

## Haematotoxic snakebite: Regional snake species variation, clinical profile and outcome from South India

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**Abstract:** Snake venoms are made up of numerous proteinacious products and has varied functional effects on different cells of the body. Since the toxic components found in the venom does vary between species, the victims can present with numerous life-threatening manifestations related to the neurotoxic and haemotoxic effects of venom. Thus, snakebite is one of the world's most neglected tropical diseases. Some of the snake venoms show strong haemotoxic properties that has effects on blood pressure, clotting factors and platelets, and thereby causing haemorrhage.

This study was conducted from March 2014 to March 2017. We included only snakebites with hematotoxic manifestations. A total of 137 snake bite patients were studied during this period with a male to female ratio of 4:1. The majority of patients belonged to rural areas; most of them were bitten during outdoor activity. 60% of snakes were identified. The peak time of snake bite was between 6pm and 11pm. 75% bites were in the lower limb. The most common symptom was pain at the local site. Majority (97%) of patients with signs of systemic envenomation survived.

**Keywords:** haemotoxic, snakebite, South India

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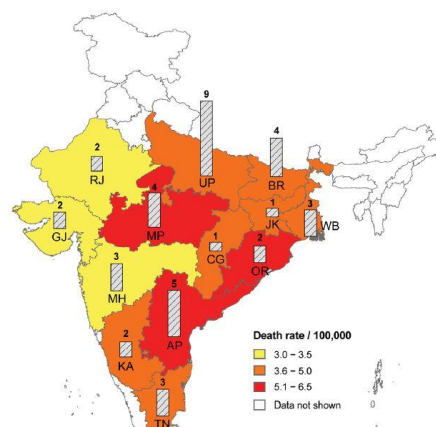
### I. Introduction:

India is a diversified nation where the geo-climatic conditions changes completely as we move from different regions throughout the country. Of the numerous snake species found in India, the medically important species are few. There are 216 species of snakes in India with 52 being poisonous[1,2]. A vast majority of snake envenomation associated mortality and morbidity have been attributed to 4 snakes- The Indian big four.

1. Russel's viper
2. Saw scaled viper
3. Indian cobra (Naja Naja)
4. Common krait (Bungarus caeruleus)

The million death study estimated that approximately 50,000 people die of snake bite every year in India indicating that this is a major public health problem[3]. The exact estimate from south India, Kerala was not estimated from most of the studies including the million death study since the data regarding the same was scarce from this region.

Million Death Study . Mortality trends due to snake bites in India



Mohapatra et al. (2011) PLoS Negl Trop Dis 5(4): e1018. doi:10.1371/journal.pntd.0001018

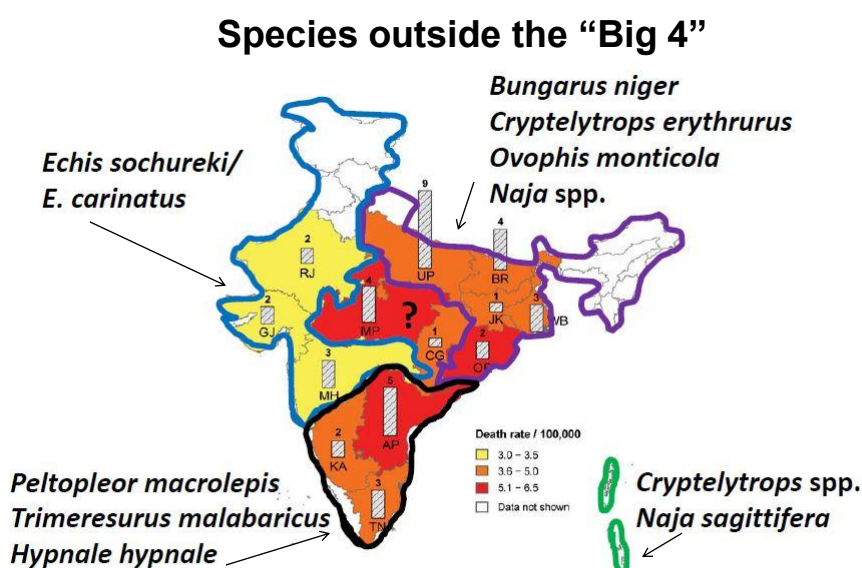
The clinical manifestations may differ with the region and this may be due to various factors such as the prevalence of the snake species, variation in venom constituents within the species, timing of bites and the percentage of dry bites. This may be the reason why about 50% of bites by Russell's viper, 30% of bites by Cobras and 5-10% of bites by Saw-scaled viper do not result in any symptoms or signs of envenoming[4].

