytopenia, falling hemoglobin with MAHA evidenced by markedly increased LDH, mild indirect bilirubinemia, and presence of schistocytes on a peripheral smear, also noted to have an oliguric renal failure.

During hospital stay he developed a cellulitis, which was treated conservatively with antibiotics. She was intiated on early plasmapheresis and hemodialysis in

view of probable Thrombotic Microangiopathy and worsening renal failure, requiring 4 sessions of plasmapharesis and 2 sessions of hemodialysis.

Snake Envenomation syndrome: Pure Thrombotic Microangipathy

TMA Spectrum: Thrombocytopenia, MAHA, schistocytes and End organ damage.

	0	**3**	**6**	**Discharge**	**3 months**
Hb (g%)	12.9	11.1	8.6	9.0	10.0
Platelets (cumm)	2,43,000	46,000	19,000	1,76,000	2,28,000
Creatinine (mg/dL)	4.02	4.99	5.7	10.55	0.90
Schistocytes (%)	0.8	1	1.2	nil	
LDH(IU/dL)	5225	3014	1320		
PT/INR	0.97				
aPTT(s)	24.6				

Treatment	Requirement
Hospital Stay (days)	10
ICU Stay (days)	-
Dialysis (sessions)	2
Plasmapharesis (sessions)	4
Surgical intervention	-
Transfusion	
Packed Red cells	-
Cryoprecipitate/supernatant	40
Fresh Frozen Plasma	-
Platelets	-
Outcome	Discharged

Patient was discharged in a stable condition, persisted to have a non oliguric renal failure, not requiring further dialysis, follow up at 3 months showed resolved Acute kidney injury with a normal creatinine.

Initial End organ damage likely caused by a Thrombotic Microangiopathy.

Patient 3:

36 year old male, vegetable vendor from Vellore, presented to CMCH, 11 hours after snake bite. He had initial symptoms of severe pain and bleeding from bite site. He did not seek medical attention and at 8 hours post bite he developed bleeding from gums with hematuria. At presentation he was noted to have a deranged WBCT and hence was given a total of 20 vials of ASV.

At time of admission he was noted to have a mild thrombocytopenia, falling hemoglobin with MAHA evidenced by markedly increased LDH, indirect bilirubinemia, and presence of schistocytes on a peripheral smear, also noted to have an oliguric renal failure.

During hospital stay he developed a cellulitis, which was treated conservatively with antibiotics. He was intiated on early plasmapheresis and hemodialysis in view of probable Thrombotic Microangiopathy and worsening renal failure, after 1st session of plasmapharesis, he developed fever and worsening cellulitis and hence was only continued on cryosupernatant and 14 sessions of hemodialysis.

Snake Envenomation syndrome: Hemotoxic with Acute Kidney injury
TMA Spectrum: Thrombocytopenia, MAHA, schistocytes and End organ damage.

	0	3	6	Discharge	3 months
Hb (g%)	13.4	11.1	9.3	8.6	10.7
Platelets (cumm)	1,72,000	46,000	19,000	1,76,000	7,17,000
Creatinine (mg/dL)	2.89	7.40	7.25	7.39	1.56
Schistocytes (%)	0.5	1.2	4	nil	
LDH(IU/dL)	8892	6832	1810		
PT/INR	2.16				
aPTT(s)	39.7				

Treatment	Requirement
Hospital Stay (days)	18
ICU Stay (days)	-
Dialysis (sessions)	14
Plasmapharesis (sessions)	1
Surgical intervention	-
Transfusion	
Packed Red cells	2
Cryoprecipitate/supernatant	16
Fresh Frozen Plasma	-
Platelets	-
Outcome	Discharged

Patient was discharged in a stable condition, persisted to have a non oliguric renal failure, not requiring further dialysis, follow up at 3 months showed resolving Acute kidney injury with persistently elevated creatinine.
Initial End organ damage, was caused by a Thrombotic Microangiopathy.

Patient 4:

37 year old house-wife from Chittoor, presented to CMCH, 12 hours after snake bite. Initial symptoms developed within 30 minutes, with bleeding from site and some minimal gum bleeding.
She had received first aid from local hospital and first ASV was administered at approximately 6 hours and 30 minutes (18 vials). At 8 hours she noticed that she was having gross hematuria and decreased urine output.

At time of admission he was noted to have a severe thrombocytopenia, falling hemoglobin with MAHA evidenced by high LDH, mild indirect bilirubinemia, and presence of schistocytes on a peripheral smear, also noted to have an oliguric renal failure.
During hospital stay she developed a cellulitis, which was treated conservatively with antibiotics. She was initiated on early plasmapharesis with cryosupernatants, receiving 4 sessions in view of a likely Thrombotic Microangiopathy.

Snake Envenomation syndrome: Hemotoxic and Acute Kidney injury
TMA Spectrum: Thrombocytopenia, MAHA, schistocytes and End organ damage.

	0	3	6	Discharge	3 months
Hb (g%)	11.6	9.2	6.8	6.7	Lost to follow up
Platelets (cumm)	72,000	32,000	75,000	1,93,000	
Creatinine (mg/dL)	2.00	3.51	2.58	0.65	
Schistocytes (%)	5	2	3.5	4	
LDH(IU/dL)	3780	2006	810		
PT/INR	2.5				
aPTT(s)	42.9				

Treatment	Requirement
Hospital Stay (days)	11
ICU Stay (days)	-
Dialysis (sessions)	-
Plasmapharesis (sessions)	4
Surgical intervention	-
Transfusion	
Packed Red cells	-
Cryoprecipitate	-
Fresh Frozen Plasma	16
Platelets	4
Outcome	Discharged

Patient was discharged in a stable condition, with a completely resolved Acute Kidney injury and normal creatinine.

End organ damage in this patient was due to Thrombotic Microangiopathy.

Patient 5:

30 year old house-wife, from Gudiyatham, presented to CMCH, 12 hours after snake bite. Initial symptoms developed within 15 minutes, with pain and bleeding from bite site. She had received first aid from local hospital and first ASV was administered at approximately 45 minutes (18 vials).

She was referred to CMCH as he developed gross hematuria decreased urine output.

At time of admission she was noted to have a severe thrombocytopenia, falling hemoglobin with MAHA evidenced by high LDH, mild indirect bilirubinemia, and presence of schistocytes on a peripheral smear, also noted to have an oliguric renal failure.

In hospital she developed worsening breathlessness, and 3 episodes of hemoptysis, requiring NIV and subsequently was started on mechanical ventilation for 2 days. During hospital stay she developed a cellulitis, which was treated conservatively. She was initiated on hemodialysis in view of worsening renal failure, requiring 5 sessions of hemodialysis. As she had a probable Thrombotic Microangiopathy she was given 10 units of cryosupernatant.

Snake Envenomation syndrome: Hemotoxic with Neurotoxicity and Acute Kidney injury

TMA Spectrum: Thrombocytopenia, MAHA, schistocytes and End organ damage.

	0	**3**	**6**	**Discharge**	**3 months**
Hb (g%)	9.2	7.5	7.3	9.1	9.4
Platelets (cumm)	35,000	21,000	66,000	4,45,000	2,90,000
Creatinine (mg/dL)	3.79	3.59	4.49	7.26	0.74

Schistocytes (%)	0.9	2	1	nil	
LDH(IU/dL)	4371	2331	1477		
PT/INR	1.12				
aPTT(s)	33.7				

Treatment	**Requirement**
Hospital Stay (days)	12
ICU Stay (days)	8
Dialysis (sessions)	5
Plasmapharesis (sessions)	-
Surgical intervention	-
Transfusion	
Packed Red cells	-
Cryoprecipitate	10
Fresh Frozen Plasma	-
Platelets	2
Outcome	Discharged

Patient was discharged in a stable condition, persisted to have a non oliguric renal failure, not requiring further dialysis, follow up at 3 months showed a completely resolved Acute Kidney Injury, with normal creatinine.

Patient 6:

42 year old house-wife, from Vellore, presented to CMCH, 2 hour after snake bite. Initial symptoms developed within 15 minutes, with pain and bleeding from bite site. She had received first aid from local hospital and first ASV was administered at approximately 1 hour (20 vials).

She was referred to CMCH for further management.

At time of admission she was noted to have a mild thrombocytopenia, falling hemoglobin with MAHA evidenced by high LDH, mild indirect bilirubinemia, and presence of schistocytes on a peripheral smear, also noted to have an oliguric renal failure.

In hospital she developed worsening breathlessness and fluid overload, hence was admitted to ICU for NIV and monitoring. During hospital stay she developed a cellulitis, which was treated conservatively. She was initiated on hemodialysis in view of worsening renal failure, requiring multiple sessions of hemodialysis.

Snake Envenomation syndrome: Hemotoxic with Neurotoxicity and Acute Kidney injury

TMA Spectrum: Thrombocytopenia, MAHA, schistocytes and End organ damage.

	0	3	6	Discharge	3 months
Hb (g%)	6.0	7.9	8.3	6.5	7.8
Platelets (cumm)	1,01,000	33,000	77,000	2,61,000	2,62,000
Creatinine (mg/dL)	3.13	3.02	5.39	7.27	9.79
Schistocytes (%)	1.8	0.5	1	nil	
LDH(IU/dL)	2956	4685	4572		
PT/INR	1.18				
aPTT(s)	45.9				

Treatment	Requirement
Hospital Stay (days)	13
ICU Stay (days)	4
Dialysis (sessions)	7
Plasmapharesis (sessions)	-
Surgical intervention	-
Transfusion	
Packed Red cells	3
Cryoprecipitate	-
Fresh Frozen Plasma	12
Platelets	-
Outcome	Discharged

Patient was discharged in a stable condition, persisted to have a non oliguric renal failure, but persisted to require further dialysis, follow up at 3 months

showed that he had a persistently elevated creatinine but had decreased significantly hence renal biopsy was done which showed:

Renal Biopsy(at 3 months): Cortical parenchymal necrosis with confluent glomerular, tubular, arteriolar and arterial necrosis.

IF: Focal segmental trapping of IgM and C3 in sclerosed tufts.

End organ damage in this patient was likely due to Thrombotic Microangiopathy and Acute Tubular Necrosis.

Patient 7:

20 year old, male student from Villupuram, presented to CMCH, 12 hours after snakebite. Initial symptoms developed within 30 minutes, with bleeding from site and some minimal gum bleeding.

He had received first aid from local hospital and first ASV was administered at approximately 6 hours (30 vials). At 8 hours it was noticed that he was having gum bleeding, gross hematuria and ptosis.

At time of admission he was noted to have a mild thrombocytopenia, falling hemoglobin with MAHA evidenced by elevated LDH, mild indirect bilirubinemia, and presence of schistocytes on a peripheral smear, also noted to have a non oliguric renal failure.

During hospital stay he developed a cellulitis, which was treated conservatively with antibiotics. He was treated conservatively for the renal failure.

Snake Envenomation syndrome: Hemotoxic, Neurotoxicity and Acute Kidney injury

TMA Spectrum: Thrombocytopenia, MAHA, schistocytes and End organ damage.

	0	**3**	**6**	**Discharge**	**3 months**
Hb (g%)	12.6	12.0	10.5	10.4	11.5
Platelets (cumm)	1,29,000	1,86,000	3,10,000	3,81,000	3,80,00
Creatinine (mg/dL)	3.25	10.76	10.94	2.06	1.07
Schistocytes (%)	0.3	0.5	0.8	nil	
LDH(IU/dL)	1514	1210	980		
PT/INR	1.22				
aPTT(s)	31.5				

Treatment	**Requirement**
Hospital Stay (days)	13
ICU Stay (days)	-
Dialysis (sessions)	-
Plasmapharesis (sessions)	-
Surgical intervention	-
Transfusion Packed Red cells	-

Cryoprecipitate Fresh Frozen Plasma Platelets **Outcome**	- 4 - Discharged

Patient was discharged in a stable condition, with a completely resolved Acute Kidney injury and normal creatinine.

End organ damage in this patient was due to Thrombotic Microangiopathy/ Pigment nephropathy.

Patient 8:

41 year old, male farmer from Chittoor, presented to CMCH, 8 hours after snakebite. Initial symptoms developed within 30 minutes, with bleeding from site. After about 4 hours he noticed that he was having ptosis.

He had received first aid from local hospital and first ASV was administered at approximately 2 hours (2 vials). He was shifted for further management to CMCH. In CMCH he was noticed to have a deranged WBCT, hence was given 10 vials of ASV.

At time of admission he was noted to have a mild thrombocytopenia, falling hemoglobin with MAHA evidenced by elevated LDH, mild indirect bilirubinemia, and presence of schistocytes on a peripheral smear, also noted to have a non oliguric renal failure.

During hospital stay he developed a cellulitis, which was treated conservatively with antibiotics. He was treated conservatively for the renal failure.

Snake Envenomation syndrome: Hemotoxic, Neurotoxicity and Acute Kidney injury

TMA Spectrum: Thrombocytopenia, MAHA, schistocytes and End organ damage.

	0	**3**	**6**	**Discharge**	**3 months**
Hb (g%)	15.7	11.9		13.5	Lost to follow up
Platelets (cumm)	1,00,000	89,000		1,10,000	
Creatinine (mg/dL)	1.31	1.64		0.83	
Schistocytes (%)	Nil	0.5		nil	
LDH(IU/dL)	1310	960			
PT/INR	>10				
aPTT(s)	48.9				

Treatment	**Requirement**
Hospital Stay (days)	5
ICU Stay (days)	-
Dialysis (sessions)	-
Plasmapharesis (sessions)	-
Surgical intervention	-
Transfusion	
Packed Red cells	-
Cryoprecipitate	-
Fresh Frozen Plasma	-
Platelets	-
Outcome	Discharged

Patient was discharged in a stable condition, with a completely resolved Acute Kidney injury and normal creatinine.

End organ damage, though transient was likely due to Thrombotic Microangiopathy/ Acute Tubular Necrosis.

Summary of cases with full spectrum TMA disorder in Prospective cohort(8 cases)

The following tables below show summary of 8 patients with full spectrum of thrombotic microangiopathy, laboratory values during the course of hospital stay with treatment and outcomes.

In the clinical profile of the patients who had developed a full spectrum of thrombotic microangiopathy disorder, patients were identified with the presence of fall in hemoglobin, platelets and presence of microangiopathy which was evidenced by high LDH, and mild indirect bilirubinemia and schistocytes.

Table 15 Profiles of Patients who had Thrombotic Microangiopathy (Prospective): Laboratory Values during admission

	Hb (g%)				**Plt (cumm)**				**Creatinine (mg/dL)**					**Sch (%)***				**LDH (IU/dL)**				**INR**	**aPTT (s)**	**Time for Normalisation of INR to 1.4**
	0	3	6	D	0	3	6	D	0	3	6	D	3m	0	3	6	D	0	3	6	D			
1	12.4	7.1	7.3	8.6	0.09	0.08	0.53	4.83	7.46	5.9	9.5	4.99	2.54	1	4	3	0	14749	9541	3462	-	1.35	51	-
2	12.9	11.1	8.6	9.0	2.43	0.46	0.19	1.76	4.02	4.99	5.7	10.5	0.9	1	1	1	0	5225	3014	1320	-	0.97	24.6	-
3	13.4	11.1	9.3	8.6	1.72	0.46	0.19	1.76	2.89	7.40	7.25	7.39	1.56	1	1	4	0	8892	6832	1810	-	2.16	39.7	12h
4	11.6	9.2	6.8	6.7	0.72	0.32	0.75	1.93	2.00	3.51	2.58	0.65	-	5	2	4	4	3780	2006	810	-	2.5	42.9	18h
5	9.2	7.5	7.3	9.1	0.35	0.21	0.66	4.45	3.79	3.59	4.49	7.26	0.74	1	2	1	0	4371	2331	1477	-	1.12	33.7	-
6	6.0	7.9	8.3	6.5	1.01	0.33	0.77	2.61	3.13	3.02	5.39	7.27	9.79	2	1	1	0	2956	4685	4572	-	1.18	45.9	-/
7	12.6	12.0	10.5	10.4	1.29	1.86	3.10	3.81	3.25	10.7	10.9	2.06	1.07	0	1	1	0	1514	1210	980	-	1.22	31.5	-
8	15.7	11.9	-	13.5	1.00	0.89	-	1.10	1.31	1.64	-	0.83	-	0	1	-	-	1310	960	-	-	>10	48.9	24h

* Schistocyte figures have been rounded of to the nearest whole number

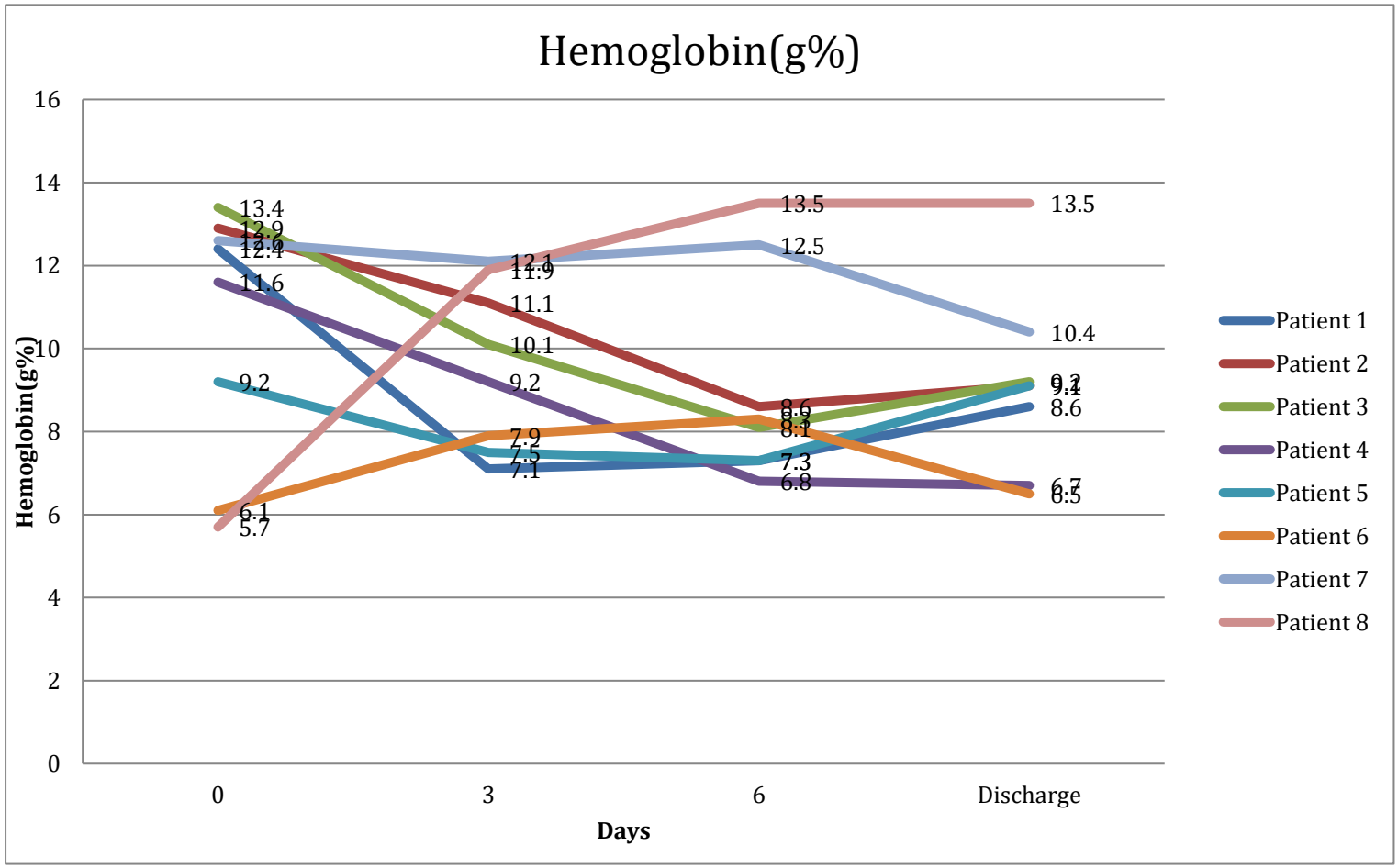
Table 16 Profiles of patients who had Thrombotic Microangiopathy: Treatment and Outcomes

	Hospital Stay (days)	**ICU Stay (days)**	**Dialysis (sessions)**	**Plasmapharesis (sessions)**	**Surgical Intervention**	**Transfusion**				**Outcome**
						PRBC	**Cryo***	**FFP**	**PRC**	
1	26	-	8	-	Fasciotomy	4	-	-	-	Discharged
2	10	-	2	4	Conservative	-	40	-	-	Discharged
3	18	-	14	1	Conservative	2	16	-	-	Discharged
4	11	-	-	4	Conservative	-	-	16	4	Discharged
5	12	8	5	-	Conservative	-	10	-	2	Discharged
6	13	4	7	-	Conservative	3	-	12	-	Discharged
7	13	-	-	-	Conservative	-	-	-	-	Discharged
8	5	-	-	-	Conservative	-	-	-	-	Discharged

*** Cryosupernatant**

Temporal profiles of Laboratory values in patients with TMA:

Figure 9 Temporal profile of Hemoglobin



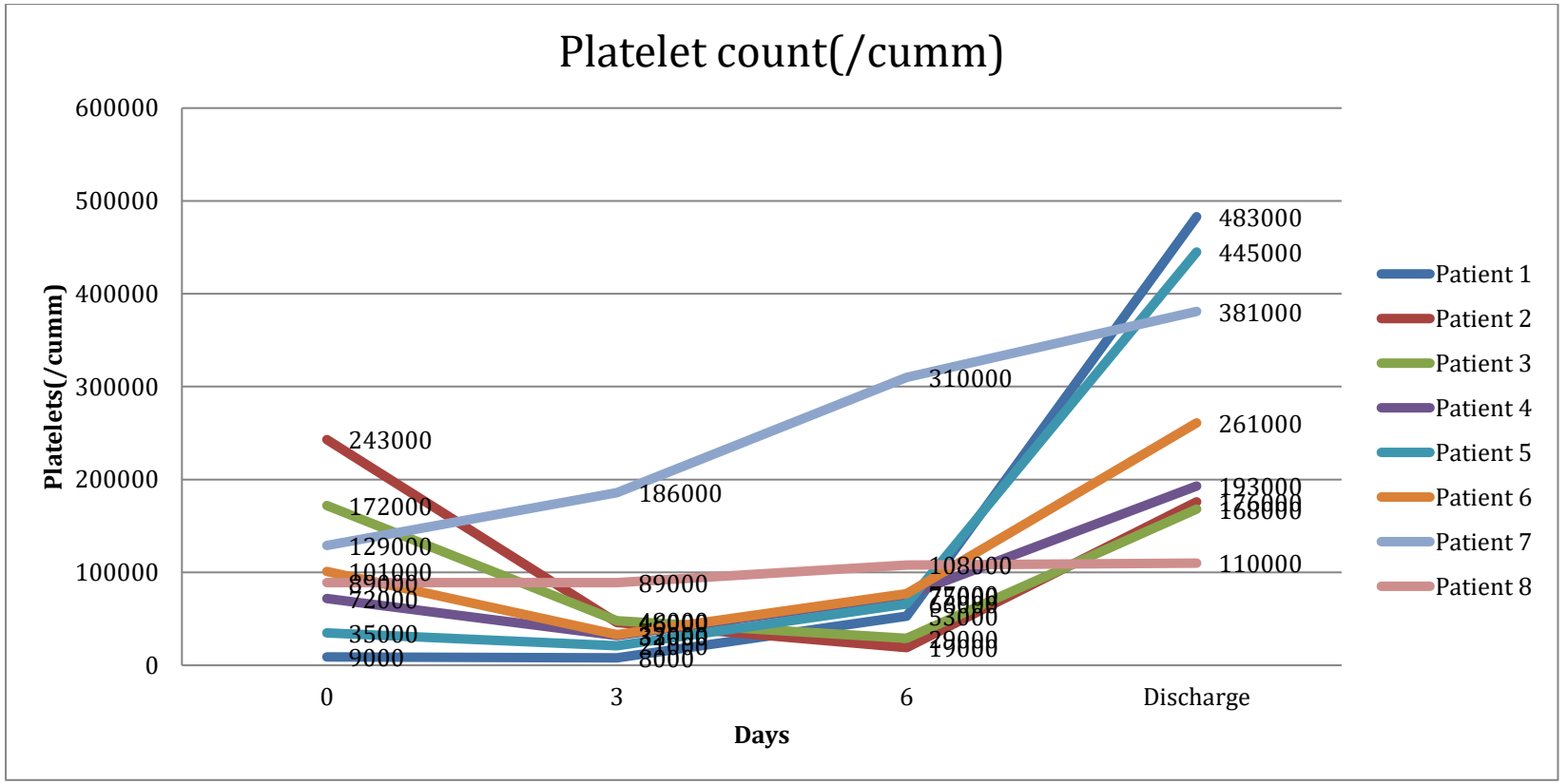


Figure 10 Temporal profile of Platelets

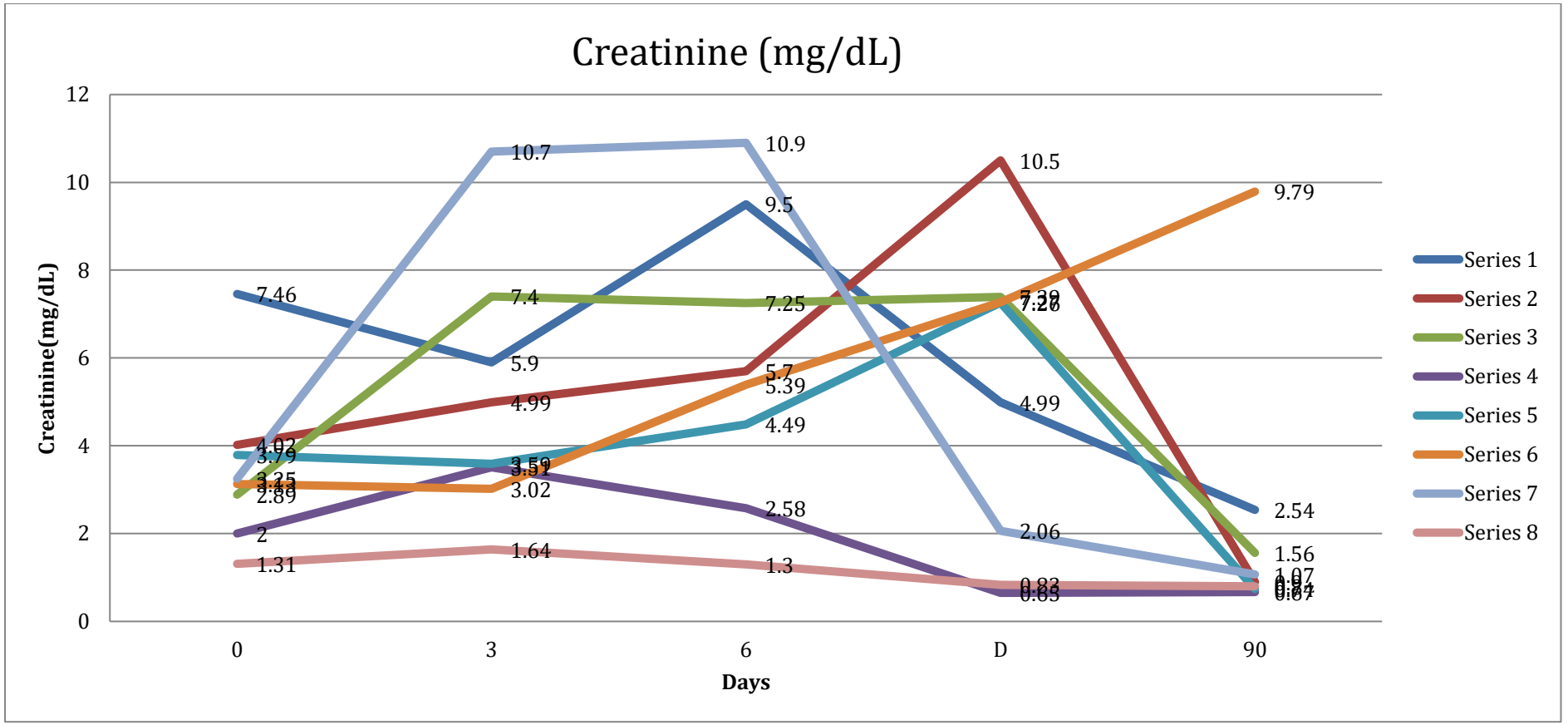


Figure 11 Temporal profile of Creatinine

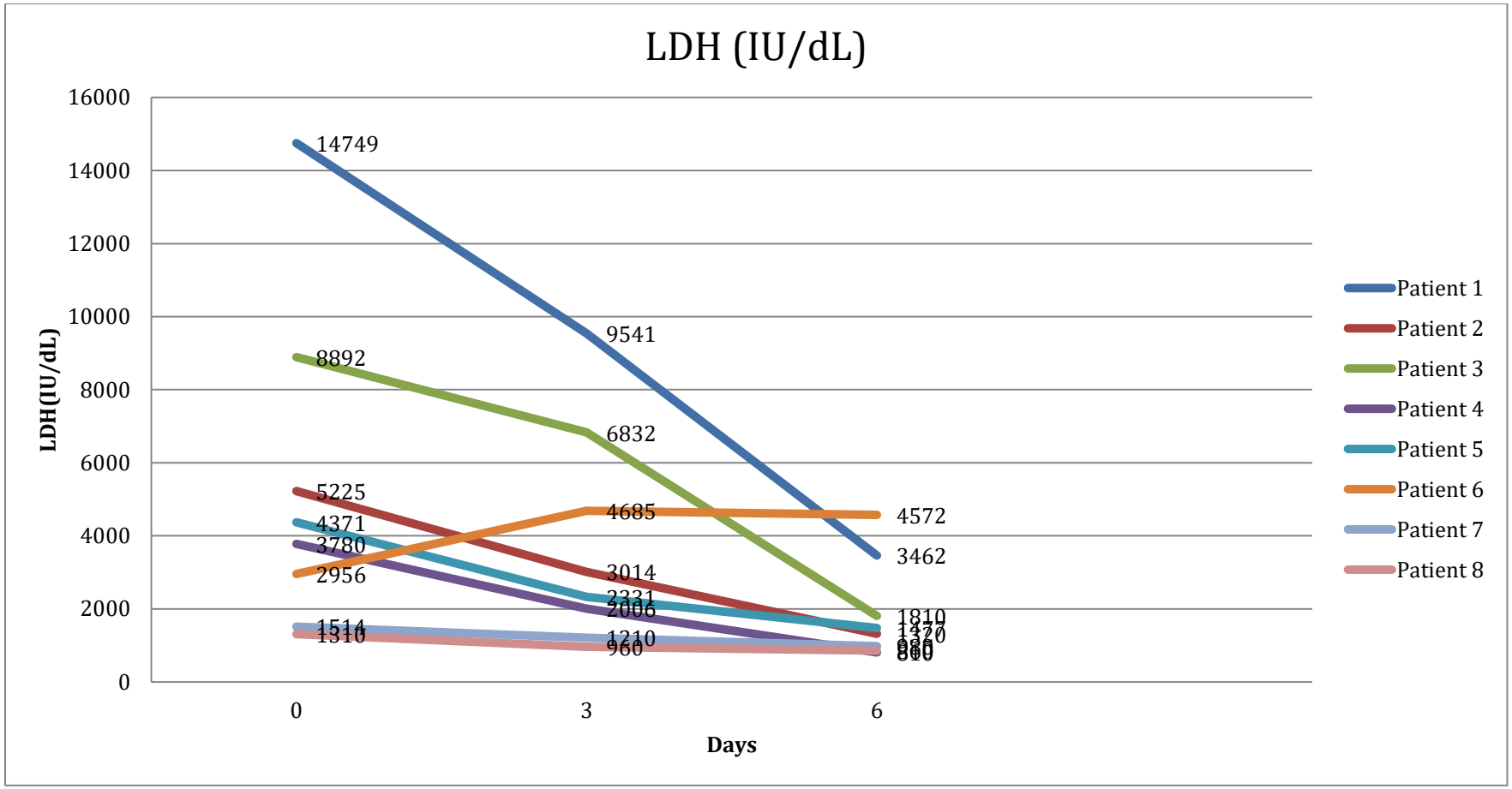


Figure 12 Temporal profile of LDH

Clinical picture of patients with full spectrum TMA disorder in the prospective cohort (8 patients)

The clinical syndrome in 8 patients were:

All the 8 patients had Russell's viper envenomation syndrome. 7 patients developed cellulitis. 7 patients had clinical bleeding, (VICC present in 3 patients): all had minor bleeding from bite site or mucosal bleeding, 4 patients had gross hematuria. There was not major systemic bleeding in any of the cases.

Laboratory Values of patients who had full spectrum TMA in the prospective cohort (Refer to table 13)

Patients were noted to have a fall in hemoglobin and platelets between 6th day, with nadir between day 3-6, after which there was a gradual improvement. Similar findings were noted in the platelet count, where it was noted that the maximal fall in platelet count occured till the 3rd day after which there was a plateau till the 6th day, after which there was steady improvement. Renal functions worsened from the first day of admission till the 3rd day after which there was improvement. Most patients had achieved nadir creatinine by discharge and 75% of patients achieved this by 3 months. 2 patients persisted to have renal dysfunction, hence renal biopsies were done, which showed cortical necrosis in one patient and glomerulonephritis in the other patient.

LDH reached peak on day 0 after which there was a gradual decline. However the LDH was elevated even at discharge. In 7 out of 8 patients schistocytes were present till day 6. The peak schistocyte percentage was between day 3-6. In one patient schistocytes were present even at discharge. 3 patients had an abnormal INR, which normalized by between 12 -24 hours in all patients.

Treatment and outcomes of patients who had full spectrum TMA in the prospective cohort (Refer to table 13)

3(37.5%) received early plasmapharesis. Six patients required transfusion therapy, cryosupernatant (3 patients), FFP (2 patients), PRC (2 patients) and packed cells (3 patients). In all these patients transfusion was for TMA and not for clinical bleeding. 5 patients required dialysis. 1 patient required fasciotomy. All patients had improvement of renal functions and at 3 months they had normalized creatinine levels. In all the patients in the prospective cohort, the final outcomes were good and all patients were discharged from hospital.

The overall clnical picture suggests that VICC resolved within 48 hours. However the TMA picture evolved over 3-6 days with worsening hemoglobin, platelet count, creatinine and persisting schistocytes which gradually improved after 6 days and a proportion of patients having persisting renal dysfunction.

Salient Findings of the study:

1. Spectrum disorder:

The thrombotic microangiopathy is spectrum disorder ranging from isolated thrombocytopenia (52.1%), thrombocytopenia with microangiopathic hemolytic anemia (MAHA) (7.4%), thrombocytopenia with microangiopathic hemolytic anemia and renal failure (40.5%).

There were no cases with neurological involvement suggestive of thrombotic thrombocytopenic pupura (TTP) or TTP/hemolytic uremic syndrome (HUS) overlap.

Patients who had full spectrum disorder TMA with thrombocytopenia, MAHA, renal failure and schistocytes had the most severe form of disorder.

Patients with renal failure without schistocytes were not as severe as the full spectrum disorder.

2. Association with envenomation syndrome:

TMA spectrum is strongly associated only with Russell's viper envenomation syndrome (69.3%). Pure hemotoxicity is associated with milder forms of the disorder (81% had thrombocytopenia). There were no cases of full spectrum disorder with pure hemotoxicity.

Typical Russell's viper envenomation syndrome is associated with full spectrum TMA disorder (full spectrum disorder in Russell's viper envenomation 39.5%).

3. TMA association with VICC:

The majority of patients had VICC (81%). About 19 % of TMA picture did not have VICC. TMA picture with VICC had milder forms of the TMA spectrum.

TMA picture without VICC had more severe forms of the TMA spectrum.

The severity of the thrombocytopenia did not correlate to the presence of VICC suggesting that it was not the VICC process that was inducing the thrombocytopenia.

In the majority of patients TMA and VICC occur together. However TMA can also occur independently of VICC.

However the VICC resolves within 24 hours and TMA process progresses over 3-6 days. Therefore VICC precedes the onset of TMA.

4. Outcome of TMA:

The full spectrum disorder was associated with higher ASV dose, blood products, dialysis and plasmapharesis, requirement of ICU care, longer duration of ICU admission and hospitalization and more mortality.

5. Comparison of prospective and retrospective arms of study:

There was a difference in the clinical profile, treatment and outcome of TMA spectrum in the retrospective and prospective study groups.

The full TMA spectrum disorder frequency was higher in the prospective study suggesting that there was higher index of suspicion for diagnosis

The proportion of patients with full spectrum disorder without VICC was also greater.

The proportion of patients dialysed, required blood transfusion, who underwent plasmapharesis, ICU admission and duration of hospitalization and ICU care was greater in the prospective study.

The clinical outcome of full spectrum disorder had significantly improved in the prospective arm compared to the retrospective arm.

6. Descriptive study of full spectrum disorder in prospective arm

The descriptive study of 8 cases of full spectrum disorder in the prospective study showed that:

Nearly all the cases except one had VICC/bleeding which resolved in <24 hours and was associated with minor bleeding. The syndrome was associated with worsening hemoglobin, platelet count and renal functions and presence of schistocytes, all of which peaked over 3-6 days and then improved by discharge. Five patients required dialysis, blood or blood product transfusion and 3 required plasmapharesis. The most common products used were packed cells and cryosupernatant.

Overall the full TMA spectrum disorder had a good clinical outcome.

DISCUSSION

This study was designed to determine the prevalence of TMA in hemotoxic snakebites and its correlation to envenomation syndromes and venom induced consumption coagulopathy.

1. Prevalence of TMA spectrum and full spectrum disorder

The study determined that the overall prevalence of TMA spectrum was 51.35% in the prospective cohort and full spectrum TMA disorder was 21.6%. The prevalence of TMA spectrum in the retrospective cohort was 35.9% and full spectrum TMA disorder was 7.74%.

2. TMA as a spectrum Disorder

The study confirmed that the disorder of TMA in hemotoxic snake bites is a spectrum disorder which varies from isolated thrombocytopenia, thrombocytopenia with MAHA and thrombocytopenia, MAHA and renal failure (see figure below)

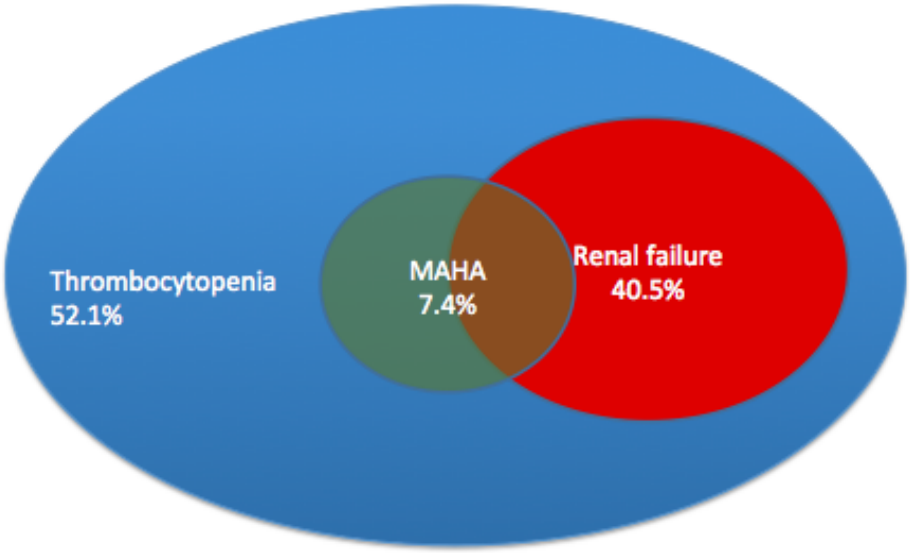


Figure 13 TMA spectrum Disorder

3. Thrombotic microangiopathy relationship with envenomation syndrome

It was noted that a majority of the hemotoxic snakebites had a Russell's viper like envenomation syndrome (69.4%). More importantly all the patients (30 subjects) who had full spectrum TMA had presented with Russell's viper envenomation syndrome. We are unable to identify the exact species of biting snake, as the snake was not brought to hospital, and venom detection assays were not performed. Based on envenomation syndromes, Russell's viper is likely to have been the biting species in all the patients with the full spectrum disorder.

4. Relationship between VICC and TMA

When we looked at Venom induced consumption coagulopathy it was clear that a majority of hemotoxic snakebites presented with VICC (81%). In correlation to TMA, we noted that there was a patient group who did not have VICC, but presented with Thrombocytopenia (19%). Subjects, who had presented with VICC, had a less severe form of TMA and most patients had isolated thrombocytopenia (58.1%) with less number of patients having the full spectrum of TMA. Majority of the patients had a mild thrombocytopenia (56.1%). Where as in the patients without VICC there was a higher incidence of the full spectrum (60.9%) and these patients had more severe thrombocytopenia (30.4% as compared to 23.5%). The group of patients with TMA spectrum without VICC, had more severe manifestations and outcomes.

The results suggest that VICC and TMA are co-existing and overlapping conditions. The majority of patients with TMA have VICC (80%). However TMA can occur independently of VICC in 20% of cases. VICC resolves in 24 hours and TMA evolves over 3-6 days. Therefore it is possible that VICC is the initiating factor for TMA.

5. Severity and outcomes of TMA

The coagulopathy, which is attributed to venom induced consumption coagulopathy (VICC), resolves rapidly and there is a transient fall in the platelet count. In patients who have a TMA, there is a persistent thrombocytopenia, which in our patients started resolving around the 6th day of admission. In patients who had renal failure, the renal injury usually resolves in about 1-6 weeks. Most patients had almost complete resolution of acute kidney injury. In our patients we have not done renal biopsies unless there was a persistent renal failure at 12 weeks. Of the patients who had a TMA, only 2 patients persisted to have renal dysfunction and renal biopsy was performed on them. The first patient had glomerulonephritis, with C3 and IgM deposition and the second showed a cortical necrosis.