It is known that there is regional variation of the venomous snakes and the snake syndromes from different parts of India. Examples of snakes outside the "big four" from our location are

- Hump nosed pit viper ( *Hypnale Hypnale* )
- Malabar pit viper ( *Trimeresurus malabaricus* )

#### Hump-nosed pit viper

This is a pit viper mostly reported from South India. It causes local swelling, hemotoxicity, and nephrotoxicity similar to saw-scaled viper. The polyvalent ASV does not neutralize the venom of hump-nosed viper effectively. One other feature of pitviper bite is persistent coagulopathy which can extend for several weeks. Hence, this species is causing problems with the management of snake bites in South India.[5]



#### Regional Variability in Distribution of Syndromes

- Northern and Eastern India hospitals have predominantly neurotoxic .
- Southern India has predominantly haemotoxic
- Centres in Western India have both haemotoxic and neurotoxic snake bite .

#### Variation in Practice: Indication for ASV

- ❖ Local Signs : Variable indications .
- ❖ Neurotoxicity : used as indication of snake bite in all centres
- ❖ Vasculotoxicity :
- Some centres : prolonged WBCT >20 mins or BT/CT abnormality

#### Study Objectives

1. Geographical variability of snake envenomation .
2. Snakebite syndromes and clinical outcome.

## II. Materials and Methods

#### Inclusion criteria:

1. All patients with signs of haematotoxic envenomation were included in the study.
2. Patients with neurotoxic features and with history of unknown bite with or without a characteristic snake envenomation symptom.

Exclusion criteria:

1. Patients who did not give consent and who did not want to participate in the study were excluded.

### Study Design

Prospective observational cohort study

### Data entry

Documentation of clinical data was done in a written proforma along with a web-based internet data entry page, which is secured with a user id and password.

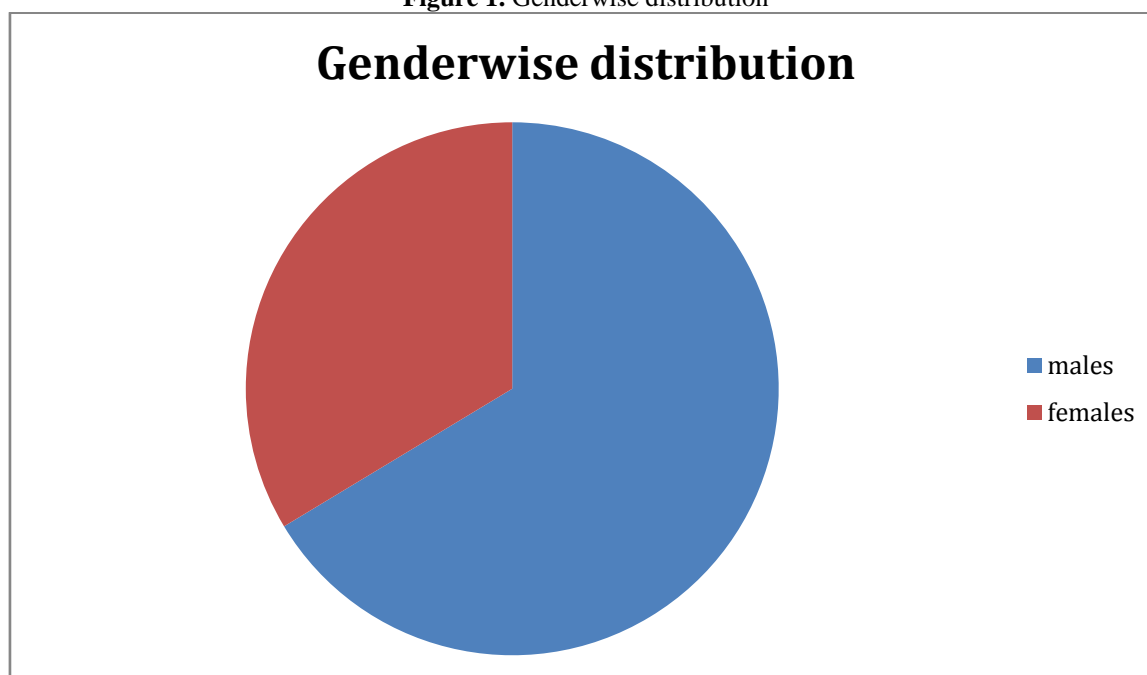
### Ethics statement

This study was approved by “Institutional Ethics Committee” of Academy of Medical Sciences, Pariyaram.