In the prospective cohort it was noted that the patients who had developed TMA had a delay in administration of ASV although it was not statistically significant. In most cases, the ASV was administered more than four hours after envenomation. This finding is similar to Isbister et al, in case of Australian tiger snake TMA (reference).

We additionally looked at severity and outcomes of illness in patients with TMA. Here we have shown that patients who had a full spectrum of thrombotic microangiopathy with renal failure had a more severe illness, based on the clinical and laboratory values, compared to the other groups in the spectrum. Patients in this group had lower hemoglobin, platelets counts and had the highest creatinine values, which was inversely proportional to the coagulopathy, where PT/INR and aPTT was lower as compared to the other groups. Treatment outcomes were also noted to be worse in the TMA spectrum with renal failure,

requiring higher doses of ASV with longer hospital/ICU stay, and with 73.3% of these patients requiring dialysis. Hence it is clear that patients who developed a TMA full spectrum disorder have a more severe illness with worse outcomes.

6. Pathogenesis of TMA

Based on the clinical data we suggest a two-step process in occurrence of thrombotic microangiopathy.

Step 1

1. The VICC process of activation of Factor V and X in Russell's viper envenomation may lead to thrombin activation and formation of fibrin clot which may induce intra-vascular thrombosis.
2. In addition to this Russell's viper venom may induced endothelial injury and injury to the basement membrane which may cause platelet aggregation and activation of coagulation cascade through VII activation.

Step 2

The intravascular thrombosis, which occurs in step 1, could lead to microangiopathy with thrombocytopenia, haemolytic anaemia and renal failure.

(See diagram of pathogenesis of TMA and relationship to VICC)

Figure 14 Hypothesis for pathogenesis of TMA and relationship to VICC

Step 1:
a – Activators of Factor X and V, in Russell's viper venom, intiate VICC
b – Endothelial damage by Russell's Viper venom
Both cause platelet aggregation and activation of the coagulation cascade

Step 2:
Intravascular thrombosis which occurs in step 1 causes microangiopathy – thrombocytopenia, MAHA and renal injury

7. Differences and similarities of TMA spectrum in snake envenomation from other TMA disorders

The TMA spectrum of snake envenomation is probably unrelated to the primary TMA disorders where the thrombi consist of platelets and vWF and not red cells and fibrin. The TMA disorder is probably unlike Shiga toxin induced HUS, drug induced TMA, autoimmune disease with inhibitors to ADAMTS13 activity or inherited deficiency of ADMTS 13. In the primary TMA the deficiency of activity of ADMTS 13 is important in the formation of vWF multimers that induce formation of microthrombi. Primary TMAs have prominent neurological manifestations. The TMA spectrum of snake envenomation is probably similar to the secondary TMA with severe infections and DIC, malignancies and abruption placenta, where there is prolongation of PT INR, APTT and there is activation of the coagulation cascade. The paucity of neurological manifestations and prominent coagulopathy suggest that the pathogenesis is through activation of the coagulation cascade.

8. Comparison of the results of the study with other studies of snake bite induced TMA

A study of HUS in snake bite from Christian Medical College in 1986 of 24 patients showed a similar clinical picture to the present study. Seven cases were identified as Russell's viper envenomation. A kidney biopsy was performed in 15 cases which showed acute tubular necrosis in 13 cases and acute cortical necrosis in 2 cases. (43)

A case report from Sri Lanka of Russell's viper envenomation with thrombotic microangiopathy, showed a similar clinical picture to our study. They suggested that the TMA combined with VICC to produce a DIC picture. Plasmapharesis may be beneficial only if the ADAMTS 13 activity is deficient. Therefore the role of plasmapharesis in snake bite envenomation induced TMA is unclear. (44)

A case report of two patients with viper induced TMA were treated with with hemodialysis and plasmapheresis. Renal biopsy showed thrombi within glomeruli and arterioles and cortical necrosis. One patient developed end stage renal disease. (37)

In a study of 103 patients with snake bite induced renal failure, 18.5% developed TMA. All patients required dialysis and patients who developed TMA required higher doses of ASV and longer hospitalisation. There was no difference in outcome of those who were treated with plasmapheresis and those who were not. (38)

The clinical profile in these studies is very similar to that which we observed in this study.

Thrombotic manifestations of Russell's viper bite have been described such as the presence of strokes. However in this study we could not demonstrate any such large vessel thrombotic manifestations. The clinical picture was that of arteriolar Microangiopathy.

9. Treatment of TMA

Treatment modalities that were used in patients with TMA in our study were: plasmapharesis, transfusion of blood products, and dialysis. Compared to the retrospective cohort, more patients were treated with plasmapharesis (15.8% compared to 2.9%), in the prospective cohort patients. Those who were treated with plasmapharesis had good outcomes and all of the patients had resolved acute kidney injury at the end of 3 months, as compared to the retrospective cohort where 3 patients had received plasmapharesis, in which 1 patient died and the other persisted to have elevated creatinine and had non oliguric chronic kidney disease at follow up. Therefore it is still unclear whether plasmapharesis should be used as a standard treatment for TMA. Surprisingly patients who had received cryosupernatant/cryoprecipitate had similar outcomes to those who underwent plasmapharesis. In the prospective cohort, 1 patient received cryosupernatant and had a complete resolution of acute kidney injury and TMA. In the retrospective cohort 2 patients received cryoprecipitate/cryosupernatant, out of which 1 patient died and the other had improvement in acute kidney injury and TMA, but persisted to have a non oliguric chronic kidney disease at follow up. There did not appear to be difference in the outcome between cryosupernatant/cryoprecipitate. Since cryosupernatant transfusion is cheaper, it can be used in the treatment of patients thrombotic microangiopathy, especially in hospitals, which do not have facilities to carry out plasmapharesis.

Further well-designed studies are required to validate these findings and to prove benefit of plasmapharesis and cryosupernatant transfusions in TMA. The mechanism whereby blood products benefit the management of snakebite induced TMA is unclear. It could replace ADAMTS 13 or enable the creation of equilibrium between the pro-coagulant and fibrinolytic system.

LIMITATIONS

1. ADAMTS/ Complements have not been looked at, and a consumption of ADAMTS 13, may be the reason for Thrombotic Microangiopathy in snakebites.
2. Study was not designed to examine the effects of different treatment modalities and compare benefits in these patients.

CONCLUSION

1. The TMA disorder is a spectrum disorder consisting of isolated thrombocytopenia, thrombocytopenia with MAHA, Thrombocytopenia with MAHA and renal failure. The most severe form of the disorder is the full spectrum disorder, with thrombocytopenia and MAHA, schistocytes and renal failure, associated with a mortality of 20%.

2. The TMA spectrum disorder is probably due to Russell's viper envenomation. The full spectrum disorder occurs only in Russell's viper envenomation.

3. The TMA disorder and VICC are usually coexistent and closely related. VICC resolves in the first 24 hours followed by TMA spectrum which evolves over 3rd to 6th day. In one-fifth of patients TMA can occur independent of VICC. VICC may play a role in initiating the TMA spectrum.

4. The TMA spectrum disorder affects predominantly the hematological and renal system sparing the central nervous system.

5. The quality of care for full spectrum disorder has improved with greater recognition of the TMA syndrome, use of product transfusions, plasmapharesis and overall improvements of care, which have led to reduction of mortality.

CLINICAL IMPLICATIONS

1. Clinicians need to have a high index of suspicion of TMA in hemotoxic envenomation.

2. Simple tests including peripheral blood smear for schistocytes, platelet count, hemoglobin, LDH and serum creatinine should be monitored for the first few days after hemotoxic snake bites.

3. Early appropriate antivenom therapy in hemotoxic snake bite may play a role in preventing TMA.

4. Patients with full spectrum disorder should be managed with good supportive care and individualized management including product support, dialysis and plasmapheresis where required. Cryosupernatant therapy may be considered as the product of choice for cost-effective transfusion therapy.

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ANNEXURE 1: IRB Approval

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
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Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
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Dr. Anna Benjamin Pulimood, M.B.B.S., MD., Ph.D.,
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Dr. Biju George, M.B.B.S., MD., DM.,
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Additional Vice-Principal (Research)

August 19, 2017

Dr. Anil Mathew Philip,
PG Registrar,
Department of Medicine,
Christian Medical College,
Vellore – 632 002.

Sub: **Fluid Research Grant NEW PROPOSAL:**
Thrombocytopenia, Microangiopathy and End Organ damage in Snake Bites.
Dr. Anil Mathew Philip, PG Registrar/ General Medicine/ Unit I. Dr. Anand Zachariah, Head of the Unit 1, General Medicine, Dr. Gina Chandy, Assistant Professor, Employment number: 29122, Dr. Joy Mammen, Employment number: 14379, Professor& Head, Dr. Sukesh Chandra Nair, Employment number: 13758, Professor, Department of Transfusion Medicine and Immunohematology, Dr. J.V. Peter, Employment Number: 13328, Professor and Head, Professor and Head, Dr. KPP Abhilash, Employment Number: 28585, Associate Professor, Department of Accident and Emergency. Dr. O C Abraham, Employment Number: 05638, Professor and Head, Dr. Thambu David, Dr. SowmyaSathyeandra, Employment Number: 28181, Dr. Ramya I, Employment Number : 31571, Dr. Ravikar Ralph, Employment Number : 28852, Dr. Alice Mathuran, Employment Number : 28529Mrs. Vishali, Employment Number: 31093, Department of Biostatistics.

Ref: IRB Min. No. 10625 [OBSERVE] dated 03.04.2017

Dear Dr. Anil Mathew Philip,

I enclose the following documents:-

1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Biju George, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. BIJU GEORGE
MBBS., MD., DM.
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board
Cc: Dr. Anand Zachariah, Dept. of Medicine, CMC, Vellore

1 of 4

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788, 2284481 E-mail: research@cmcvellore.ac.in

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

Dr. B.J. Prashantham, M.A., M.A., Dr. Min (Clinical)
Director, Christian Counseling Center,
Chairperson, Ethics Committee.

Dr. Anna Benjamin Pulimood, M.B.B.S., MD., Ph.D.,
Chairperson, Research Committee & Principal

Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

August 19, 2017

Dr. Anil Mathew Philip,
PG Registrar,
Department of Medicine,
Christian Medical College,
Vellore – 632 002.

Sub: **Fluid Research Grant NEW PROPOSAL:**
Thrombocytopenia, Microangiopathy and End Organ damage in Snake Bites.
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Ref: IRB Min. No. 10625 [OBSERVE] dated 03.04.2017

Dear Dr. Anil Mathew Philip,

The Institutional Review Board (**Blue**, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "Thrombocytopenia, Microangiopathy and End Organ damage in Snake Bites" on April 03rd 2017.

The Committee reviewed the following documents;

1. IRB Application format
2. Consent forms (English, Tamil, Telugu)
3. Cvs of Drs. Alice Mathuram, Anand Zachariah, Anil, Ravikar, KPP Abhilash, O C Abraham, Joy, Sukesh, Thambu David, J VPeter, Ramya,Visali,Sowmya.
4. Proforma.
5. No. of documents 1 – 4.

2 of 4

Ethics Committee Blue, Office of Research, 1st Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
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Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on April 03rd 2017 in the CK Job Hall, Christian Medical College, Bagayam, Vellore 632002.

Name	Qualification	Designation	Affiliation
Dr. Biju George	MBBS, MD, DM	Professor, Haematology, Research), Additional Vice Principal , Deputy Chairperson (Research Committee), Member Secretary (Ethics Committee), IRB, CMC, Vellore	Internal, Clinician
Dr. B. J. Prashantham	MA(Counseling Psychology), MA (Theology), Dr. Min (Clinical Counselling)	Chairperson, Ethics Committee, IRB. Director, Christian Counseling Centre, Vellore	External, Social Scientist
Dr. Ratna Prabha	MBBS, MD (Pharma)	Associate Professor, Clinical Pharmacology, CMC, Vellore	Internal, Pharmacologist
Dr. Rekha Pai	BSc, MSc, PhD	Associate Professor, Pathology, CMC, Vellore	Internal, Basic Medical Scientist
Dr. Jayaprakash Muliyil	BSC, MBBS, MD, MPH, Dr PH (Epid), DMHC	Retired Professor, CMC, Vellore	External, Scientist & Epidemiologist
Mr. C. Sampath	BSc, BL	Advocate, Vellore	External, Legal Expert
Ms. Grace Rebekha	M.Sc., (Biostatistics)	Lecturer, Biostatistics, CMC, Vellore	Internal, Statistician
Dr. Sowmya Sathyendra	MBBS, MD (Gen. Medicine)	Professor, Medicine III, CMC, Vellore	Internal, Clinician
Dr. Santhanam Sridhar	MBBS, DCH, DNB	Professor, Neonatology, CMC, Vellore	Internal, Clinician
Dr. Thomas V Paul	MBBS, MD, DNB, PhD	Professor,Endocrinology, CMC, Vellore	Internal, Clinician
Dr Sneha Varkki	MBBS, DCH, DNB	Professor, Paediatrics, CMC, Vellore	Internal, Clinician

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Director, Christian Counseling Center,
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Dr. Anna Benjamin Pulimood, M.B.B.S., MD., Ph.D.,
Chairperson, Research Committee & Principal

Dr. Biju George, M.B.B.S., MD., DM.,
Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

Dr. Sathish Kumar	MBBS, MD, DCH	Professor, Child Health, CMC, Vellore	Internal, Clinician
Dr. Anuradha Rose	MBBS, MD, MHSC (Bioethics)	Associate Professor, Community Health, CMC, Vellore	Internal, Clinician
Dr. Ajith Sivadasan	MD, DM	Professor, Neurological Sciences, CMC, Vellore	Internal, Clinician
Dr. Visalakshi. J	MPH, PhD	Lecturer, Biostatistics, CMC, Vellore	Internal, Statistician
Mrs. Pattabiraman	BSc, DSSA	Social Worker, Vellore	External, Lay Person
Dr. Mathew Joseph	MBBS, MCH	Professor, Neurosurgery, CMC, Vellore	Internal, Clinician
Dr. Shyam Kumar NK	MBBS, DMRD, DNB, FRCR, FRANZCR	Professor, Radiology, CMC, Vellore	Internal, Clinician

We approve the project to be conducted as presented.

Kindly provide the total number of patients enrolled in your study and the total number of withdrawals for the study entitled: "Thrombocytopenia, Microangiopathy and End Organ damage in Snake Bites" on a monthly basis. Please send copies of this to the Research Office (research@cmcvellore.ac.in).

Fluid Grant Allocation:

A sum of 1,00,000/- INR (Rupees One Lakh Only) will be granted for 2 years. 50,000/- INR (Rupees Fifty Thousand only) will be granted for 12 months as an 1st Installment. The rest of the 50,000/- INR (Rupees Fifty thousand only) each will be released at the end of the first year as 2 nd Installment

Yours sincerely,

Dr. Biju George
Secretary (Ethics Committee)
Institutional Review Board

Dr. BIJU GEORGE
MBBS., MD., DM.
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

IRB Min. No. 10625 [OBSERVE] dated 03.04.2017

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ANNEXURE 2: Consent Forms

Thrombocytopenia, Microangiopathy and End Organ damage in Snake Bites

Investigator: **Dr.Anil Mathew Philip**

Please initial each box & sign at bottom

1.	I confirm that I have read and understood the 'Patient Information Sheet' for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
2.	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected	☐
3.	I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by responsible individuals from CMC Hospital. I give permission for these individuals to have access to my records.	☐
4.	I consent to my data being retained if I withdraw from the study	☐
5.	I agree to take part in the above study.	☐

…… …… ……
Name of patient/ Date / Signature

…… …… ……
Researcher Name/ Date / Signature

సమ్మతి ఫారం

1. **Thrombocytopenia, Microangiopathy and End Organ damage in Snake Bites**
2. **Characterisation of Venom Induced Consumption Coagulopathy (VICC) in patients with Haemotoxic Snake Bite and the effects of Blood Products on Coagulation Parameters**
3. **Clinical profile and transfusion requirements in VICC**

పరిశోధకులుగా: Dr. ఫిలిప్, Dr. జెస్ ఎలిజబెత్ రసలాం, Dr. రాచన షెనోయ్

దయచేసి దిగువ ప్రతి పెట్టెను & సైన్ని తనిఖీ చేయండి

1.	పై అధ్యయనాల కోసం 'పేషెంట్ ఇన్ఫర్మేషన్ షీట్'ను నేను చదివాను మరియు అర్థం చేసుకున్నానని నేను నిర్ధారిస్తున్నాను. నేను సమాచారాన్ని పరిశీలి 0 చే అవకాశ 0 ఉ 0 ది, ప్రశ్నలను అడగాలి, ఈ ప్రశ్నలకు స 0 తృప్తికరమైన జవాబు లభి 0 చి 0 ది.	☐
2.	నా పాల్గొనడం స్వచ్ఛందమని నేను అర్థం చేసుకున్నాను మరియు ఎటువంటి కారణం లేకుండా, నా వైద్య సంరక్షణ లేదా చట్టపరమైన హక్కులు లేకుండానే ఏ సమయంలోనైనైనా ఉపసంహరించుకోవడం నాకు ఉచితం. నేను అధ్యయనం కోసం పూర్తి చేసిన ఏ అదనపు పరీక్షల కోసం చెల్లించవలసిన అవసరం లేదని కూడా నేను అర్థం చేసుకున్నాను.	☐
3.	ఈ అధ్యయనంలో సేకరించిన నా వైద్య గమనికలు మరియు సమాచారంలోని సంబంధిత సెక్షన్లు CMC హాస్పిటల్ నుండి బాధ్యులైన వ్యక్తులు చూస్తారని నేను అర్థం చేసుకున్నాను. ఈ వ్యక్తులు నా రికార్డులను ప్రాప్తి చేయడానికి నేను అనుమతినిస్తున్నాను.	☐
4.	నేను అధ్యయనం నుండి ఉపసంహరించుకుంటే నా డేటాను నిలుపుకోవటానికి నేను అంగీకరిస్తున్నాను	☐
5.	పై అధ్యయనంలో పాల్గొనడానికి నేను అంగీకరిస్తున్నాను.	☐

…… …… ……

రోగి పేరు **తేదీ** **సంతకం**

…… …… ……

పరిశోధకుడు తేదీ సంతకం

ஒப்புதல் படிவம்

1.Thrombocytopenia, Microangiopathy and End Organ damage in Snake Bites
2.Characterisation of Venom Induced Consumption Coagulopathy (VICC) in patients with Haemotoxic Snake Bite and the effects of Blood Products on Coagulation Parameters
3.Clinical profile and transfusion requirements in VICC

விசாரணை: மருத்துவர். பிலிப்,
மருத்துவர். ரஸலம்,
மருத்துவர். ஷெனோ

கீழே ஒவ்வொரு பெட்டியை டிக் செய்யவும்

6.	***மேற்கூறிய ஆராய்ச்சிக்கு 'நோயாளி தகவல் தாள்' என்பதை நான் படித்து புரிந்து கொண்டேன் என்பதை உறுதிப்படுத்துகிறேன். இந்த தகவலைக் கருத்தில் கொள்ளவும், கேள்விகளைக் கேட்டு, திருப்திகரமாக பதிலளித்திருந்தேன்.***	☐
7.	***என் பங்களிப்பு முழுவதும் என் சுய முடிவு என்பதை நான் புரிந்துகொள்கிறேன், எப்போது வேண்டுமானாலும் விடுதலையைத் தவிர்த்தேன், என் மருத்துவ கவனிப்பு அல்லது சட்ட உரிமைகள் இல்லாமல் பாதிக்கப்படாமல் விடுகிறேன். ஆய்வின் நோக்கத்திற்காக செய்யப்படும் கூடுதல் பரிசோதனைகளுக்கு நான் பணம் செலுத்த வேண்டியதில்லை எனவும் எனக்குப் புரிகிறது.***	☐
8.	***ஆய்வின் போது சேகரிக்கப்பட்ட எனது மருத்துவ குறிப்புகள் மற்றும் தரவுகளின் எந்த பகுதியும் சம்பந்தப்பட்ட பிரிவுகளை*** CMC ***வைத்தியசாலையிலிருந்து பொறுப்புள்ள தனிநபர்கள் பார்த்துக் கொள்ளலாம் என்பதை நான் புரிந்து கொள்கிறேன். எனது பதிவுகளை உபயோகிப்பதற்கு இந்த நபர்களுக்கு அனுமதி தருகிறேன்.***	☐
9.	***நான் படிப்பிலிருந்து விலகி இருந்தால் என் தரவு தக்கவைத்துக்கொள்ள ஒப்புக்கொள்கிறேன்***	☐
10.	***மேற்கண்ட ஆய்வுகளில் பங்கேற்க நான் ஒப்புக்கொள்கிறேன்.***	☐

…… ……
……
நோயாளியின் பெயர் தேதி கையொப்பம்

…… ……
……
ஆராய்ச்சியாளர் தேதி கையொப்பம்

ANNEXURE 3: Patient Information Sheet

Thrombocytopenia, Microangiopathy and End Organ damage in Snake Bites

You are being invited to take part in a research study. Before you decide whether to takepart, it is important for you to understand why the research is being done and what it willinvolve. Feel free to discuss the study with others if you wish. Please take time to decidewhether or not you wish to take part.

…….

1. What is the purpose of this study?
The aim of this study is to collect information on patients such as yourself who have had a snake bite to determine what effects snake venom has on the blood vessels and blood.

The study will follow patients with snakebite admitted to CMC Hospital over a period oftime to see how well they do. The type of treatment patients receive will not be altered bytaking part in this study.

The results from this study will enable clinicians to make a more informed decision aboutwhich treatment option will be best for individual patients.

We aim to analyse all the information collected in order to:
a. Understand the effects of snake bite on the blood clotting mechanisms.
b. Try to understand and study different methods to assess the severity of snakebite
c. Understand how different people recover from the snake bite and what the clinical
course is.

2. Why have I been invited?
You have been invited to take part in this study because you have been diagnosed with asnake bite and have admitted to CMC Hospital, Vellore. Your doctor will have identified youas a patient who is eligible for the study, and your treatment remains the same.

3. Do I have to take part?
No. Your participation in this study is entirely voluntary. If you decide to take part you willbe asked to sign a consent form. You are under no pressure to take part and may withdrawfrom the study if you wish at any time, without having to explain why. If you decide not totake part, the quality of medical and nursing care you receive will not be affected. With yourpermission we will keep the information we have already collected about you. You will notbe contacted again about the study.

4. What will happen to me if I take part?
If you agree to take part you will be observed from the time you agree to take part until youleave the hospital. No additional tests will be undertaken as part of the study, but you willbe asked to give permission for your medical records to be examined in detail, in order tocollect information about your health status and any treatments that you have throughoutyour hospital stay.
Your treatment options will not be altered in any way by taking part in this study. Yourdoctor will decide on the best treatment for you. Participation in the study does not restrictyour ability to change from one treatment option to another.
There will be no additional visits as part of the study.

5. What are the possible disadvantages and risks of taking part?
There are no anticipated disadvantages or risks involved in this study as it is an observational study of the routine care for patients with snake bite.

6. What are the benefits of taking part?
There are no direct benefits to yourself from taking part in this study but the informationwe get may help to improve the treatment of other people with snake bite in the future.

7. What if there is a problem?
If you have a concern about any aspect of this study, you can speak with the researcherswho will do their best to answer your questions. If you remain unhappy and wish tocomplain formally, you can do this through the CMC Hospital Complaints Procedure. Detailscan be obtained from your doctor.

8. Will my taking part in the study be kept confidential?
All information that is collected about you during the course of this study will be kept
strictly confidential. Paper records regarding your case and your study number will be heldsecurely. Electronic information will be kept on computers that are

protected by passwords.
The electronic data stored for this study will be kept on a database, but we will not keepany identifiable information.When the study is reported it will not be possible to identify you personally.Confidentiality will be maintained at all times.

9. What will happen to the results of the research study?
The results of the study will be written up and published in scientific journals and presentedat scientific meetings. You will not be identified in any report/publication.

10 . Who is organising and funding the research?
The study is being organised and run by the Departments of Accident and Emergency,
Internal Medicine, Medical Intensive Care Unit and Transfusion Medicine and Immunohaematology at CMC Hospital Vellore.The doctor and the research team conducting the research are not receiving additionalpayments for including you in this study.

11. Who has reviewed the study?
This study was reviewed and approved by the Institutional Review Board and Ethics
Committee of Christian Medical College Hospital Vellore.

Contact details:
In the first instance please contact **Dr. Anil Mathew Philip** at Department of Medicine Unit I (2nd Floor, OPD building, CMC Hospital, Vellore-632002, Mobile Number-9567263773)

Alternatively, you can speak to one of the supervising Consultants –
Dr. Anand Zachariah, Department of Internal Medicine Tel: 04162282089

Thank you for taking time to read this sheet and for considering taking part in this study.

Thrombocytopenia, Microangiopathy and End Organ damage in Snake Bites (Telugu)

మీరు పరిశోధనా అధ్యయనంలో పాల్గొనడానికి ఆహ్వానించబడ్డారు. మీరు తీసుకునే నిర్ణయం తీసుకునే ముందు, పరిశోధన ఎందుకు జరుగుతుందో అర్థం చేసుకోవడం మరియు అది ఏమయిందో అర్థం చేసుకోవడం చాలా ముఖ్యం. మీరు కోరుకుంటే, ఇతరులతో అధ్యయనం గురించి చర్చించండి. మీరు పాల్గొనడానికి కోరుకున్నారో లేదో నిర్ణయించుకోవడానికి సమయం పడుతుంది.

.....

1. ఈ అధ్యయనం యొక్క ఉద్దేశ్యం ఏమిటి?

ఈ అధ్యయనం యొక్క లక్ష్యం ఏమిటంటే పాము విషం రక్త నాళాలు మరియు రక్తం మీద ఏ ప్రభావాలను కలిగి ఉందో తెలుసుకోవడానికి ఒక పాము కాటు కలిగి ఉన్న మీ వంటి రోగులపై సమాచారాన్ని సేకరించడం.

ఈ అధ్యయనంలో సిఎంసి ఆసుపత్రికి చికిత్స చేస్తున్న రోగులను వారు ఎంత బాగా చేస్తారో చూడడానికి కొంతకాలం పాటు తీసుకుంటారు. చికిత్స పొందిన రోగుల రకాన్ని ఈ అధ్యయనంలో భాగమైన మార్పును మార్చలేరు.

ఈ అధ్యయనం యొక్క ఫలితాలు వైద్య నిపుణులు మరింత సమాచారం తీసుకునే నిర్ణయం తీసుకునేలా చేస్తుంది, ఇది ఏమైనా రోగులకు ఉత్తమ చికిత్సగా ఉంటుంది.

మేము సేకరించిన మొత్తం సమాచారం విశ్లేషించడానికి మేము లక్ష్యంగా పెట్టుకున్నాము:

ఒక. రక్తం గడ్డ కట్టే విధానాలపై పాము కాటు యొక్క ప్రభావాలను అర్థం చేసుకోండి.

బి. పాముబైట్ యొక్క తీవ్రతను అంచనా వేసేందుకు వివిధ పద్ధతులను అర్థం చేసుకోవడానికి మరియు అధ్యయనం చేయడానికి ప్రయత్నించండి

సి. పాము కాటు నుండి ఎలాంటి వేర్వేరు వ్యక్తులు తిరిగి రావాలో మరియు క్లినికల్ ను ఎలా అర్థం చేసుకోవచ్చో అర్థం చేసుకోండి కోర్సు ఉంది.

2. నేను ఎందుకు ఆహ్వానించబడ్డాను?

మీరు ఈ అధ్యయనంలో పాల్గొనడానికి ఆహ్వానించబడ్డారు ఎందుకంటే మీరు ఎరుపు కాటుతో బాధపడుతున్నారు మరియు *CMC* హాస్పిటల్, వెల్లూర్లో చేరినందున. మీ డాక్టర్ మిమ్మల్ని గుర్తించి, అధ్యయనం కోసం అర్హులైన రోగిని గుర్తించి, మీ చికిత్స అదే విధంగా ఉంటుంది.

3. నేను పాల్గొనాలా?
ఈ అధ్యయనంలో మీరు పాల్గొనడం పూర్తిగా స్వచ్ఛందంగా ఉంది. మీరు పాల్గొనడానికి నిర్ణయించుకుంటే మీరు ఒక సమ్మతి రూపంలో సంతకం చేయమని కోరారు. మీరు ఎప్పుడైనా కోరుకుంటే, ఎందుకు పాల్గొనడానికి ఒత్తిడి చేయకుండా మరియు అధ్యయనం నుండి ఉపసంహరించుకోవచ్చు. మీరు పాల్గొనడానికి నిర్ణయించకపోతే, మీరు పొందిన వైద్య మరియు నర్సింగ్ సంరక్షణ నాణ్యత ప్రభావితం కాదు. మీ రెస్టిమోషన్ తో మేము మీ గురించి ఇప్పటికే సేకరించిన సమాచారం ఉంచుతాము. మీరు ఈ అధ్యయనం గురించి మళ్లీ సంప్రదించలేరు.

4. నేను పాల్గొంటే, నాకు ఏమవుతుంది?
మీరు పాల్గొనడానికి అంగీకరిస్తే, మీరు ఆసుపత్రిలో చేరడం వరకు పాల్గొనడానికి అంగీకరిస్తున్న సమయంలో మీరు గమనించవచ్చు. అధ్యయనంలో భాగంగా అదనపు పరీక్షలు జరుగుతాయి, కానీ అదనపు ఛార్జీలు తీసుకోవు.
మీ ఆరోగ్య స్థితి గురించి మరియు మీ ఆసుపత్రిలో నివసించే అన్ని చికిత్సల గురించి సమాచారాన్ని సేకరించేందుకు మీ మెడికల్ రికార్డులను వివరంగా పరిశీలించడానికి అనుమతి ఇవ్వాలని మీరు కోరుతారు.
మీ చికిత్స ఎంపికలు ఈ అధ్యయనంలో పాల్గొనడం ద్వారా ఎలాంటి మార్పులు చేయబడవు. మీ డాక్టర్ మీ కోసం ఉత్తమ చికిత్సను నిర్ణయిస్తారు.
ఈ అధ్యయనంలో పాల్గొనడం అనేది ఒక చికిత్సా ఎంపిక నుండి మరొకదానికి మార్చడానికి పరిమితం కాదు.
అధ్యయనంలో భాగంగా అదనపు సందర్శనల ఉండదు.

5. సాధ్యం నష్టాలు మరియు పాల్గొనే ప్రమాదాలు ఏమిటి?
ఈ అధ్యయనంలో ఎటువంటి ఊహించని నష్టాలు లేదా ప్రమాదాలు లేవు ఎందుకంటే ఇది ఒక
పాము కాటు రోగులకు సాధారణ సంరక్షణ యొక్క పరిశీలన అధ్యయనం.

6. పాల్గొనే ప్రయోజనాలు ఏమిటి?
ఈ అధ్యయనంలో పాల్గొనడం నుండి మీకు ఎటువంటి ప్రత్యక్ష ప్రయోజనాలు లేవు కాని భవిష్యత్తులో ఇతర వ్యక్తుల చికిత్సను మెరుగుపర్చడానికి సమాచారం అందుతుంది.

7. సమస్య ఉంటే ఏమి చేయాలి?
మీరు ఈ అధ్యయనం యొక్క ఏ అంశంపై ఒక ఆందోళన కలిగి ఉంటే, మీరు పరిశోధకులతో మాట్లాడగలరు: మీ ప్రశ్నలకు సమాధానాలు ఇవ్వటానికి వారు ఉత్తమంగా ఉంటారు. మీరు సంతోషంగా ఉండి, అధికారికంగా అభ్యర్థన చేయాలనుకుంటే, మీరు CMC హాస్పిటల్

ఫిర్యాదుల విధానంలో దీనిని చేయవచ్చు. వివరాలు మీ డాక్టర్ నుండి పొందవచ్చు.

8. ఈ అధ్యయనంలో పాల్గొనడం రహస్యంగా ఉంచబడుతుందా?
ఈ అధ్యయన వ్యవధిలో మీ గురించి సేకరించిన సమాచారం ఉంచబడుతుంది
ఖచ్చితంగా రహస్యంగా. మీ కేసు మరియు మీ అధ్యయనం సంఖ్యకు సంబంధించి పేపర్ రికార్డులు సురక్షితంగా జరుగుతాయి. ఎలక్ట్రానిక్ సమాచారం పాస్వర్డ్ల ద్వారా రక్షించబడిన కంప్యూటర్లపై ఉంచబడుతుంది.
ఈ అధ్యయనంలో నిల్వ చేయబడిన ఎలక్ట్రానిక్ డేటా ఒక డేటాబేస్లో ఉంచబడుతుంది, కాని మేము గుర్తించదగిన సమాచారాన్ని ఉంచదు. అధ్యయనం నివేదించినప్పుడు మీరు వ్యక్తిగతంగా గుర్తించడానికి సాధ్యపడదు. అన్ని సార్లు ఎప్పుడైనా కాపాడుకోవచ్చు.

9. పరిశోధన అధ్యయనం యొక్క ఫలితాలకు ఏం జరుగుతుంది?
అధ్యయనం యొక్క ఫలితాలు శాస్త్రీయ పత్రికలలో వ్రాయబడి, శాస్త్రీయ సమావేశాలలో ప్రచురించబడతాయి. మీరు ఏ నివేదిక / ప్రచురణలో గుర్తించబడరు.

10. పరిశోధనను ఎవరు నిర్వహిస్తున్నారు మరియు నిధులు సమకూరుస్తున్నారు?
ఈ విభాగం అధ్యయనం మరియు నిర్వహించబడుతోంది మరియు డిపార్ట్మెంట్ ఆఫ్ యాక్సిడెంట్ అండ్ ఎమర్జెన్సీ, ఇంటర్నల్ మెడిసిన్, మెడికల్ ఇంటెన్సివ్ కేర్ యూనిట్ మరియు ట్రాన్స్ప్లాషన్ మెడిసిన్ మరియు
CMC హాస్పిటల్ వెల్లూర్ వద్ద ఇమ్యునోహెమటోలజీ. డాక్టర్ మరియు పరిశోధనా బృందం ఈ అధ్యయనం లో పాల్గొనడానికి అదనపు చెల్లింపులు పొందడం లేదు.

11. ఈ అధ్యయనాన్ని ఎవరు సమీక్షించారు?
ఈ అధ్యయనం ఇన్స్టిట్యూషనల్ రివ్యూ బోర్డ్ అండ్ ఎథిక్స్ ద్వారా సమీక్షించబడింది మరియు ఆమోదించబడింది
క్రిస్టియన్ మెడికల్ కాలేజీ హాస్పిటల్ వెల్లూర్ కమిటీ.

సంప్రదింపు వివరాలు:
మొదట్లో డాక్టర్ అనిల్ మాథ్యూ ఫిలిప్పు మెడికల్ డిపార్ట్మెంట్ ఆఫ్ డిపార్ట్మెంట్ ఆఫ్ I. (2 వ అంతస్తు, OPD భవనం, CMC హాస్పిటల్, వెల్లూరు -632002, మొబైల్ నెంబర్ -9567263773) సంప్రదించండి.

ప్రత్యామ్నాయంగా, మీరు పర్యవేక్షించే కన్సల్టెంట్లలో ఒకదానికి

మాట్లాడగలరు -
డా. ఆనంద్ జఖారియా, అంతర్గత వైద్య విభాగము సెల్: 04162282089

ఈ షీట్ చదవడానికి మరియు ఈ అధ్యయనంలో పాల్గొనడానికి ఆలోచిస్తున్నందుకు సమయం తీసుకున్నందుకు ధన్యవాదాలు.

Thrombocytopenia, Microangiopathy and End Organ damage in Snake Bites (Tamil)

ஆராய்ச்சியில் பங்கு பெறுவதற்கு நீங்கள் அழைக்கப்படுகிறீர்கள். எடுத்துக் கொள்ளலாமா என்பதைத் தீர்மானிக்கும் முன், ஆராய்ச்சியை ஏன் செய்ய வேண்டும், அது என்னவென்பதை புரிந்து கொள்வது முக்கியம். நீங்கள் விரும்பினால் மற்றவர்களுடன் இந்த ஆய்வு பற்றி விவாதிக்கலாம். நீங்கள் பங்கேற்க விரும்புகிறீர்களா இல்லையா என்பதை முடிவு செய்ய நேரம் எடுத்துக்கொள்ளுங்கள்.

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1. இந்த ஆய்வின் நோக்கம் என்ன?

இந்த ஆய்வின் நோக்கம் என்னவென்றால், பாம்பு விஷம் இரத்த நாளங்கள் மற்றும் இரத்தத்தின் மீது என்ன விளைவுகளை ஏற்படுத்துகிறது என்பதை நிர்ணயிக்க பாம்பு கடித்தால் உங்களைப் போன்ற நோயாளிகளுக்கு தகவல் சேகரிக்க வேண்டும்.

இந்த ஆய்வில், சி.எம்.சி வைத்தியசாலையில் உள்ள நோயாளிகளில் சிகிச்சையினால் எவ்வாறு பயனடைகிறார்கள் என்பது பார்க்கப்படும் . நோயாளிகளின் சிகிச்சை மாற்றியமைக்கபடாது.

இந்த ஆய்வின் முடிவுகள் மருத்துவத் தகவல்கள் தெரிந்தால், நோயாளிகளுக்கு சிறந்த சிகிச்சை அளிக்க முடியும் .

ஆய்வு குறிக்கோள்கள்:

அ. இரத்தம் உறையும் வழிமுறைகள் மீது பாம்பின் விஷம் ஏற்படுத்தும் விளைவுகளை புரிந்து கொள்ளுங்கள்.

ஆ. பாம்பின் விஷத்தின் தீவிரத்தை மதிப்பிடுவதற்கு பல்வேறு முறைகளை புரிந்துகொண்டு படிக்கவும்

இ. பாம்பு கடியினால் வெவ்வேறு விதமாக மக்கள் குணமாகும் முறைகள் .

2. நான் ஏன் அழைக்கப்பட்டேன்?

இந்த ஆய்வில் கலந்து கொள்ள நீங்கள் அழைக்கப்பட்டுள்ளீர்கள், ஏனென்றால் நீங்கள் பாம்பு கடித்ததாக கண்டறியப்பட்டு, CMC வைத்தியசாலையில் அனுமதிக்கப்பட்டுள்ளீர்கள், வேலூர். ஆய்வில் தகுதியுடைய ஒரு நோயாளி என்று உங்களை உங்கள் மருத்துவர் அடையாளம் கண்டுகொள்வார், உங்கள் சிகிச்சையில் மாற்றம் எதுவும் இருக்காது .

3. நான் கண்டிப்பாக பங்கேற்க வேண்டுமா?

இல்லை. இந்த ஆய்வில் நீங்கள் கலந்துகொள்வது முற்றிலும் உங்கள் விருப்பம் . நீங்கள் பங்கேற்க முடிவு செய்தால் நீங்கள் ஒரு ஒப்புதல் படிவத்தில் கையொப்பமிட வேண்டும். நீங்கள் கலந்துகொள்ள எந்தவொரு அவசியமும் இல்லை, நீங்கள் எப்போது வேண்டுமானாலும் விரும்பினால்,விளக்கமளிக்காமல் ஆய்விலிருந்து விலகி கொள்ளலாம் நீங்கள் பங்கேற்கவில்லை எனில், உங்களுக்கு மருத்துவ மற்றும் மருத்துவ பராமரிப்பு

தரத்தை பாதிக்காது. உங்கள் விருப்பத்துடன் நாங்கள் உங்களிடம் ஏற்கனவே சேகரித்த தகவலை வைத்திருப்போம். ஆய்விற்கு நீங்கள் மீண்டும் தொடர்பு கொள்ளபட மாட்டீர்கள்.

4. நான் பங்கேற்றால் எனக்கு என்னவாகும்?
நீங்கள் பங்கேற்க ஒப்புக்கொள்கிறீர்கள் என்றால் நீங்கள் மருத்துவமனையில் அனுமதிக்க பட்டிருக்கும் வரை நீங்கள் ஆய்வில் . ஆய்வின் பகுதியாகசெர்கபடுவீர்கள் கூடுதல் சோதனைகள் மேற்கொள்ளப்படும், ஆனால் அதற்கான கூடுதல் கட்டணங்களும் எடுக்கப்படாது.
உங்களுடைய மருத்துவ பதிவுகள் உங்கள் ஆரோக்கிய நிலை பற்றிய தகவல்களையும் உங்கள் மருத்துவமனையில் தங்கியிருக்கும் எந்தவொரு சிகிச்சையும் பற்றிய தகவலை சேகரிப்பதற்காக, உங்கள் மருத்துவ பதிவேடுகளை விரிவாக ஆய்வு செய்ய அனுமதியுங்கள்.
இந்த சிகிச்சையில் பங்கேற்பதன் மூலம் உங்கள் சிகிச்சை விருப்பங்கள் எந்த விதத்திலும் மாற்றப்படாது. உங்களுக்கான சிறந்த சிகிச்சை பற்றி உங்கள் மருத்துவர் தீர்மானிப்பார். ஆய்வில் பங்கேற்பது, சிகிச்சைக்கு எந்த ஒரு மாற்றத்தையும் ஏற்படுத்தாது .
ஆய்வின் பகுதியாக கூடுதல் வருகைகள் தேவை இல்லை.