### III. Results

A total n=137 patients were studied. Among this 100(73%) were males and 37(27%) were females. Maximum number of cases belonged to 30-50 years age group(48%) and least belonged to the <30 years age group. Of these 137, 104(76%) patients showed definite signs of envenomation and received ASV.

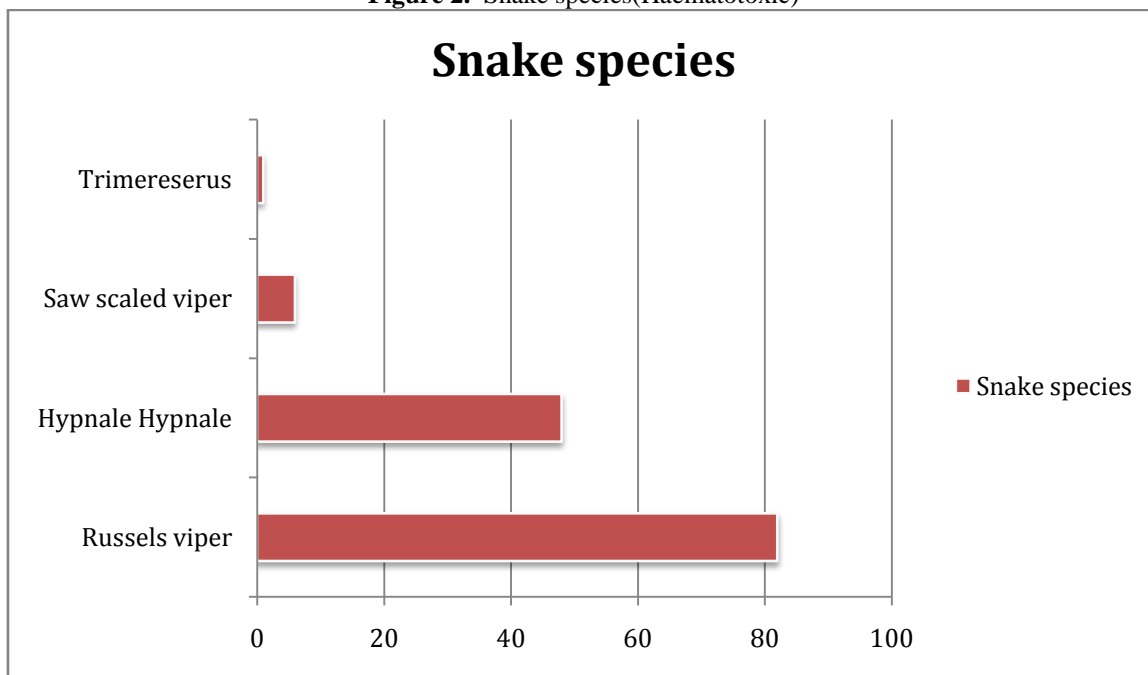
**Figure 1.** Genderwise distribution



Out of haematotoxic snakes most of them were Russels viper(60%) followed by Hump-nosed pit viper(35%), and then a few Saw-scaled vipers and one Malabar pit viper. Persistent coagulopathy was noted in Hypnale Hypnale bite(Hump-nosed pit viper) which extended for weeks. This feature was peculiar and trademark for Hypnale bites. Mortality rate was maximum in Russels viper bite patients.

Malabar pit viper's are quite a rare kind of species even in the Malabar region of northern Kerala. Many different colour morphs are known to exist, including colours such as yellow, green, and brown. These are mostly tree dwelling and this snake had a greenish hue to the overall skin texture. The snake was captured live by the patient. The patient showed no signs of envenomation. Its venom usually causes moderate pain and swelling to humans. It was likely that the snake had not injected enough venom during the bite and bite was not found deep, but just a graze which looked like an abrasion.