5. சாத்தியமான தீமைகள் மற்றும் பங்கேற்பின் அபாயங்கள் யாவை?
இந்த ஆய்வில் எந்தவொரு எதிர்பார்க்கப்படாத குறைபாடுகளும் அல்லது அபாயங்களும் ஏதும் இல்லை
பாம்பு கடித்த நோயாளிகளுக்கு வழக்கமான பராமரிப்பு பற்றிய ஆய்வு .

6. பங்கு பெறும் நன்மை என்ன?
இந்த ஆய்வில் பங்கெடுப்பதில் இருந்து நேரடியான நன்மைகள் எதுவும் இல்லை ஆனால் எதிர்காலத்தில் பாம்பு கடி கொண்டு மற்றவர்களின் சிகிச்சையை மேம்படுத்துவதற்கு தகவல் பெறலாம்.

7. ஒரு பிரச்சனை என்றால் என்ன?
இந்த ஆய்வின் எந்தவொரு அம்சத்தையும் பற்றி நீங்கள் கவலையைப் பெற்றிருந்தால், ஆராய்ச்சியாளருடன் நீங்கள் பேசலாம். நீங்கள் மகிழ்ச்சியற்றவராகவும், முறையாகக் கோருவதிலும் விரும்பினால், நீங்கள் CMC வைத்தியசாலையின் புகார் அளிக்கும் நடைமுறை மூலம் செய்யலாம்.
விவரங்கள் உங்கள் மருத்துவரிடம் இருந்து பெற்றுக்கொள்ளலாம்.

8. ஆய்வில் பங்கேற்ப் பு ரகசியமாக வைக்கப்படுமா?
இந்த ஆய்வின் போது நீங்கள் சேகரிக்கப்பட்டுள்ள அனைத்து தகவல்களும் கண்டிப்பாக ரகசியமகா வைக்கப்படும். உங்கள் ஆவணங்கள் மற்றும் உங்கள் ஆய்வு எண்ணைப் பற்றிய காகிதப்பதிவுகள். கடவுச்சொற்கள் மூலம் பாதுகாக்கப்படும் கணினிகளில் மின்னணு தகவளில் வைக்கப்படும்.
இந்த ஆய்விற்காக சேமிக்கப்பட்டிருக்கும் மின்னணு தகவல்கள் ஒரு தரவுத்தளத்தில் வைக்கப்படும், ஆனால் நாங்கள் அடையாளம் காணக்கூடிய தகவலை வைத்திருக்க மாட்டோம். ஆய்வறிக்கை வெளியிடப்பட்டால், அது உங்களை தனிப்பட்ட முறையில் அடையாளப்படுத்த முடியாது

9. ஆராய்ச்சியின் முடிவுகளுக்கு என்ன நடக்கும்?
ஆய்வின் முடிவுகள் விஞ்ஞான பத்திரிகைகளில் வெளியிடப்பட்டு, விஞ்ஞானக் கூட்டங்ளில் முன்வைக்கபடும். எந்த அறிக்கையிலும் வெளியீட்டிலும் நீங்கள் அடையாளம் காணப்படமாட்டீர்கள்.

10. ஆராய்ச்சி ஏற்பாடு செய்வது மற்றும் நிதியளிப்பது யார்?
இந்த ஆய்வானது விபத்து மற்றும் அவசரநிலை திணைக்களங்களால் ஏற்பாடு செய்யப்பட்டு,
உள் மருத்துவம், மருத்துவ தீவிர பராமரிப்பு அலகு மற்றும் மாற்று மருத்துவம் மற்றும்
சி.எம்.சி மருத்துவமனையிலுள்ள இம்முனோஹெமாமாட்டாலஜி வெல்லூர்.
இந்த ஆய்வில் நீங்கள் சேர்த்துக் கொள்ளும் மருத்துவர் மற்றும் ஆராய்ச்சிக் குழுவானது கூடுதலான பரிசோதனைகள் பெறவில்லை.

11. ஆய்வுக்கு மதிப்பளித்தவர் யார்?
இந்த ஆய்வு நிறுவன மதிப்பாய்வு வாரியம் மற்றும் ஒழுக்கவியல் மூலம் மதிப்பாய்வு செய்யப்பட்டது
கிறிஸ்தவ மருத்துவக் கல்லூரி மருத்துவமனை வேலூர்

தொடர்பு விபரங்கள்:
முதல் ஆய்வாளர்
டாக்டர் அனில் மேத்யூ பிலிப்
மருத்துவப் பிரிவு I- ல்
(2 வது மாடி, OPD கட்டிடம், CMC மருத்துவமனை, வேலூர் -632002,
மொபைல் எண்- 9567263773)

மாற்றாக, கண்காணிப்பு ஆலோசகர்களில் ஒருவரோடு நீங்கள் பேசலாம் -
டாக்டர் ஆனந்த் ஜகாரியா, உள் மருத்துவத் துறை தொலைபேசி: 04162282089

இந்தத் தாள்களைப் படிக்கவும், இந்த ஆய்வில் பங்கேற்கவும் நேரம் எடுத்துக்கொண்டத்தற்கு நன்றி.

ANNEXURE 4: Case Report Form

Snake Envenomation Proforma

Name: Date: ☐☐☐☐☐☐

(dd/mm/yy)

H.No: Age (years): Serial No:

Sex: Male (0) ☐
Female (1) ☐

Occupation:
Locality:

Time of presentation to CMCH: (24-hour scale) ☐☐☐☐

Time of snakebite: (24-hour scale) ☐☐☐☐

Site of bite: Upper limb (0) ☐
Lower limb (1) ☐
Face (2) ☐
Other (3) ☐

Time to onset of symptoms: (24-hour scale) ☐☐☐☐

First aid: Yes (0) ☐
No (1) ☐

Time to first dose of ASV administration:(24-hour scale) ☐☐☐☐

Within 1 hour ☐
1- 6 hours ☐
6-12 hours ☐
12-24 hours ☐
After 24 hours ☐

Number of ASV vials given outside: Less than ☐
10 (0) ☐
☐

10

(1)

More than

10 (2)

Type of product transfused: (if any) FFP ☐

(0) ☐

☐

Cryo (1) ☐

PRC (2)

Platelets (3)

Number of products transfused outside:

Time to first bleeding manifestation:(24-hour scale) ☐☐☐☐

Envenomation Syndrome:

LOCAL:

Fang marks ☐
Bruising ☐
epistaxis/gum bleed ☐
Local necrosis ☐
hematuria/hematemesis/melena
Cellulitis
hematochezia/hemoptysis/intracerebral/
intrabdominal

HEMOTOXIC:

Bleeding from bite site ☐
Minor bleed- ☐

Major bleed-

☐

NEUROTOXICITY:

Altered sensorium ☐
Ptosis ☐
Diplopia/ blurring of vision ☐
Limb paralysis ☐
Respiratory failure ☐

NON-SPECIFIC:

Nausea/Vomiting ☐
Pain abdomen ☐
Loose stools ☐
Headache ☐
Diaphoresis ☐
Sudden collapse/ Shock ☐
Seizure ☐
Cardiac arrest ☐

Whole blood clotting time: <20min (0) ☐
>20min (1) ☐

Number of ASV vials given at CMCH: Less than ☐
10 (0) ☐
10(1) ☐
More than
10 (2)

Laboratory parameters:

Test \ Time	At presentation
Hemoglobin (g/dL)	
Total count <4,000 or >11,000 4,000-11,000	
Platelets >1,50,000 <1,50,000	
PT/INR >1.4 <1.4	
aPTT	
Fibrinogen >100 <100	
Urea/Creatinine AKI No AKI	
Electrolytes	
CPK Normal Elevated	

Daily Lab parameters:

Test / Post-bite day	Peripheral Smear for schiztocytes	Hb	Platelets	Creatinine	LDH	TB/DB	Retics
Day 1							
Day 2							
Day 3							
Day 4							
Day 5							
Day 6							
Day 7							
Day 8							
Day 9							
Day 10							
Day 11							
Day 12							

Daily clinical assessment:

System

Post-bite day

	Local reaction	CNS	Renal	Coagulation
Day 1				
Day 2				
Day 3				
Day 4				
Day 5				
Day 6				
Day 7				
Day 8				
Day 9				
Day 10				
Day 11				
Day 12				

CNS:
Sensorium- Alert/ Drowsy/ Stuporous/ Comatose
Cranial nerve palsy- Ptosis/ Diplopia/ Facial deviation/ Absent gag
Limb palsy- Power in all limbs
Respiratory effort - single breath count

Renal:

Urine output- >0.5mL/kg/hour or <0.5mL/kg/hour
Puffiness of face/ Pedal edema/ Anasarca

Coagulation:
Bleeding manifestations

Local reaction:
Cellulitis/local necrosis/ bruising

<u>Outcome:</u>

- TMA Spectrum
  - Thrombocytopenia only ☐
  - Thrombocytopenia + MAHA ☐
  - Thrombocytopenia + MAHA + schiztocytes ☐
  - Thrombocytopenia + MAHA + Schiztocytes + End organ damage ☐

- Snake Envenomation Syndrome
  - No envenomation ☐
  - Local envenomation ☐
  - Pure Hemotoxicity ☐
  - Hemotoxicity with AKI ☐
  - Hemotoxicity with Neurotoxicity ☐

- Need for product transfusion — Yes (0) ☐ / No (1) ☐

- VICC — Yes(0) ☐ / No(1) ☐

- Amount of product required
  - Cryoprecipitate — <6 units ☐ / 6-12 units ☐ / >12 units ☐
  - FFP — </=4 units ☐ / >4 units ☐
  - Packed red cells — </=2 unit ☐ / >2 units ☐
  - Platelet Rich Concentrate — </=4unit ☐ / >4 units ☐

- Requirement of dialysis

Yes ☐
No ☐

- Requirement of Plasmapheresis
  Yes ☐
  No ☐

- Duration of Hospital Stay

  <5 days ☐
  >5 days ☐

- Duration of ICU Stay

  Yes ☐
  No ☐

- Final outcome

  Discharge (0) ☐
  Death (1) ☐
  DAMA(2)

ANNEXURE 5: Thesis Data

Sno	datead	hospno	age	sex	occupation	Bitetime	Presentation	site	firstaid	firstasv	ASVnumO	Prodstransout	Localsym	Hemotoxic	Neurotox	WBCT	ASV	Hbb	INRb	TCb	APTTb
1	25-Jul-2018	"026325	61	0	1	00:30:00	13:00:00	1	1	08:00:00	0	1	2	1		1	10	14.4	1.69	14,800	31.0
2	16-Jul-2018	"189400	18	0	3	08:00:00	16:00:00	1	0	01:00:00	2	1	0	0	1	1	12	16.7	3.35	18,300	36.9
3	27-Jun-2017	"566813	48	0	1	06:00:00	10:00:00	1	1	04:00:00	0	1	0	2		1	20	17.8	3.65	19,300	39.4
5	21-Aug-2017	"933944	38	0	2	12:00:00	00:00:00	1	1	12:00:00	0	1	0	1		1	10	15.0	4.36	14,000	43.6
6	28-Aug-2017	"934715	25	0	2	12:30:00	03:00:00	1	0	01:00:00	4	1	2	0	1	1	10	13.8	1.96	19,800	44.9
7	02-Apr-2018	"180008	48	0	1	05:30:00	01:30:00	1	0	01:00:00	20	1	0	0	2	0	0	13.9	2.52	15,300	34.5
8	13-Jul-2017	"930146	47	0	1	06:00:00	15:00:00	1	0	02:00:00	6	0	2	1		1	10	14.5	10.00	21,800	180.0
9	24-Oct-2017	"576567	50	1	4	12:00:00	21:00:00	1	0	02:00:00	10	1	2	2		1	10	12.7	2.81	17,300	34.8
1	19-Jun-2014	"910326	48	0	1	04:45:00	16:30:00	1	0	00:30:00	6	1	2	0	1	1	20	15.8	2.69	24,100	92.0
2	05-Jun-2012	"218619	54	1	2	04:00:00	12:00:00	1	0	00:30:00	6	1	2	0	1	1	4	15.0	1.78	21,800	25.4
3	12-May-2012	"200454	52	1	2	19:30:00	07:30:00	1	0	00:30:00	10	1	2	2	1	1	18	11.1	2.11	20,400	36.1
4	02-Mar-2012	"139412	46	0	1	20:00:00	20:30:00	1	0	00:30:00	0	1	2	0		1	9	15.3	10.00	8,800	180.0
5	01-Apr-2012	"170009	72	0	1	09:00:00	09:30:00	1	0	00:30:00	4	1	2	2	1	1	14	13.0	8.03	26,800	180.0
6	21-Sep-2012	"304412	23	0	2	17:30:00	20:30:00	1	1	03:00:00	6	1	2	0	1	1	21	15.1	10.00	18,100	160.0
9	03-Jul-2016	"514132	47	1	4	04:00:00	16:00:00	1	0	00:45:00	6	1	2	2	1	1	18	13.0	6.37	24,000	47.8
11	22-Oct-2016	"531107	38	0	1	10:00:00	18:00:00	1	0	01:00:00	10	1	2	0	1	1	10	15.6	1.27	11,300	24.5
13	11-Oct-2016	"530298	41	1	4	10:00:00	18:00:00	1	0	00:30:00	50	1	2	2	1	1	20	8.4	2.39	22,800	99.7
14	19-Sep-2016	"526385	59	0	1	11:00:00	16:00:00	0	0	01:00:00	4	1	2	0		1	20	13.4	10.00	15,700	180.0
15	20-Aug-2016	"521590	55	0	1	07:30:00	18:30:00	0	0	02:00:00	6	1	2	0		1	6	17.1	10.00	10,900	180.0
16	15-Aug-2016	"521031	60	0	1	13:00:00	09:00:00	0	0	01:00:00	10	1	2	0	0	1	10	13.4	10.00	14,100	180.0
17	29-Jun-2016	"518430	63	0	1	03:15:00	15:30:00	1	0	01:00:00	4	1	0	2	0	1	10	15.0	1.06	11,200	35.8
18	30-Sep-2018	"527316	66	0	1	04:30:00	16:00:00	1	0	00:30:00	4	1	2	0	1	1	10	15.0	1.63	17,500	29.3
19	10-Jun-2016	"511947	40	1	4	18:30:00	08:00:00	0	0	01:00:00	14	1	2	2	1	1	10	10.0	1.92	14,600	108.5
20	20-May-2016	"508345	59	1	2	16:00:00	20:00:00	1	0	00:30:00	4	1	2	0	1	1	14	15.6	3.78	18,800	23.5
21	25-Feb-2014	"756616	49	0	2	04:00:00	17:00:00	1	0	04:00:00	0	1	2	0	1	1	10	8.8	10.00	12,100	180.0
23	29-Sep-2012	"295943	51	0	1	18:30:00	23:30:00	1	1	08:00:00	0	1	2	0	1	1	12	13.0	10.00	18,600	180.0
25	06-Jan-2016	"995152	19	0	3	19:30:00	23:00:00	1	0	03:00:00	8	1	2	0	1	1	10	14.9	2.10	17,500	35.0
27	03-Mar-2016	"108055	68	1	2	19:00:00	23:00:00	1	0	00:30:00	8	1	2	0	1	1	10	12.0	1.39	25,500	68.0
28	22-Jun-2012	"227618	35	1	4	20:30:00	21:30:00	0	1	02:00:00	0	1	2	2		1	10	10.0	10.00	8,200	180.0
29	15-Feb-2012	"133312	34	1	4	12:00:00	19:00:00	1	0	00:30:00	5	1	2	0		1	12	10.5	2.44	26,800	61.0
30	22-Jan-2014	"753456	53	0	1	09:00:00	18:00:00	1	0	00:30:00	4	0	2	0	1	1	20	14.1	2.70	19,320	33.2
31	15-Nov-2013	"713926	19	0	3	19:00:00	23:00:00	1	0	01:30:00	2	1	2	0		1	10	15.7	2.68	26,000	35.5
32	25-Nov-2015	"988201	40	0	2	11:00:00	12:30:00	1	1	01:30:00	0	1	2	2	0	1	20	15.0	2.54	13,200	68.0
33	12-Jun-2014	"909400	35	0	2	07:30:00	20:00:00	1	0	00:15:00	2	1	2	0	1	1	10	13.0	10.00	23,500	180.0
34	26-Feb-2014	"756616	54	0	1	04:00:00	16:00:00	1	0	01:30:00	2	0	0	1	2	1	13	8.8	10.00	12,100	180.0
38	24-Dec-2013	"406667	71	0	2	11:00:00	21:00:00	1	0	02:00:00	0	1	0	0	1	1	18	15.6	2.36	11,700	27.6
39	15-Oct-2013	"696213	60	0	1	18:30:00	03:00:00	1	0	05:00:00	0	1	2	0	1	1	20	12.0	10.00	9,600	160.0
41	25-Sep-2012	"304640	31	0	1	05:00:00	22:00:00	2	0	08:00:00	8	1	2	0		1	10	13.8	1.62	17,800	26.2
42	18-Nov-2014	"931102	23	1	3	09:00:00	21:30:00	1	0	05:00:00	8	1	2	2	1	1	10	11.2	1.40	41,900	51.2
43	01-Aug-2012	"261148	66	1	2	21:00:00	01:00:00	1	0	04:30:00	0	1	2	1		1	8	6.5	10.00	11,300	180.0
45	16-Oct-2014	"355127	58	0	2	09:30:00	15:00:00	1	0	03:00:00	16	1	0	1		1	8	13.0	1.66	2,000	35.5
46	04-Jan-2013	"379990	60	0	1	08:00:00	15:00:00	1	0	15:00:00	0	1	2	0		1	10	13.0	4.98	11,700	24.0
47	31-Jul-2012	"252963	31	1	4	02:15:00	17:00:00	1	0	17:00:00	0	1	2	2		1	12	6.3	2.03	16,100	33.3
48	16-Feb-2014	"914052	25	1	3	15:00:00	20:00:00	0	0	05:00:00	12	1	2	0		0	0	10.1	1.74	24,900	37.0
51	14-Jul-2014	"912898	29	1	4	16:00:00	01:00:00	0	0	02:00:00	10	1	2	0		1	7	11.9	1.96	3,700	25.4
55	24-Sep-2012	"309481	30	0	2	05:30:00	09:00:00	1	0	04:00:00	0	1	0	0		1	6	17.3	2.59	16,900	36.0
55	19-Oct-2014	"926501	49	0	1	14:00:00	10:00:00	1	0	20:00:00	0	1	2	0	1	1	12	15.9	10.00	29,000	31.0
57	02-Oct-2012	"309765	64	0	1	05:00:00	07:00:00	1	0	03:00:00	0	1	1	0	1	1	10	15.6	10.00	14,100	180.0
58	21-May-2015	"958027	33	0	1	13:00:00	02:00:00	1	0	20:00:00	0	1	2	0	1	1	10	16.3	3.15	21,000	30.1
59	15-Apr-2016	"687126	53	0	2	02:00:00	07:00:00	1	0	02:00:00	6	1	2	0	1	1	10	15.8	1.71	5,900	66.3
60	11-Jun-2014	"909854	39	0	2	10:00:00	02:00:00	1	0	04:00:00	8	1	2	2	1	1	10	11.9	1.81	41,150	111.0
61	13-Oct-2013	"696050	23	0	3	14:00:00	17:00:00	1	0	02:00:00	0	1	1	2	2	1	10	14.8	2.14	14,300	33.4
80	12-May-2015	"965724	63	0	1	11:00:00	16:00:00	0	0	01:00:00	0	1	0	1		1	10	13.8	10.00	11,300	64.8
81	24-May-2014	"907618	54	0	1	15:00:00	20:00:00	1	0	01:00:00	2	1	0	0		1	8	16.0	1.23	4,200	25.4
83	16-Feb-2012	"137776	30	0	1	19:00:00	23:00:00	1	0	02:00:00	6	1	2	1		1	9	14.4	1.78	26,500	27.2
84	22-Aug-2015	"973188	59	0	1	18:30:00	23:00:00	1	0	01:00:00	10	1	0	0		1	0	11.5	10.00	6,600	38.1
86	06-Aug-2013	"630773	57	0	1	08:30:00	12:00:00	1	0	04:00:00	0	1	2	0	1	1	12	16.1	6.08	13,800	28.0
87	05-Oct-2015	"978288	53	0	1	18:30:00	23:00:00	1	0	01:00:00	10	1	0	0		1	10	14.4	10.00	14,700	125.0
95	12-Aug-2014	"915771	52	0	1	07:30:00	18:00:00	1	0	01:30:00	4	1	1	1		1	9	14.4	10.00	18,200	110.0
96	12-Apr-2012	"180010	28	0	2	14:00:00	02:00:00	1	0	04:00:00	0	1	0	2	1	1	12	15.7	1.43	29,300	25.7
97	17-Mar-2016	"500264	42	0	1	04:00:00	10:20:00	1	0	02:00:00	6	1	2	0		1	15	14.5	3.15	15,200	32.0
99	26-Sep-2013	"675287	51	0	2	08:30:00	12:00:00	1	0	03:30:00	0	1	2	0		1	10	12.2	10.00	11,100	180.0
100	23-Aug-2015	"973303	45	0	1	20:30:00	23:10:00	1	0	00:30:00	10	1	0	1	1	1	4	16.8	2.84	14,500	25.0
101	27-Sep-2015	"977432	62	0	2	04:00:00	20:45:00	1	1	16:00:00	0	1	2	1		1	10	13.0	4.24	19,500	180.0
102	17-Jul-2015	"967533	58	1	4	08:00:00	20:10:00	1	0	04:00:00	6	1	2	0		1	15	12.0	10.00	12,500	180.0
10	29-Jun-2017	"567147	35	0	1	18:00:00	08:00:00	1	0	03:00:00	10	1	2	2	1	1	10	13.6	1.25	13,800	36.7
11	11-Jul-2017	"930013	51	0	1	21:20:00	19:00:00	1	0	02:00:00	5	1	2	2	1	1	20	11.0	2.63	24,100	94.8
10	17-Sep-2015	"975406	20	0	2	10:00:00	17:00:00	1	0	01:00:00	5	1	2	0	1	1	12	13.3	10.00	14,700	180.0
53	27-Sep-2015	"977579	48	0	1	04:00:00	08:00:00	1	0	04:00:00	0	1	2	2		1	10	14.6	10.00	14,000	180.0
54	24-Jul-2015	"967756	49	0	2	05:00:00	03:00:00	1	0	02:00:00	6	1	2	2	1	1	20	14.4	10.00	3,400	180.0
90	18-Sep-2013	"671443	45	1	2	15:00:00	01:00:00	1	0	01:00:00	0	1	2	0	2	1	16	12.0	3.05	35,100	25.9
4	12-Oct-2017	"939581	48	0	2	16:00:00	18:00:00	0	0	02:00:00	0	1	2	0		1	10	13.7	1.63	6,900	27.6
35	28-Jun-2014	"910944	67	0	1	06:00:00	19:00:00	1	0	02:00:00	8	1	2	0	1	1	18	13.1	4.71	3,300	38.3
49	18-Sep-2012	"299455	48	1	4	10:00:00	13:30:00	1	0	01:00:00	8	1	0	2	1	1	14	16.0	2.71	27,200	180.0
68	26-Jul-2012	"252354	38	0	2	10:45:00	19:45:00	1	0	01:00:00	8	1	2	0	1	1	12	16.5	4.56	28,900	40.1
12	13-Jul-2018	"189068	42	1	4	21:00:00	20:00:00	1	0	01:00:00	20	1	0	0		0	0	6.0	1.18	21,500	45.9
13	03-Jul-2018	"188283	30	1	4	06:00:00	18:00:00	0	0	03:00:00	18	1	2	2		0	0	9.2	1.12	21,000	33.7
14	02-Jul-2018	"188210	42	1	4	11:30:00	05:00:00	0	0	06:30:00	6	1	2	2		1	20	11.6	2.50	12,700	42.9
15	30-May-2018	"185278	41	0	1	05:30:00	13:30:00	1	0	02:00:00	2	1	2	1	2	1	10	15.7	10.00	4,300	48.9
16	12-Jul-2017	"930106	20	0	3	03:00:00	11:00:00	3	0	06:00:00	30	0	0	2	1	0	10	12.6	1.22	15,700	31.5
17	25-Jul-2018	"350167	35	0	1	23:00:00	11:00:00	0	1	13:00:00	0	0	2	2		1	20	13.4	2.16	18,900	39.7
18	18-Aug-2018	"352170	36	1	4	08:00:00	07:00:00	1	0		0	1	2	0		0	0	12.9	0.97	5,300	24.6
19	23-Mar-2018	"599184	18	0	3	13:30:00	12:30:00	1	0	04:30:00	10	1	2	1	1	0	0	12.0	1.35	35,400	51.0
7	07-Apr-2016	"501890	55	0	1	04:30:00	16:00:00	1	0	04:30:00	10	1	2	0	1	1	10	13.9	1.15	13,000	164.0
12	16-Jan-2016	"530620	36	1	4	16:00:00	05:30:00	1	0	06:30:00	10	1	2	0		1	6	14.0	1.27	29,800	32.8
37	05-Aug-2014	"710941	44	1	4	11:00:00	18:00:00	0	0	07:00:00	0	0	0	0	1	1	6	12.6	1.70	20,400	26.0
62	07-Feb-2012	"130885	29	0	2	04:00:00	12:00:00	1	0	06:00:00	4	1	2	1	1	1	22	16.9	10.00	20,500	180.0
63	11-Jul-2014	"514924	52	0	1	07:00:00	16:00:00	1	0	05:00:00	20	1	2	1	1	1	6	12.6	5.50	27,000	180.0
64	23-May-2015	"949208	35	0	1	19:00:00	23:00:00	1	0	04:30:00	12	0	2	2	1	1	18	15.5	1.74	4,000	49.3
65	04-Apr-2013	"429574	70	0	1	20:30:00	21:30:00	1	0	04:30:00	0	1	2	0	1	1	10	6.6	1.29	7,400	25.0
66	10-Jul-2014	"912627	48	0	2	03:00:00	12:00:00	1	0	01:30:00	18	1	2	1	1	1	6	17.0	1.72	30,950	56.9
67	11-Feb-2016	"105317	31	0	1	18:00:00	07:00:00	1	0	05:20:00	47	1	2	2	1	0	0	16.8	1.35	26,800	35.5
69	05-Mar-2014	"759027	45	1	4	18:00:00	22:00:00	1	0	04:00:00	0	1	2	1	1	1	20	12.9	10.00	16,700	180.0
70	16-Sep-2015	"950294	36	0	2	23:30:00	09:00:00	1	0	06:00:00	10	1	2	2	1	1	10	10.8	1.09	35,700	38.0
71	12-Apr-2016	"028405	71	0	1	12:30:00	16:30:00	1	0	02:00:00	0	1		1		1	20	15.5	3.05	5,800	41.0
72	06-Apr-2013	"441221	20	0	3	14:00:00	19:00:00	1	0	03:00:00	5	1	2	2	1	1	10	12.5	2.05	38,800	46.7
73	16-Apr-2014	"902269	50	0	2	18:00:00	10:00:00	1	1	04:00:00	6	1	2	1		1	10	11.2	1.26	19,700	31.3
74	16-Oct-2016	"530620	36	1	4	16:30:00	05:30:00	1	0	04:00:00	10	1	2	0		1	6	14.0	1.27	29,800	32.8
75	07-Apr-2016	"501890	55	0	1	04:30:00	16:00:00	1	0	03:45:00	10	1	2	0	1	1	10	13.9	1.15	57,400	164.0
76	17-Apr-2012	"180040	42	1	2	21:00:00	10:00:00	1	0	04:00:00	3	1	1	1	2	1	18	13.3	2.26	45,700	48.6
77	10-Jan-2012	"110128	62	0	2	21:00:00	11:00:00	1	0	13:00:00	0	1	2	2	1	1	14	14.2	10.00	29,800	180.0
78	10-Mar-2013	"422596	30	1	4	05:00:00	09:00:00	1	0	04:00:00	17	1	2	2	1	1	12	10.7	1.96	24,900	31.4
79	26-Mar-2016	"500932	73	0	1	10:00:00	09:00:00	1	0	04:00:00	19	1	2	0	1	0	0	12.6	1.78	20,700	26.0
82	14-Jul-2013	"611889	70	0	1	19:10:00	12:00:00	0	0	04:45:00	72	0	2	0	2	0	0	10.9	1.52	33,500	26.0
88	10-Dec-2014	"932900	59	0	1	18:20:00	16:00:00	1	0	06:30:00	6	1	1	2	2	1	10	12.9	2.11	53,500	34.8
8	04-Oct-2015	"647473	55	0	1	13:30:00	18:00:00	1	0	01:00:00	6	0	2	0	1	1	10	19.0	3.72	16,600	22.6
22	29-May-2015	"934094	51	0	2	04:30:00	10:30:00	1	0	07:00:00	0	1	2	1	1	1	10	15.2	10.00	20,100	180.0
24	16-Jun-2014	"910171	46	0	2	02:30:00	20:00:00	0	1	07:00:00	15	1	2	0	1	1	10	12.7	1.72	8,830	43.0
26	18-Apr-2014	"917183	23	0	2	19:00:00	08:00:00	1	0	00:45:00	4	0	2	0		1	20	14.4	10.00	13,200	33.4
36	09-Mar-2013	"422518	53	0	2	19:00:00	04:00:00	1	0	09:00:00	0	0	2	0	1	1	13	14.6	1.18	15,300	29.5
40	28-Jun-2014	"910578	29	1	4	04:00:00	23:00:00	1	0	19:00:00	8	0	2	2	0	1	16	9.3	1.59	19,659	46.7
45	04-Apr-2013	"441438	41	1	4	19:30:00	00:00:00	1	0	06:00:00	0	1	2	2	1	1	10	13.4	10.00	23,000	180.0
50	02-Aug-2012	"258893	44	0	1	14:00:00	15:30:00	1	0	01:00:00	0	1		2		1	8	12.9	10.00	19,900	180.0
52	18-Jul-2013	"967043	75	1	1	07:00:00	06:00:00	1	0	03:00:00	20	1	2	0		0	0	11.0	1.69	18,200	31.6
85	10-May-2014	"904721	29	1	4	11:00:00	16:00:00	1	0	02:00:00	10	1	2			1	8	10.7	1.39	17,400	31.1
89	03-Jun-2012	"308741	50	0	2	07:00:00	09:00:00	1	0	02:00:00	2	1	2	1		1	6	13.0	10.00	19,400	180.0
91	08-Apr-2015	"950201	38	0	2	23:00:00	00:00:00	3	0	02:00:00	20	1	2	0	2	1	6	16.5	1.26	16,700	51.3
92	31-May-2015	"958933	44	0	1	08:00:00	07:00:00	1	0	01:00:00	6	1	2	2	2	1	10	16.6	2.17	8,300	33.3
93	03-Sep-2014	"836672	43	0	2	04:30:00	16:00:00	1	0	01:00:00	6	1	0	2		1	14	14.8	10.00	4,300	180.0
94	28-Aug-2013	"639728	29	0	1	15:30:00	18:30:00	1	0	04:30:00	0	1	1	2	2	1	10	15.6	7.45	15,700	180.0
98	15-Apr-2013	"448504	46	0	1	21:30:00	08:00:00	1	0	01:00:00	8	1	0	0		1	10	13.3	1.67	20,100	25.0

PlatB	fibrinogenb	Creatb	Nab	Kb	CPKb	V42	ldhd1	tbd1	dbd1	reticsd1	schizd2	hbd2	pltd2	creatd2	ldhd2	tbd2	dbd2	retd2	schzd3	hbd3	pltd3
115,000	172.00	1.16	136.00	4.40	268	1.05	486	0.90	0.10		0.0	13.70	130,000	0.90	680	0.60	0.20				
139,000	35.00	0.92	141.00	3.50	229	0.78	760	0.70	0.24												
260,000	20.00	1.35	141.00	3.60	768	1.35	755	1.61	0.36		0.0	11.90	130,000	1.17	851	1.80	0.25		0.0	10.50	111,000
158,000	98.00	1.07	138.00	3.90	628	1.02	410	0.74	0.25		0.0	12.60	137,000	1.00	460	0.70	0.22				
154,000	180.00	1.14	139.00	4.40	2,071	1.14	2,057	2.33	0.10		0.0	11.90	133,000	0.78	980	1.00	0.10				
153,000	167.00	1.40	139.00	4.30	2,842	1.40	1,501	1.60	0.20		0.0	13.70	117,000	1.44	1,064	1.40	0.10		0.0	12.80	105,000
109,000	114.00	0.80	138.00	3.20	559	0.80	560	1.50	0.60		0.0	12.20	217,000	0.98	622	1.00	0.52		0.0	11.30	224,000
145,000	90.00	1.31	139.00	3.70	496	1.31	980	0.60	0.20		0.0	9.90	120,000	1.17	978	0.40	0.16		0.0	10.50	80,000
24,000		0.88	136.00	3.40	138	0.88		0.90	0.20												
17,000		0.73	138.00	3.70																	
16,000		0.51	136.00	3.60	3,156	0.54	2,196	1.80	0.40				138,000	0.71							
11,000		1.18	139.00	3.30									128,000								
9,000		0.92																			
8,000		1.17	134.00	3.10	2,737																
37,000	14.60	0.67	138.00	3.10	303	0.67		1.10	0.10		0.5	10.70	189,000	0.67					0.0	10.40	153,000
114,000		0.97	136.00	3.20	363	0.97		1.30	0.30			14.70	209,000								
83,000		0.83	143.00	3.70	21,719	0.83	1,570	2.20	1.10			7.10	67,000	0.65		1.20	0.70		0.0	6.40	67,000
131,000		1.13	135.00	3.70		0.91		1.30	0.30												
125,000		1.22	139.00	3.30		0.96		2.90	0.90												
129,000	0.00	0.95	139.00	3.20	209	0.62		0.90	0.20		0.0	13.60	389,000	0.61							
135,000		0.76	134.00	3.40	297	0.76		1.00	0.40												
930,000		1.12	141.00	3.90																	
127,000		1.34	145.00	3.10	702	0.80		1.10	0.50		0.0	10.20		0.81							
420,000		0.70	134.00	3.50	1,526	0.70		0.90	0.10		0.0	13.50	298,000	0.65					0.0	12.50	238,000
67,000		1.14	133.00	3.00	160	0.82		0.40	0.20		0.0	7.70	187,000	0.94							262,000
48,000		1.14	137.00	3.10		1.17															
28,000		0.57	137.00	2.70	563	1.13		0.90	0.20		0.0	13.40	220,000	0.55							
37,000		1.39	138.00	2.40	324	0.75		0.60	0.10				261,000	0.68							
36,000		0.88	133.00	3.10		0.80						8.70	75,000								128,000
34,000		0.67	132.00	3.50		0.67		0.40	0.20		0.0	8.90	214,000	0.81							
27,000		1.28	136.00	4.70	960	1.28		2.40	0.90		0.0		151,000	1.15						12.10	111,900
52,000		1.32	146.00	4.00	2,108	0.91	712							1.12							
59,000	121.00	0.83	136.00	2.80	142	0.83		0.45	0.10			12.60	312,000	0.56							
64,000		0.87	139.00	3.50	2,118	0.87		3.30	0.30		0.0	13.20	84,000	1.13						13.80	110,000
67,000		1.15	133.00	3.80	160	1.15		0.40	0.20		0.0	9.50	175,000	0.82					0.0	7.70	187,000
77,000		1.03	139.00	3.40	146	1.03		1.70	0.40		0.0	14.40	165,000	0.90							
83,000		0.93	137.00	3.60		0.50		0.80	0.20		0.0		96,000						0.0		116,000
87,000		1.30	133.00	4.30	120	1.30					0.0	12.50	85,000	1.20							
93,000	249.00	0.65	136.00	3.30	2,813	0.65		3.55	0.50		0.0	9.10	55,000	0.59					0.0	9.80	30,000
94,000		0.90	137.00	3.20		0.90					0.0	6.20	80,000								
99,000		1.12	137.00	2.90		1.12		2.60	1.10												
99,000		1.28	136.00	3.90	128	1.28		1.40	0.20		0.0	12.40	148,000	1.10					0.0	11.90	139,000
101,000	44.10	1.20	127.00	4.40		1.20		3.20	1.10												
102,000	267.00	1.18	147.00	3.10	951	1.18		0.38	0.20		0.0		79,000	0.66					0.0	11.60	88,000
109,000		0.84	139.00	3.40	455	0.84	1,200	1.20	0.70		0.0	10.80	83,000	0.90							
114,000		1.16	135.00	4.30																	
119,000		1.33	136.00	3.50		1.33		3.40	1.00					1.03							
120,000		0.99	137.00	3.20	252	0.99		1.20	0.50		0.0	12.20	134,000	0.92							
121,000		1.11	138.00	3.60	270	1.11		3.57	0.30		0.0	12.60	94,000	1.03							
122,000		0.93	134.00	3.30		0.93		1.10	0.20		0.0	13.00	130,000	0.54					0.0	12.10	105,000
123,000	320.00	1.14	147.00	3.70	11,380	1.12	1,230	7.70	0.20		0.0	10.00				6.40	0.20		0.0	10.20	320,000
126,000		0.90	140.00	3.60		0.90					0.0	14.10	120,000	0.94		2.80	1.00		0.0	11.80	114,000
14,200		1.19	142.00	3.70																	
143,000		0.83	137.00	3.30	2,189	0.75															
143,000		1.20	132.00	3.80																	
144,000		0.95	136.00	3.40		0.89	667							0.52							
144,000		1.32	139.00	3.90																	
145,000	77.90	0.82	136.00	3.70		0.67	342	2.70	0.40		0.0	11.20	100,000	0.57							
133,000		0.67	132.00	3.20																	
130,000		1.69	140.00	3.10																	
130,000		1.23	142.00	3.30		0.89	834	2.90	1.00		0.0	13.50	108,000	0.81	294	1.50	0.60				
128,000		1.14	133.00	4.20		0.94	768	1.48	1.10												
128,000		0.80	132.00	3.20	10,134	0.66	1,234	0.80	0.10		0.0	14.10	100,000						0.0	14.60	367,000
128,000		1.02	142.00	3.40	617	0.80	682														
127,000	49.40	0.97	138.00	3.80		0.97		3.40	0.50		0.0	10.30	148,000			0.70	0.20				
41,000	150.00	1.00	137.00	4.10	540	1.00	1,241	3.38	0.50		0.0	11.50	236,000	0.98	780	1.12	0.50				
110,000	245.00	3.23	144.00	5.10	12,133	3.78	4,600	4.69	0.12		0.0	10.30	93,000	5.25	4,117	3.20	0.24		0.0	10.00	69,000
28,000	0.00	0.70	140.00	3.60	303	0.71					0.0			0.69						12.30	200,000
114,000		1.13	135.00	3.80	208	1.13	693	2.50	0.40		0.0	13.20	161,000	0.90							
114,000		0.84	135.00	3.60	321	0.84		4.80	0.50		0.0	14.00	72,000	0.76	756				0.0	12.50	94,000
139,000	109.00	0.88	139.00	4.40	1,320	0.88		0.30	0.10					1.05						10.00	
199,000	140.00	0.82	138.00	4.00	1,683	1.54	746	0.70	0.24		0.5	12.60	118,000	1.14	733	0.59	0.20		0.8	13.00	120,000
73,000	33.10	0.89	139.00	3.70	805	1.05		4.00	1.00		0.4	10.00	64,000	0.60		1.20	0.60		0.8	10.70	48,000
102,000		1.02	137.00	3.00	301	1.02		1.90	0.20		0.1	15.80									
39,000	160.00	1.20	136.00	3.70	4,930	1.19	2,343	1.40	0.30		1.0	12.90	213,000	1.21							
101,000	251.00	3.13	133.00	5.20	206	3.13	2,956	0.67	0.40	2.94	1.0	7.60	55,000	1.67	3,881	0.92	0.25		0.5	7.90	33,000
35,000	190.00	3.79	137.00	4.50	7,295	3.79	4,271	2.92	1.71	1.18	0.8	7.90	18,000	4.84	3,313	2.76	0.90		2.0	7.50	21,000
74,000	108.00	2.00	138.00	3.70	138	2.00	3,780	4.96	0.25	1.29	2.0	10.60	36,000	2.39	2,603	5.94	0.34		2.0	9.20	32,000
100,000	0.00	1.31	141.00	3.50	1,415	1.31	1,310	6.99	1.14		0.3	11.90	89,000	1.64	1,007	4.58	0.60		0.5	13.00	100,000
129,000	152.00	3.25	138.00	4.20	2,459	7.83	1,514	1.50	0.46		0.5	12.60	176,000	8.54	1,310				0.3	12.00	186,000
172,000	32.00	2.89	126.00	4.60	302	4.76	8,892	7.58	0.68		0.5	10.10	24,000	7.10	10,993	3.68	0.90		1.2	9.30	14,000
243,000		0.59	138.00	3.80	193	0.59	62,486	2.40	0.50		0.5	12.40	46,000	4.02	5,225	1.58	0.35		0.8	11.10	22,000
9,000	155.00	7.50	127.00	5.50	4,930	7.46	14,749	2.21	0.16		5.0	7.50	16,000	8.44	11,821	1.98	0.40		4.0	7.10	8,000
57,400	107.00	1.83	137.00	5.20	1,596	2.76		1.00	0.30		1.0	8.70	9,000			1.80	0.90		0.5	7.80	14,000
148,000	104.90	2.34	142.00	5.60	363			1.20	0.40			11.50	75,000	1.65						9.10	60,000
77,000		2.80	139.00	3.50	83	2.81	611	1.20	0.80		0.0	11.20	45,000	4.12					0.0	10.00	60,000
18,000		1.84	135.00	3.40	989	2.49	1,893	2.80	0.20		1.0	9.30	8,000	4.97	2,808	2.10	0.70		1.0	8.30	14,000
144,000	188.00	2.32	139.00	5.20	20,111	2.32	1,891	7.20	0.70		1.2	10.60	62,000	2.00	2,234				2.0	9.20	54,000
36,000	173.00	3.19	132.00	3.90	1,532	3.88	1,822	1.71	0.40		0.2	6.70	22,000	5.96	2,145	7.90	6.20		1.0	8.30	14,000
43,000		0.99	135.00	3.70		3.00	980	0.30	0.10		0.3	6.20	151,000	5.56	1,031	0.40	0.10		0.2	5.40	133,000
43,000	116.00	3.65	139.00	3.40		3.60	3,404	14.00	1.90		1.2	12.70	11,000	4.20	4,310						
43,000	410.00	1.59	138.00	2.60	14,847	1.09	2,923	3.30	1.30		1.0	13.30	30,000	0.90	1,202				1.0	10.10	29,000
50,000	118.00	0.96	136.00	3.10	434	1.00	762	0.77	0.20		0.0	9.70	92,000	1.90					0.2	8.70	83,000
9,000	325.00	4.12	133.00	4.00	3,206	4.57	1,540	0.40	0.10		0.0	10.70	8,000	2.43	1,750	0.70	0.10		0.4	9.60	35,000
59,000		0.98	136.00	3.40	157	2.24		0.80	0.10		0.6	11.80	132,000	3.91					0.3	11.60	140,000
60,000		4.01	137.00	4.40	7,237	2.70	3,493	8.50	3.20	1.21	1.0	9.30	10,000	4.00	2,989				2.0	8.60	25,000
74,000	403.00	4.69	140.00	4.40	853	4.68	1,370	2.10	0.10		1.6	11.20	49,000	4.25	979				1.8	10.00	31,000
148,000	104.90	2.34	142.00	5.60		1.65	2,324	1.20	0.40		1.0	11.50	75,000	1.68					1.0	9.10	60,000
13,000	107.00	1.83	137.00	5.20	1,596	2.76	5,737	1.00	0.30		1.4	8.70	9,000	3.26	5,218	1.80	0.90		2.0	7.80	14,000
110,000		2.79	137.00	4.20	3,801	2.79	5,899	2.70	0.20		0.2	8.20	47,000	3.92	5,690				0.4	7.90	54,000
102,000	293.00	2.90	140.00	3.90		2.90	2,490	0.80	0.20		2.0	9.70	49,000	5.30	3,129	1.00	0.50		1.0	7.70	26,000
108,000	22.60	2.43	137.00	4.30	207	2.43	2,890	4.20	0.20		2.0	8.60	108,600	4.70	2,459	1.90	0.50		2.0	8.30	109,000
75,000		2.70	137.00	3.70	1,533	4.25	1,039	2.60	1.00		0.3	11.20	71,200	5.87	1,340				0.5	11.50	74,000
143,000		2.40	141.00	3.50	2,097	3.00	1,365	1.20	0.40		1.2	9.90	120,000	2.10	954				0.0	12.00	127,000
140,000		4.06	142.00	3.80	23,200	4.06	5,200	4.50	0.60		0.2	8.50	32,000	6.13	4,620				0.8	9.40	33,000
30,000	0.00	1.79	129.00	4.50	339	2.87		4.20	0.20		0.0	13.30	110,000	5.36					0.0	13.80	99,000
650,000	69.50	1.06	140.00	3.00	375	1.24		1.50	0.20			13.60	150,000	1.67							
46,000	48.00	1.87	147.00	2.80	220	1.40		1.27	0.90				24,000	0.88							39,000
42,000		1.70	138.00	3.00	489	1.70		0.70	0.20		0.0	12.00	87,000	1.71							
67,000		1.40	139.00	3.20	776	1.60					0.0	14.20	139,000	1.76					0.0	13.10	342,000
87,000	238.00	1.54	138.00	3.00	4,152	1.54					0.0	10.90	68,000	2.25							
99,000		1.31	131.00	3.50	2,397	1.31		3.50	0.40		0.0		318,000	2.55		10.90			0.0		248,000
102,000		1.52	140.00	4.00		1.52															
112,000		2.11	139.00	4.10		2.11		0.52	0.20		0.0	11.00	83,000	1.37					0.0	11.00	317,000
144,000		1.32	135.00	4.10	2,662	1.89	944	3.31	0.20		0.0	10.40		1.73						9.50	
139,000		1.55	145.00	3.50		1.58															
138,000	169.40	1.96	147.00	3.70	1,546	1.96	1,011	0.80	0.30		0.0	12.10	61,000	1.84					0.0	11.70	54,000
137,000	67.20	1.61	136.00	3.90	610	2.50		2.70	0.30		0.0	11.50	122,000	1.57					0.0	11.50	83,000
134,000	152.60	1.47	141.00	3.00																	
133,000	0.00	1.29	134.00	2.90	681	1.29		1.30	0.20		0.0	10.90	78,000	1.17	2,060				0.0	11.20	71,000
129,000		1.89	139.00	4.20	541	1.44	824														