**Figure 2.** Snake species(Haematotoxic)

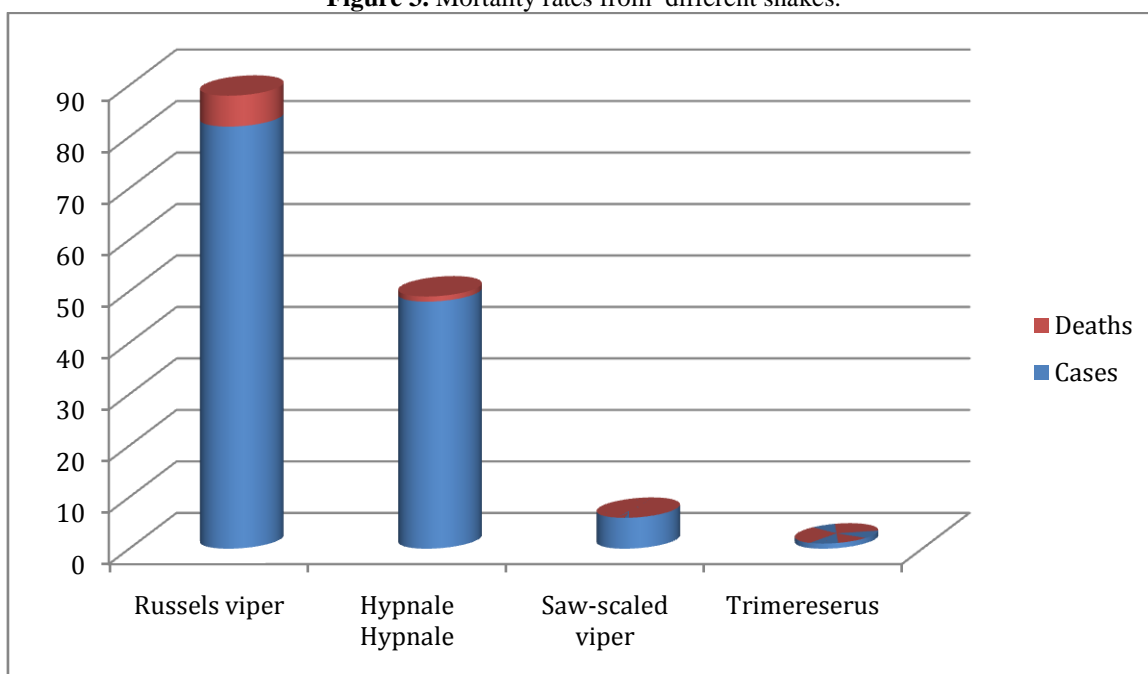


Maximum mortality was seen from Russels viper bite with DIC being the most common cause of death, then followed by Hypnale Hypnale(Hump nosed pit viper) . Mortality also depended on delay in reaching the hospital following the bite and initial treatment by traditional healers and inadequate amount of ASV(2-3 vials in total) given from primary health centres.

**Table 3.** Clinical outcome

Type of snake	No.of cases	No.of deaths(%)
Russels viper	82	4 (5%)
Hypnale Hypnale(Hump-nosed pit viper)	48	1 (2%)
Saw-scaled pit viper	6	0
Trimeresurus malabaricus(Malabar pit viper)	1	0

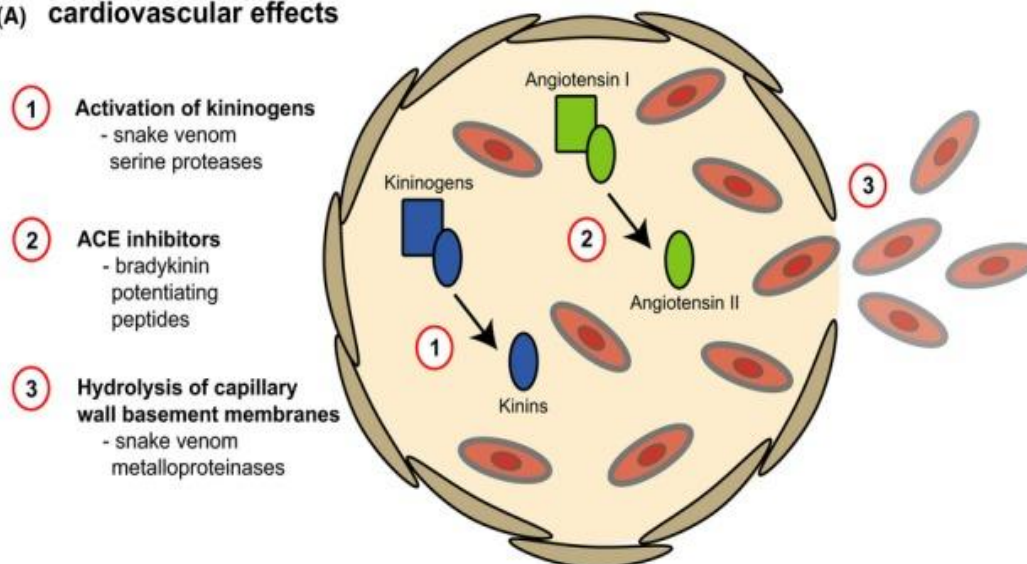
**Figure 3.** Mortality rates from different snakes.