creatd3	ldhd3	tbd3	dbd3	retd3	schzd4	hbd4	pltd4	creatd4	ldhd4	tbd4	dbd4	retd4	schzd5	hbd5	pltd5	creatd5	ldhd5	tbd5	dbd5	retd5	schzd6	hbd6	pltd6
1.12	960	1.96	0.80		0.0	10.10	160,000	1.05	850	2.12	0.60		0.0	11.20	380,000	1.04	480	1.82	0.60		0.0	13.30	282,000
1.45	960	1.22	0.28		0.0	12.80	110,000	1.06	960	1.00	0.50		0.0	11.30	101,000	1.04	940	1.00	0.56		0.0	11.60	136,000
0.91	480	0.86	0.24		0.0	12.30	260,000	0.80	410	0.75	0.24												
0.96	731	0.52	0.24		0.0	11.30	56,000	0.80	640	0.50	0.20		0.0	11.90	78,000	0.77	560	0.56	0.24		0.0	12.60	124,000
0.51					0.0	11.40	169,000	0.51					0.0	11.50	181,000	0.62							
0.89						14.20		1.08															
0.53						6.70	53,000	0.52						6.90	71,000	0.57						7.00	116,000
0.66					0.0	11.90	437,000	0.60															
1.36																							
1.08			11.00	1.09			369,000	0.89															
0.51																							
0.84																							
0.94	0				0.0	9.00	262,000	1.36															
0.65																							
0.55					0.0	8.40	33,000	0.55					0.0	8.20	66,000	0.43					0.0	9.10	133,000
1.00																							
						11.60							0.0	12.00	90,000	0.50							
0.74																							
0.80																							
0.58					0.0		145,000	0.62					0.0			0.93		0.50	0.20		0.0	12.40	146,000
5.54	3,810	2.10	0.76		0.0	9.50	72,000	5.99	3,100	1.27	0.54		0.0	8.20	108,000	5.81	2,680	0.80	0.50		0.0	8.10	112,000
0.81	1,385	7.80	0.40			11.60	154,000	0.71	1,042	2.60	0.40												
0.66		1.80	0.50																				
1.09																							
1.09	782	0.50	0.25																				
0.67					0.0	10.60	44,000	0.69		0.42	0.20												
0.50								0.49					0.2	14.20	385,000	0.65		2.00	0.40				
3.02	4,865	0.75	0.20		1.2	8.30	33,000	4.42	4,685	0.76	0.24		1.0	7.20	30,000	3.16	4,480	0.80	0.50		1.0	8.30	77,000
3.39	2,331	1.90	0.86		2.0	7.30	36,000	3.59	2,110	1.30	0.76		1.4	6.50	31,000	5.02	1,798	0.92	0.36		1.0	7.30	66,000
3.51	2,006	3.19	0.54		1.8	8.10	30,000	3.81	1,476	3.18	0.34		6.0	10.20	34,000	3.28	1,278	3.00	0.32		3.5	6.80	75,000
1.23	960	2.26	0.75		0.0	13.50	110,000	0.83	860	1.70	0.30												
10.76	1,210	1.00	0.50		1.0	11.50	225,000	11.10	982				0.8	11.20	256,000	12.65	980	0.52	0.24		0.8	10.50	310,000
7.40	6,832	2.10	0.74		2.0	7.40	17,000	7.75	5,830	1.02	0.69		3.0	6.50	170,000	7.09	4,320	0.90	0.20		4.0	8.60	27,000
4.99	3,014	1.20	0.50		1.0	8.60	11,000	4.97	1,784	1.00	0.60		0.8	7.10	19,000	5.66	1,320	1.00	0.50		1.2	8.60	46,000
5.90	9,541	1.76	0.42		6.0	6.50	33,000	5.52	7,360	1.46	0.50		4.0	7.90	53,000	7.53	4,564	1.24	0.56		3.2	7.30	20,000
3.26	5,737	2.83	1.60		2.0	10.10	41,000	4.19					2.0	9.30	7,000	3.79					5.0	8.30	16,000
3.43						7.90	77,000	5.94							120,000	6.26							
4.36								3.08															
7.36	2,280				2.0	7.90	25,000	4.55	1,155				2.0	7.00	48,000	3.95	1,239				1.0	6.20	64,000
2.93					2.0	8.70	43,000	3.81	2,498	3.50	1.00		2.0	7.20	32,000	5.60	2,978				1.0	7.00	37,000
6.23	2,144				1.0	7.70	4,000	3.69	1,476				1.2	6.90	8,000	3.82	1,428				0.0	6.80	12,000
5.57	1,023				1.0	8.10	148,000	6.50	1,041	0.50	0.10		0.0	8.60	253,000	7.47					0.0	8.10	234,000
0.94					0.2	11.40	51,000	0.68					0.0	13.40	91,000	0.48							
1.65					1.0	8.10	219,000	1.42					0.0	9.80	220,000	1.19							
3.11	1,644	0.70	0.10		0.8	8.50	26,000	5.43	1,623	0.60	0.30		1.0	7.90	13,000	6.44	1,502	0.60	0.30		1.2	8.30	25,000
5.25					0.0	10.80	144,000	6.23								6.56							
8.98	2,279	1.00	0.40		1.0	8.40	23,000	6.76	2,218	1.00	0.40		2.0	8.40	23,000	8.98					0.8	7.40	36,000
5.84	980				1.8	10.20	35,000	4.07	988				1.0	10.40	56,000	8.28					2.0	10.00	94,000
3.43					2.2	7.90	77,000	4.69					3.0	8.30	121,000	5.94					3.0	8.30	312,000
4.19	4,310	2.82	1.00	3.79	5.0	10.10	7,000	5.47	3,401				4.0	8.30	16,000	3.28	2,702	2.70	1.80		4.0	8.10	13,000
3.36					0.5	8.00	45,500	3.36					0.0	8.20	55,000	6.64					0.0	6.90	40,000
6.50					0.8	6.40	18,000	8.69					0.4	6.10	35,000	9.66	2,976	1.60	0.80		0.0	5.60	50,000
5.64					3.0	7.00	86,000	7.09	2,234				3.0	6.60	92,000	6.43					4.0	6.10	124,000
5.57					0.0	10.70	66,000	7.25	980				0.0	10.00	107,000	7.80					0.0	10.00	173,000
0.89																							
6.10	3,142				1.0	8.80	30,000	6.08	2,428	2.80	2.20		0.8	8.40	33,000	6.94	1,634				1.0	6.00	58,000
6.57	1,570				0.0	13.60	59,000	7.42					0.0	13.60	127,000	8.13					0.0		169,000
1.45																							
0.61							67,000	0.99															
0.69																							
1.51																							
3.87					0.0	10.20	290,000	4.02	1,520				0.0	9.80	292,000	3.81						11.00	
1.03																							
1.33	961	0.40	0.20			12.20		0.91															
1.21					0.0	12.40	73,000	1.00					0.0	12.21	103,000	0.86						13.20	163,000
1.32					0.0	11.60	87,000	1.30															
1.65																							

creatd6	ldhd6	tbd6	dbd6	retd6	schzd7	hbd7	pltd7	creatd7	ldhd7	tbd7	dbd7	retd7	schzd8	hbd8	pltd8	creatd8	ldhd8	tbd8	dbd8	retd8	schzd9	hbd9	pltd9
1.13	460	1.02	0.50																				
0.89	826	0.90	0.60		0.0	11.20	210,000	0.90	761	0.80	0.24		0.0	10.20	202,000	0.76	680	0.82	0.32				
0.76	482	0.50	0.20																				
							216,000	0.68															
0.40						9.80	269,000	0.40															
0.83																							
6.02	1,898	0.45	0.34		0.0	7.80	110,000	9.32	1,489	0.45	0.34		0.0	7.80	176,000	8.26	0	0.32	0.12				
					0.0	14.00	320,000	0.70		1.90	0.40					0.76					0.0	14.70	
5.39	4,572	0.76	0.26		1.0	6.90	77,000	4.10	2,100	0.82	0.34		0.2	7.00	155,000	6.12	2,120	0.81	0.26		0.0	6.50	190,000
4.49	1,477	0.86	0.50		2.0	7.80	108,000	5.54	1,467	0.92	0.50		1.2	8.50	142,000	2.95	1,271	0.76	0.24		0.1	9.10	242,000
2.58	810	2.30	0.24		0.8	6.60	189,000	1.64	481	1.60	0.20		2.5	6.60	210,000	1.38	649	1.00	0.20		2.0	6.60	193,000
10.94	813				0.0	10.40	381,000	6.99	740	0.46	0.24		0.0	10.40		2.06	462						
7.25	1,810	0.75	0.25		1.2	8.30	184,000	8.41	1,740	0.54	0.39		1.0	7.40	292,000	6.89	1,161	0.70	0.25		0.0	7.20	483,000
5.70	675	0.90	0.50		0.6	7.60	86,000	7.35	680	0.80	0.40		0.2	7.80	132,000	10.57	779	0.60	0.32		0.2	8.20	194,000
9.50	3,462	1.49	0.50		5.0	6.70	55,000	9.90					4.0	6.10	102,000	13.10	2,714	1.25	0.50		4.0	7.30	138,000
5.47					4.0	7.80	13,000	3.28		2.70	1.80		4.0	8.10	18,000	4.02							
6.44						8.30	312,000	6.44					3.0	9.60		6.29						9.70	
4.14	980						90,000	3.14															
6.40	2,989	1.90	1.10		1.0	8.00	54,000	7.65	2,322				0.0	7.00	94,000	7.59	2,223				0.0	6.30	118,000
2.87	1,699				0.8	7.90	21,000	8.98	1,051				1.0	6.70	32,000	5.70	1,051				0.0	5.90	48,000
5.60					0.0	8.60	310,000	5.14					0.0	8.90	323,000	3.61					0.0	8.50	
7.86	1,422				1.0	10.50	31,000	3.87					0.8	10.50	15,000	4.35	1,625	5.20	2.70		1.0	9.10	8,000
6.90								6.08								5.71							
8.35					0.0	6.60	78,000	11.11					0.0	7.20	116,000	8.50					0.0	7.60	142,000
10.70					0.8	10.20	301,100	11.20															
6.26					3.0	9.60	311,000	5.80					2.2	9.70		6.29					3.0	9.10	
4.02					4.0	8.10	18,000	4.02															
8.22					0.0	5.50	109,000	5.94					0.0	8.00	121,000	8.12					0.0	7.70	151,000
5.39	2,380				0.0	7.00	88,600	4.90	1,290				0.0	6.60	130,000	5.23					0.0	6.50	142,000
7.95		0.57	0.34		1.0	10.30	154,000	7.96					0.8	9.50	231,000	9.43					0.0	9.10	242,000
7.33	708																						
7.50					0.0	7.40	179,000	8.30					0.0			10.36					0.0		
6.21						16.00	169,000	4.99								3.20							
3.72																							
0.87		0.70	0.40																				

creatd9	ldhd9	tbd9	dbd9	retd9	schzd10	hbd10	pltd10	creatd10	ldhd10	tbd10	dbd10	retd10	schzd11	hbd11	pltd11	creatd11	ldhd11	tbd11	dbd11	retd11	schzd12
0.71		0.70	0.40																		
4.15	2,715	0.76	0.28		0.0	6.80	203,000	3.17	2,384	0.72	0.24		0.0	7.00	261,000	5.05	1,892	0.72	0.24		0.0
3.15	1,113	0.50	0.24		1.0	7.90	263,000	6.56	948	0.50	0.26		1.0	8.50	332,000	5.27	642	0.52	0.24		0.0
1.36	660				4.0	6.70	193,000	1.03	690												
8.24	1,142				0.0	6.60	692,000	5.24	1,112				0.0	6.80	690,000	6.28	1,106				0.0
7.58	786	0.37	0.19		0.2	9.00	176,000	10.55	726	0.30	0.10										
14.26					3.0	7.90	298,000	11.60	2,128	1.00	0.50		4.0	7.30	371,000	7.50					2.0
5.28								5.40								3.43					
7.69	1,594				0.0	8.50	173,000	7.69	1,176				0.0	9.30	207,000	7.13					0.0
7.05					1.0	8.50	85,000	7.05					0.0	7.20	237,000	6.22					0.0
2.67		0.20	0.10																		
3.12					1.0	7.70	32,000	2.25					0.0	7.70	32,000	2.21					0.0
7.40		1.00	0.40		0.0	7.60	200,000	7.33					0.0	8.60	228,000	6.81					0.0
5.40								3.43								3.09					
7.74																					
7.11	560				0.0	6.60	182,000	8.85					0.0	6.80	242,000	10.31					0.0
7.25					0.0	10.00	264,000	8.35					0.0	10.10	291,000	6.94					0.0
9.59					0.0			6.92													
1.57																					

hbd12	pltd12	creatd12	ldhd12	tbd12	dbd12	retd12	lrd1	cnsd1	renald1	coagd1	lrd2	cnsd2	renald2	coagd2	lrd3	cnsd3	renald3	coagd3	lrd4	cnsd4	renald4	coagd4
							1	2	2	1	1	2	2	2								
							1	1	2	1	1	1	2	2								
							1	2	2	1	2	2	2	1	2	2	2	2	2	2	2	2
							1	2	2	1	1	2	2	1								
							1	1	2	1	1	1	2	2								
							2	1	1	2	2	1	1	2	2	1	1	2	2	1	2	2
							1	2	2	1	1	2	2	2	1	2	2	2	1	2	2	2
							1	2	2	1	1	2	2	2	1	2	2	2	1	2	2	2
							1	1	2	1												
							1	1	2	1												
							1	1	2	1	1	1	2	1								
							1	2	2	1	1	2	2	2								
							1	1	2	1												
							1	1	2	1												
							1	1	2	1	1	1	2	1	1	1	2	2	1	1	2	2
							1	1	2	1	1	1	2	2	1	1	2	2	1	1	2	2
							1	1	2	1	1	1	2	2	1	1	2	2	1	1	2	2
							1	2	2	1	1	2	2	2								
							1	2	2	1	1	2	2	2								
							1	2	2	2	2	2	2	2								
							1	1	2	2	1	1	2	2								
							1	1	2	2	1	1	2	2	1	1	2	2	1	1	2	2
							1	1	2	1	1	1	2	2	1	1	2	2	1	1	2	2
							1	1	2	1												
							1	1	2	1	1	1	2	2	1	1	2	2				
							1	1	2	1	1	1	2	2	1	1	2	2				
							1	2	2	1	1	2	2	2	1	2	2	2				
							1	2	2	1	1	2	2	2								
							1	1	2	1	1	1	2	2	1	1	2	2	1	1	2	2
							1	2	2	1	1	2	2	2								
							1	2	2	1	1	2	2	2	1	2	2	2	1	2	2	2
							1	1	2	1	1	1	2	2	1	1	2	2				
							2	1	2	1	2	1	2	2	2	2	2	2	2	2	2	2
							1	1	2	1	1	1	2	2	1	1	2	2				
							1	1	2	1	1	1	2	2	1	1	2	2	1	2	2	2
							1	2	2	1	1	2	2	2								
							1	1	2	1	1	1	2	2	1	1	2	2	1	1	2	2
							1	2	2	1	1	2	2	2	1	2	2	2				
							1	2	2	1	2	2	2	2								
							1	2	2	1	1	2	2	2	1	2	2	2				
							1	2	2	1	1	2	2	2								
							1	2	2	1	1	2	2	2	1	2	2	2				
							1	2	2	1	1	2	2	2								
							1	2	2	1												
							1	1	2	1	1	1	2	2								
							1	2	2	1	1	2	2	2	2	2	2	2				
							1	1	2	1	1	1	2	2	1	1	2	2				
							1	1	2	1	1	1	2	2	1	1	2	2				
							1	1	2	1	1	1	2	2	1	1	2	2	1	1	2	2
							1	1	2	1	1	1	2	2	1	1	2	2	1	1	2	2
							1	2	2	1	1	2	2	2								
							1	2	2	1												
							1	2	2	1												
							1	2	2	1	2	2	2	1								
							1	1	2	1	1	1	2	2								
							1	2	2	1	1	2	2	1	1	2	2	2				
							1	2	2	1	1	2	2	1								
							1	2	2	1												
							1	2	2	1	1	2	2	2								
							1	2	2	1	1	2	2	2								
							1	1	2	1	1	1	2	2	1	1	2	2	1	1	2	2
							1	2	2	1	1	2	2	2								
							1	2	2	1	1	2	2	2								
							1	1	2	1	1	1	2	2	1	1	2	2				
							1	1	1	1	1	1	1	2	1	1	1	2	1	1	1	2
							1	1	2	1	1	1	2	2	1	1	2	2	2	2	2	2
							2	2	2	1	2	2	2	2	2	2	2	2				
							1	1	2	1	1	1	2	2	1	1	2	2	1	2	2	2
							1	1	1	1	1	1	2	2	1	1	2	2	1	1	2	2
							1	2	1	2	1	2	2	2	1	2	2	2				
							1	1	2	1	1	1	2	2	1	1	2	2	1	1	2	2
							1	1	2	1	1	1	2	2	1	1	2	2	1	1	2	2
							1	1	2	1	1	1	2	2	1	1	2	2				
6.50	318,000	7.27	1,613	0.70	0.25		1	2	1	1	1	2	1	2	1	2	1	2	1	2	1	2
9.10	445,000	7.26	480	0.52	0.24		1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2
							1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2
							1	1	1	1	1	1	1	2	1	1	2	2	1	1	2	2
							1	1	1	1	1	1	1	2	1	1	1	2	1	1	1	2
6.50	623,000	7.39	927				1	2	1	1	1	2	1	2	1	2	1	2	1	2	1	2
							1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2
8.60	483,000	7.95	1,273	0.40	0.22		1	1	1	2	1	1	1	2	1	1	1	2	1	1	1	2
							1	2	1	1	2	2	1	2	2	2	1	2	2	2	1	2
		3.09					1	1	1	2	1	1	1	2	1	1	1	2	1	1	1	2
							1	1	1	1	2	1	1	2	2	1	1	2	2	1	1	2
							1	1	1	1	1	1	1	2	1	1	1	2	1	1	1	2
8.70	215,000	6.12	986	0.60	0.50		1	1	1	1	1	1	1	2	1	1	1	2	1	1	1	2
8.20	323,000	3.43					1	1	1	1	1	1	1	2	1	1	1	2	1	1	1	2
							1	1	1	1	1	1	1	2	1	1	1	2	1	1	1	2
							1	1	1	1	1	1	1	2								
							1	1	1	1	1	1	2	2	1	1	2	2	1	1	2	2
							1	1	1	1	1	1	1	2	1	1	1	2	1	1	2	2
7.10	89,000	3.31					1	1	1	1	1	1	1	2		1	1	2	1	1	1	2
							2	2	1	1	2	2	1	1	2	2	1	2	2	2	1	2
8.60	367,000	4.48					1	1	1	1	1	1	1	2	1	1	1	2	1	1	1	2
							1	1	1	1	1	1	1	2	1	1	1	2	1	1	1	2
							1	1	1	1	1	1	1	2	1	1	1	2	1	1	1	2
							1	1	1	1	1	1	1	2	1	1	1	2	1	1	1	2
							1	1	1	1	1	1	1	2	1	1	1	2	1	1	1	2
6.90	284,000	8.87					1	1	1	1	1	1	1	2	1	1	1	2	1	1	1	2
10.20	320,000	3.66					1	1	1	1	1	1	1	2	1	1	1	2	1	1	1	2
							1	1	1	2	1	1	1	2	1	1	1	2	1	1	1	2
							1	2	1	1	1	2	1	2	1	2	1	2	1	2	1	2
							1	1	1	1	1	1	1	2	1	1	1	2	1	1	1	2
							1	1	1	1	1	2	1	1	1	2	1	2	2	2	1	2
							1	1	1	1	1	1	2	2	1	1	2	2	1	1	2	2
							1	1	1	1	1	1	2	2	1	1	2	2	1	1	2	2
							1	2	1	1	1	2	1	2	1	2	2	2	1	2	2	2
							1	1	1	2	1	1	1	2	1	1	1	2				
							1	1	1	1	1	1	1	2								
							1	1	1	1	1	1	1	2	1	1	1	2	1	2	1	2
							2	2	2	1	2	2	2	2								
							2	2	2	1	2	2	2	2	2	2	2	2				
							1	2	1	1	1	2	1	2	1	2	2	2				
							1	2	1	1	1	2	2	2								
							1	1	1	1	1	1	1	2	1	1	1	2	1	1	1	2
							1	1	1	1	1	1	1	1	1	1	1	2	1	1	2	2
							1	2	1	1	1	2	2	2								
							1	1	2	1	1	1	1	1	1	1	1	1				
							1	2	1	1	1	2	2	2								

lrd5	cnsd5	renald5	coagd5	lrd6	cnsd6	renald6	coagd6	ldr7	cnsd7	renald7	coagd7	lrd8	cnsd8	renald8	coagd8	lrd9	cnsd9	renald9	coagd9	lrd10	cnsd10	renald10
2	2	2	2	2	2	2	2															
2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2						
1	2	2	2																			
1	1	2	2	1	1	2	2	1	2	2	2	2	2	2	2	2						
1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2						
1	1	2	2																			
1	1	2	2	1	1	2	2	1	2	2	2	2	2	2	2	2						
1	2	2	2	1	2	2	2															
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1	2	2	2	2	2	2	2															
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1	2	1	2	2	2	1	2	2	2	1	2	2	2	1	2	2	2	1	2	2	2	1
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1	2	1	2	2	2	1	2	2	2	1	2	2	2	1	2	2	2	1	2	2	2	1
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2	2	1	2	2	2	1	2	2	2	1	2	2	2	1	2							
1	2	1	2	2	2	1	2	2	2	1	2	2	2	1	2	2	2	1	2	2	2	1
1	1	1	2	1	2	1	2	2	2	1	2											
1	1	1	2	1	2	1	2	1	2	1	2	2	2	1	2	2	2	1	2	2	2	1
1	1	1	2	1	2	1	2	2	2	1	2	2	2	1	2	2	2	1	2	2	2	1
1	2	1	2	2	2	1	2	2	2	1	2	2	2	1	2	2	2	1	2			
1	2	2	2	1	2	2	2															
1	1	2	2																			
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1	1	1	2	2	1	1	2	2	2	1	2											
1	2	1	2	2	2	1	2	2	2	1	2	2	2	1	2	2	2	1	2	2	2	1
1	1	1	2	1	1	1	2	1	1	1	2	1	1	1	2							
1	1	1	2	1	1	1	2	1	1	1	2	1	1	1	2	2	2	1	2	2	2	1
1	1	1	2	1	2	1	2	1	2	1	2	2	2	1	2	2	2	1	2	2	2	1
1	1	1	2	1	2	1	2	1	2	1	2	2	2	1	2	2	2	1	2	2	2	1
1	2	1	2	1	2	1	2															
2	2	2	2																			
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2	2	1	2	2	2	1	2	2	2	1	2	2	2	1	2	2	2	1	2			
1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2							
1	1	1	2	1	2	1	2	1	2	1	2	2	2	1	2	2	2	1	2			
1	2	2	2	1	2	2	2	1	2	2	2	2	2	2	2							

coagd10	lrd11	cnsd11	renald11	coagd11	lrd12	cnsd12	renald12	coagd12	TMA	envensynd	snake	trans	VICC	cyro	FFP	PRC	prbc	Dialysis	Plasmap	stay	ICUd	outcome	ASVTotal
									1	3	1	2	1					2	2	2	0	1	10.00
									1	5	1	2	1					2	2	2	0	1	14.00
									1	7	2	2	1		2			2	2	6	2	1	20.00
									1	3	1	2	1					2	2	2	0	1	10.00
									1	5	1	2	1					2	2	2	0	1	14.00
									1	5	1	2	1					2	2	8	3	1	20.00
									1	3	1	2	1					2	2	4	0	1	16.00
									1	3	1	2	1					2	2	5	0	1	20.00
									1	5	1	1	1	0	4	0	0	2	2	2	0	1	26.00
									1	5	1	2	1	0	0	0	0	2	2	2	0	1	10.00
									1	5	1	2	1	0	0	0	0	2	2	2	0	1	28.00
									1	3	1	2	1	0	0	0	0	2	2	2	0	1	9.00
									1	5	1	2	1	0	0	0	0	2	2	2	0	1	18.00
									1	5	1	2	1	0	0	0	0	2	2	2	0	1	27.00
									1	5	1	2	1	0	0	0	0	2	2	7	0	1	24.00
									1	5	1	2	2	0	0	0	0	2	2	4	0	1	20.00
									1	5	1	2	1	0	0	0	0	2	2	8	0	1	70.00
									1	2	1	2	1	0	0	0	0	2	2	2	0	1	24.00
									1	2	1	2	1	0	0	0	0	2	2	2	0	1	12.00
									1	5	1	1	1	6	4	0	0	2	2	4	0	1	20.00
									1	5	1	2	2	0	0	0	0	2	2	2	0	1	14.00
									1	5	1	2	1	0	0	0	0	2	2	1	0	1	14.00
									1	5	1	2	1	0	0	0	0	2	2	2	0	1	24.00
									1	5	1	2	1	0	0	0	0	2	2	4	0	1	18.00
									1	5	1	2	1	0	0	0	0	2	2	4	0	1	10.00
									1	5	1	2	1	0	0	0	0	2	2	2	0	1	12.00
									1	5	1	2	1	0	0	0	0	2	2	3	0	1	18.00
									1	5	1	2	2	0	0	0	0	2	2	3	0	1	18.00
									1	3	1	2	1	0	0	0	0	2	2	3	0	1	10.00
									1	3	1	2	1	0	0	0	0	2	2	2	0	1	17.00
									1	5	1	2	1	0	0	0	0	2	2	5	0	1	24.00
									1	3	1	2	1	0	0	0	0	2	2	2	0	1	12.00
									1	3	1	2	1	0	0	0	0	2	2	4	0	1	20.00
									1	5	1	2	1	0	0	0	0	2	2	4	0	1	12.00
									1	5	1	2	1	0	0	0	0	2	2	4	1	1	15.00
									1	5	1	2	1	0	0	0	0	2	2	4	0	1	18.00
									1	5	1	2	1	0	0	0	0	2	2	4	0	1	20.00
									1	2	1	2	1	0	0	0	0	2	2	2	0	1	18.00
									1	5	1	2	2	0	0	0	0	2	2	8	2	1	18.00
									1	5	1	2	1	0	0	0	0	2	2	4	0	1	8.00
									1	7	2	2	1	0	0	0	0	2	2	2	0	1	24.00
									1	3	1	2	1	0	0	0	0	2	2	3	0	1	10.00
									1	3	1	2	1	0	0	0	0	2	2	2	0	1	12.00
									1	3	1	2	1	0	0	0	0	2	2	3	0	1	12.00
									1	3	1	2	1	0	0	0	0	2	2	2	0	1	17.00
									1	3	1	2	1	0	0	0	0	2	2	1	0	1	6.00
									1	5	1	2	1	0	0	0	0	2	2	2	0	1	12.00
									1	3	1	2	1	0	0	0	0	2	2	2	0	1	10.00
									1	5	1	2	1	0	0	0	0	2	2	3	0	1	10.00
									1	5	1	2	1	0	0	0	0	2	2	3	0	1	16.00
									1	5	1	2	1	0	0	0	0	2	2	6	0	1	18.00
									1	5	1	2	1	0	0	0	0	2	2	6	2	1	10.00
									1	3	1	2	1	0	0	0	0	2	2	2	0	1	10.00
									1	3	1	2	2	0	0	0	0	2	2	1	0	1	10.00
									1	3	1	2	1	0	0	0	0	2	2	1	0	1	15.00
									1	3	1	2	1	0	0	0	0	2	2	3	0	1	10.00
									1	6	1	2	1	0	0	0	0	2	2	2	0	3	12.00
									1	3	1	2	1	0	0	0	0	2	2	3	0	1	20.00
									1	3	1	2	1	0	0	0	0	2	2	1	0	1	13.00
									1	3	1	2	2	0	0	0	0	2	2	1	0	3	12.00
									1	3	1	2	1	0	0	0	0	2	2	3	0	1	21.00
									1	3	1	2	1	0	0	0	0	2	2	1	0	1	10.00
									1	5	1	2	1	0	0	0	0	2	2	4	0	1	14.00
									1	3	1	2	1	0	0	0	0	2	2	2	0	1	10.00
									1	3	1	2	1	0	0	0	0	2	2	2	0	1	21.00
									2	5	1	2	2					2	2	3	0	1	20.00
									2	6	1	2	1					2	2	9	0	1	25.00
									2	5	1	2	1	0	0	0	0	2	2	4	0	1	17.00
									2	7	2	2	1	0	0	0	0	2	2	3	0	1	10.00
									2	5	1	2	1	0	0	0	0	2	2	4	0	1	26.00
									2	5	1	2	1	0	0	0	0	2	2	4	0	1	16.00
									3	3	1	2	1					2	2	3	0	1	10.00
									3	5	1	2	1	0	0	0	0	2	2	6	0	1	26.00
									3	5	1	2	1	0	0	0	0	2	2	9	0	1	22.00
									3	5	1	2	1	0	0	0	0	2	2	3	0	1	20.00
2	2	2	1	2	2	2	1	2	4	4	1	1	2		2		2	1	2	12	2	1	20.00
2	2	2	1	2	2	2	1	2	4	4	1	2	2	2		2	1	1	2	12	0	1	18.00
2									4	4	1	1	2		2	2		1	1	10	4	1	26.00
									4	5	1	2	1					2	2	4	2	1	12.00
									4	5	1	1	2		4			2	2	12	3	1	40.00
2	2	2	1	2	2	2	1	2	4	4	1	1	1	16			2	1	1	12	0	1	20.00
2									4	6	1	1	2	40				1	1	14	0	1	0.00
2	1	2	1	2	1	2	1	2	4	6	1	1	2				4	1	2	26	7	1	10.00
									4	4	1	1	1	24	12	12	4	1	2	9	5	2	20.00
2	2	2	1	2	2	2	1	2	4	5	1	2	2	0	0	0	0	1	2	12	2	1	16.00
									4	5	1	2	1	0	0	0	0	2	2	4	0	3	6.00
									4	5	1	1	1	24	0	0	0	1	1	8	0	1	26.00
2	2	2	1	2	2	2	1	2	4	6	1	1	1	0	0	0	8	1	2	13	0	1	26.00
2	2	2	1	2	2	2	1	2	4	6	1	1	1	0	8	10	4	1	2	14	0	1	30.00
									4	6	1	1	1	0	0	0	4	2	2	9	0	1	10.00
									4	6	1	1	1	8	0	9	0	2	2	2	0	3	24.00
									4	5	1	2	2	0	0	0	0	2	2	6	2	2	47.00
									4	6	1	1	1	8	0	0	0	2	2	5	0	1	20.00
2	2	2	1	2	2	2	1	2	4	6	1	1	2	0	0	0	0	1	2	16	3	1	20.00
2	2	2	1	2	2	2	1	2	4	4	1	2	1	0	0	0	0	1	2	12	0	1	20.00
2	2	2	1	2	2	2	1	2	4	6	1	1	1	0	12	0	4	1	2	16	2	1	15.00
									4	6	1	2	2	0	0	0	0	1	2	8	0	3	16.00
2	2	2	1	2					4	6	1	2	2	0	0	0	0	1	2	12	0	1	16.00
									4	6	1	1	2	20	12	40	10	1	1	9	9	2	20.00
2									4	6	1	1	1	0	8	0	0	1	2	12	4	1	21.00
2	2	2	1	2	2	2	1	2	4	6	1	1	1	6	8	0	3	1	1	27	0	1	14.00
2	2	2	1	2	2	2	1	2	4	6	1	1	1	0	0	0	2	1	2	12	0	1	29.00
									4	6	1	2	2	0	0	0	0	1	2	7	0	1	19.00
									4	6	1	2	2	0	0	0	0	2	2	4	0	1	72.00
2	1	2	1	2	1	2	1	2	4	6	1	1	1	6	4	0	2	1	2	20	10	1	16.00
									5	5	1	2	1	0	0	0	0	2	2	9	0	1	16.00
									5	5	1	2	1	0	0	0	0	2	2	4	0	1	10.00
									5	5	1	2	1	0	0	0	0	2	2	4	0	1	25.00
									5	3	1	2	1	0	0	0	0	2	2	3	0	1	24.00
									5	6	1	2	2	0	0	0	0	2	2	3	0	1	13.00
									5	5	1	2	1	0	0	0	0	2	2	2	0	2	24.00
									5	5	1	2	1	0	0	0	0	2	2	8	0	1	10.00
									5	7	1	2	1	0	0	0	0	2	2	2	0	1	8.00
									5	7	2	2	1	0	0	0	0	2	2	2	0	1	20.00
									5	4	1	2	1	0	0	0	0	2	2	4	0	1	18.00
									5	4	1	2	1	0	0	0	0	2	2	2	0	1	8.00
									5	6	1	2	2	0	0	0	0	2	2	8	4	1	26.00
									5	6	1	1	1	8	5	0	0	1	2	5	2	1	16.00
									5	3	1	2	1	0	0	0	0	2	2	2	0	1	20.00
									5	6	1	1	1	6	4	0	0	2	2	2	2	2	10.00
									5	4	1	2	1	0	0	0	0	2	2	2	0	1	18.00

ANNEXURE 6: Additional Tables

Table 17 Snake Envenomation correlation with TMA spectrum

Envenomation Syndrome	**TMA Spectrum(Prospective n=19, Retrospective n=102, Total n=121)**														
	Thrombocytopenia only			**Thrombocytopenia + MAHA**			**Thrombocytopenia + MAHA + Schistocytes**			**Thrombocytopenia + MAHA + Schistocytes +End Organ Damage**			**Thrombocytopenia + End Organ Damage**		
	P(n=6) n(%)	R(n=57) n(%)	T(n=63) n(%)	P(n=1) n(%)	R(n=4) n(%)	T(n=5) n(%)	P(n=1) n(%)	R(n=3) n(%)	T(n=4) n(%)	P(n=8) n(%)	R(n=22) n(%)	T(n=30) n(%)	P(n=3) n(%)	R(n=16) n(%)	T(n=19) n(%)
Local Reaction + Hemotoxicity	3(50)	25(43.9)	28(44.5)	-	-	-	1(100)	-	1(25)	-	-	-	1(33.3)	2(12.5)	3(15.8)
Pure Hemotoxicity	1(16.7)	1(1.8)	2(3.2)	-	1(25)	1(20)	-	-	-	-	-	-	-	2(12.5)	2(10.5)
Hemotoxicity + AKI	-	-	-	-	-	-	-	-	-	4(50)	2(9.1)	6(20)	-	3(18.8)	3(15.8)
Hemotoxicity + Neurotoxicity	2(33.3)	30(52.6)	32(50.8)	1(100)	3(75)	4(80)	-	3(100)	3(75)	2(25)	4(18.2)	6(20)	1(33.3)	5(31.3)	6(31.6)
Hemotoxicity + Neurotoxicity + AKI	-	1(1.8)	1(1.6)	-	-	-	-	-	-	2(25)	16(72.7)	18(60)	1(33.3)	4(25.0)	5(26.3)

ANNEXURE 7: Abstract

OBJECTIVES:

The study was conducted to determine the prevalence of thrombotic microangiopathy in snakebites and to describe the clinical profile of these patients, with relation to the envenomation syndrome and venom induced consumption coagulopathy(VICC).

METHODS:

This study was an observational cohort, consisting of a prospective cohort (Recruited from June 2017 to July 2018) and a retrospective cohort (April 2012 to March 2017). All patients above the age of 18 years, presenting with a hemotoxic snake bite, with a platelet count <1,50,000/cumm were recruited. Patients were observed both clinically and with appropriate investigations daily till discharge. Additional information for analysis was obtained from the clinical workstation. Descriptive statistics such as mean, standard deviation were analysed using Kruskal Wallis test across TMA spectrum and lab investigations and outcomes. Categorical variables like envenomation syndrome, Fisher's exact test was used.

RESULTS:

TMA is a spectrum disorder that ranges from isolated Thrombocytopenia, thrombocytopenia with MAHA, and Thrombocytopenia, MAHA and renal failure(full spectrum TMA disorder). Prevalence of TMA spectrum was 51.35%

and full spectrum TMA disorder was 21.6% in the prospective cohort. Majority of hemotoxic snakebites had a Russell's viper like envenomation syndrome (69.4%). More importantly all the patients (30 subjects) who had full spectrum TMA had a Russell's viper like envenomation syndrome. Majority of hemotoxic snakebites presented with VICC (81%). Patient group who did not have VICC, but presented with Thrombocytopenia (19%).

Treatment outcomes were noted to be worse in the TMA spectrum with renal failure, requiring higher doses of ASV with longer hospital/ICU stay, and with 73.3% of these patients requiring dialysis. Hence it is clear that patients who developed a TMA full spectrum disorder have a more severe illness with worse outcomes.