#### IV. Discussion

Haemotoxicity appears to be one of the most common clinical signs in snakebite patients, particularly when viperidae snakes are responsible for envenomation. Generally, haemotoxic venoms can have cardiovascular and/or haemostatic effects. Cardiovascular effects are characterised by a fall in blood pressure and this can be caused by a number of different venom toxins. The proteinases SVMPs (snake venom metalloproteinases) indirectly contribute to hypotension by increasing vascular permeability via the degradation of capillary basement membranes, resulting in leakage and reductions in blood pressure [6]. Snakes can also directly induce vasodilatory effects via the injection of bradykinin potentiating peptides (BPPs) present in their venom, and this activity can be further enhanced by certain snake venom serine protease (SVSP) toxins exhibiting kallikrein-like functionalities, causing the release of bradykinins from plasma kininogens [7,8].

##### (A) cardiovascular effects



##### (B) haemostatic effects

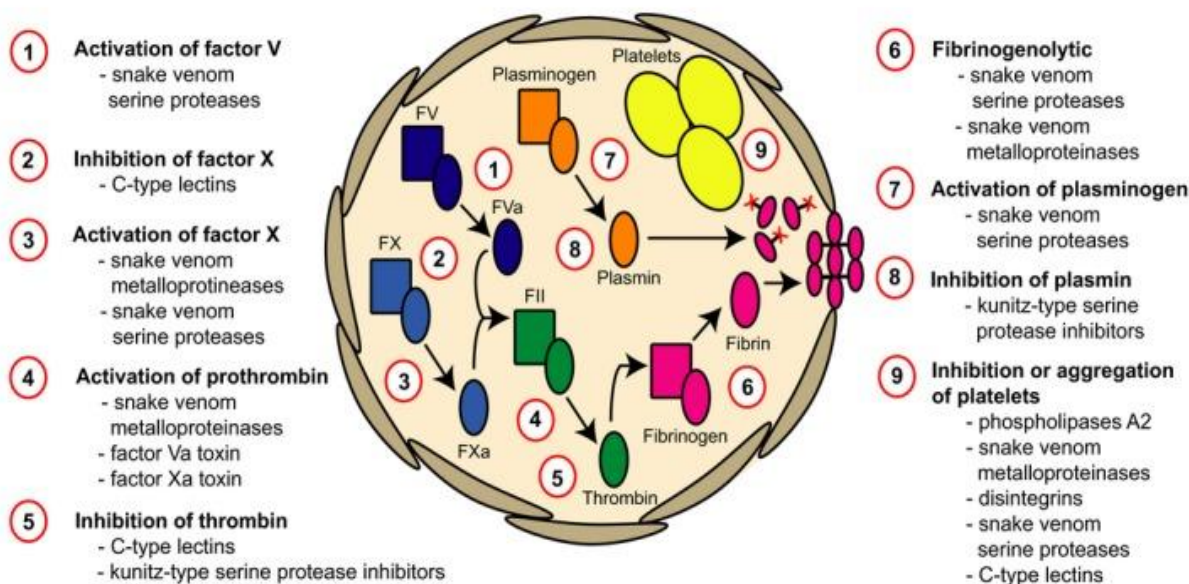


Figure 4.

A schematic overview of the physiological targets of haemotoxic snake venom toxins. (A) The targets for venom toxins that cause cardiovascular effects, which present clinically as hypotension. (B) The targets for venom toxins that cause haemostatic effects, which present as coagulopathy. Each physiological target is indicated by a red circle and the venom toxin type(s) that target these sites are listed. ACE, angiotensin-converting enzyme; FV – Factor V; FVa, activated Factor V; FX, Factor X; FXa, activated Factor X; FII, prothrombin.

As described above, SVMMP toxins increase the vascular permeability of blood vessels by degrading capillary basement membranes, resulting in extravasation[6], and therefore these toxins also exert haemorrhagic activities (Fig 4A). While spontaneous systemic bleeding therefore contributes to deaths caused by shock (hypotension), snake venom is also responsible for causing fatalities via haemorrhage, particularly when intracranial bleeding occurs [9].

VICC(venom-induced consumption coagulopathy)is a state which often complicates haemorrhage caused by snake venom in patients presenting with blood clotting disturbances). VICC, a disseminated intravascular coagulation (DIC)-like syndrome, is characterised by low or undetectable levels of fibrinogen, resulting in incoagulable blood [10,11]. However, unlike DIC, VICC does not usually result in systemic microthrombi and end-organ failure and it presents with a rapid onset and resolution[10]. Although the majority of snakes known to cause VICC are vipers, certain elapid snakes from Australasia and colubrid and natricine snakes from Africa and Asia have also been reported to cause consumptive coagulopathies via the action of their procoagulant toxins[11]. These toxins are diverse and include SVMMPs, SVSPs and toxic forms of Factor X and Factor V[7,12,13]. The targets for these toxins are also varied, with many activating clotting factors found towards the end of the clotting cascade, such as Factor X and prothrombin, while others are fibrinogenolytic (Fig 4B) [11,13].

Many of the countries where snakebite is abundant rely on simple bedside tests to detect incoagulable blood (e.g. the 20-min- whole blood clotting test),but a number of studies have demonstrated that patients suffering from VICC present with a prolonged prothrombin time (PT), and an international normalised ratio and activated partial thromboplastin time (aPTT) that are either very high or exceed the upper limits of detection [14]. Finally, many snake venom toxins are known to act on platelets. C-type lectins, disintegrins and certain metalloproteinases, to name a few, are capable of either inducing the aggregation of platelets, for example by von Willebrand factor- or collagen-mediated activation, or inhibiting their aggregation, by potently blocking integrin receptors found on the surface of platelets, such as  $\alpha_2\beta_3$  [13,15,16]. Both inhibition and activation (via hypoaggregation) result in these toxins contributing to venom-induced coagulopathies by depleting platelets, and this presents clinically as marked thrombocytopenia [15,17,18].

In our study, the maximum incidence of snakebite occurred between 6:00 PM to midnight (30%), followed by midnight to 6:00 AM (24%). This is mostly because of accidental stepping on the snake. Similar studies conducted in other parts of country showed relatively higher incidence of snake bitten cases between 6:00 PM and midnight [9, 16] as found in our study.

Nearly half of the victims were admitted to the hospital within 6 hours of snake bite. The location of hospital and the means of transportation serve as the main limiting factor apart from the usual treatment from quacks for delay in arrival at hospital.

Different studies have reported mortality rate ranging from 3% to 20%[4,19,20]. It has been found many contributors to death- Delay in arriving the hospital [19,20]. Sharma et al.; [21] found that median bite to hospital time in their study group was 9 hrs and delayed arrival was seen in patients presenting with ARF. Kalantri et al.; [22] studied 277 patients , in whom mean bite to hospital time was 6.5+10.3 hrs .In survivors it was 5,6 +10.3 hrs and in no survivors it was 11.4+14.5 hrs. Sanjib K Sharma et al.; [23] wrote in their study that simple educational messages and promotion of immediate and rapid transport of victims to a treatment center by motor cycle volunteers decreased the mortality rate and incidence of snakebite in southeastern Nepal. In particular the use of a motorcycle to transport the victim was strongly associated with survival. Suchithra N et al.; [24] stated in their study of Snakebite envenoming in Kerala, South India; Clinical profile and factors involved in adverse outcomes: Those who received ASV early (bite to needle time < 6hrs) had more severe local envenoming than those who received ASV late (bite to needle time > 6 hrs), but latter group were more likely to suffer complication and those who received ASV late had a higher risk of developing acute renal failure. Higher rates of complications were seen in those with severe coagulopathy, leucocytosis and those who received ASV late.

Majority of the studies observed this correlation between bite to hospital and complication and mortality. The incidence of complication is directly proportional to duration of venom in the blood prior to neutralization by ASV, due to lack of awareness of hazards of snake bite, belief in traditional treatment and lack of transport facilities [25].

## V. Conclusion

The geo-climatic diversity of snake species and the varied manifestations of snake bite from remote parts of the world are unknown to many toxicologists. Hemotoxic envenomations, which are more common from southern part of India and the snakes from these regions are less explored. *Hypnale Hypnale* and *Trimeresurus malabaricus* are two species which are mystifying to this region and has no antivenom to neutralize the toxins till date.

Haemotoxins from snakes exhibit diverse functionalities that can result in haemorrhagic, coagulopathic and/or hypotensive pathology in snakebite victims. The different hemotoxins act in a synergistic manner to upset the normal body homeostasis. While useful to catch the prey, these toxins can be lethal to humans during snake bite. Hence, a further understanding of the bioactivity of the toxins and the variation from one species to another is essential to design the next step in the management of snakebite.

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