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Systematic Review / Meta-analysis

Determinants of snakebite mortality in Asia: A systematic review

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ABSTRACT

Purpose: This systemic review summarizes the evidence exploring the determinants of mortality due to snakebite envenomation in Asia.

Materials and methods: The database PubMed, Web of Science and Science Direct were searched to identify the relevant literatures concerning mortality due to snakebites mortality in Asia. All the articles chosen were critically appraised for its quality using a mixed-method assessment tool by two independent reviewers with discrepancies sorted by a third person.

Results: A total of 7 studies were included in the final analysis which was 3 cross-sectional studies, 2 case reports, 1 observation prospective study and 1 randomized control trial study. Two studies were conducted in India and two studies in Sri Lanka while one study was conducted in Taiwan, Vietnam and Nepal respectively. The cases of snakebite victims were retrieved from the year of 1987 until 2017. In total, there were 762 cases of snakebite victims recorded, with 61 of those victims succumbed to death. From the final total of 7 studies, 4 of the studies showed snakebites mortality were related to delayed treatment access and 3 studies due to suboptimal care.

Conclusion: Mortality and morbidity can be reduced if there is a quick access for victims to emergency medical care, rapid transfer time to hospital and receiving immediate optimal medical treatment from trained medical staff once in the hospital or dispensary.

1. Introduction

Death from snakebite envenoming is one of the neglected tropical diseases issues in public health. Alarmingly, the World Health Organisation (WHO) reported 81,000 to 138,000 deaths, ranging from 1.8 million to 2.7 million snakebite envenoming cases per year in South Asia, South-East Asia and African countries in 2016 [1]. It is difficult to estimate the true prevalence of snakebite envenoming because the majority of the cases happened among people living in remote and rural areas of low- and middle-income countries such as farmers or those working in the agricultural sector. They often have limited options in seeking health care and may have poor health-seeking behaviour which can result in under-reporting and uncertainty of the outcomes of the incidents [2].

The effects of snakebite can be devastating where it is estimated that 400,000 people a year who survived the envenomation would suffer permanent disabilities such as blindness, extensive scarring and contractures, restricted mobility and amputation as a result of snakebite envenoming [3]. These morbidities would impair their functions to work for a living which may lead to increased socio-economic difficulties among the affected families and communities. Studies have shown that there is an association between low socioeconomic status with a high incidence of mortality from snakebite envenoming [4]. Thus, policies should be looked at improving access to healthcare facilities, providing appropriate numbers of anti-venoms and social support for affected families. Education and campaigns on the danger of snakebite should be targeting the vulnerable communities which include rural hunter-gatherers, agricultural workers, working children

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and families living in poorly constructed housing [5]. This can be done through appropriate actions from the governments involved and their health agencies.

Snakebite is an important medical emergency and a common cause of admission to hospitals. Delayed treatment and suboptimal care of snakebite victims may lead to morbidity and mortality [6]. Mortality and morbidity can be reduced if there is a quick access for victims to emergency medical care, rapid transfer time to hospital and receiving immediate optimal medical treatment from trained medical staff once in the hospital or dispensary. Even though not all hospitals have antivenom in stocks, a timely with efficient emergency and acute care of snakebite patients would help preserve the lives of victims. Therefore, administration of first aid is important to slow the progress of envenomation in a patient. According to Guidelines for the Management of Snakebites published by WHO, it is recommended for first-aiders to give reassurance, apply a pressure-pad over the bite wound, immobilize the bitten limb and transport the patient to a safer place or straight to hospital to receive medical care without delay [7]. By educating people on the danger of snake venom and on how to do first aid, they would be able to save the snakebite victims' lives.

Management of snakebite patients in hospitals involves the diagnosis of the species of snake responsible for the bite and availability of antivenom, which is the species-specific hyperimmune immunoglobulin. The snake can be identified by experts from the dead snake or photos of the snake taken by bystanders. It can also be done through inference from the resulting clinical syndrome of envenoming the patients [7]. Some venoms may cause haemorrhagic manifestations that may lead to unstoppable bleeding or neurologic signs like gradual unconsciousness of the patients. Constant monitoring is needed to observe the progression of the symptoms. The best treatment is anti-venom that has been recognised by WHO which is live-saving, and it is the only effective antidote for envenoming. However, due to the issue of cost and availability of anti-venom, it is only recommended to be used in patients with signs of systemic and or severe local envenoming in whom the benefits of treatment outweigh the risk of anti-venom reactions. Plus, the issues of design, safety profile, dosage and effectiveness need to be addressed to ensure better policy on anti-venom production and distribution to healthcare providers to prevent snakebite mortality.

Considering the urgency and importance of preventing death from snakebite envenomation, many studies were conducted to determine the causes and investigated the best way to prevent it. Thus, the objective of this study is to conduct a systematic review of snakebite envenoming in Asia and to specifically explore the determinants of mortality due to snakebite.

2. Methods

2.1. Search strategy

The systematic review was conducted from 14th until October 18, 2019 to search for published articles regarding mortality due to snakebite envenomation in Asia. The search engines used were PubMed, Web of Science and Science Direct. Following keywords: [("snakebite" OR "envenomation") AND ("mortality" OR "deaths") (AND "Asia")] were used to retrieve all the relevant articles. There was no language restriction applied during the searching process. Two authors reviewed all the search results to identify the needed articles with regards to determinants of snakebite mortality. After all the articles were identified, each of the authors screened all the selected titles and abstracts for eligibility. Only available full articles were chosen. Should there be any disagreement, a consensus was reached after discussion with the third author.

2.2. Inclusion and exclusion criteria

The target population for this search was all the victims of snakebite who did not survive the envenomation and died. The inclusion criteria are all original articles including case reports, case series and all reported cases in 48 countries in Asia [8]. Exclusion criteria for this systematic review include non-English articles, cases of snakebites envenomation which does not report any mortality and domestic animal cases of snakebite envenomation.

2.3. Operational definition

Determinants of snakebite mortality are broadly classified into 2 different groups which are delayed treatment access and suboptimal care [6]. Delayed treatment access could be fatal especially if the delay is more than 6 h. The reasons behind the delay were subjected to victims visiting faith healers for initial treatment, poor connectivity with inadequate transport, shortage of attending doctors, medical assistants, antivenom and supportive care leading to delay in the referral process and delayed diagnosis [6]. Suboptimal care could be another group that contributes to high snakebite mortality. The reasons under suboptimal care include inadequate knowledge of snakebite management, ineffective antivenom due to inadequate knowledge regarding snake species and suboptimal supportive care in the rural and urban area [6].

2.4. Data extraction tool

All researchers independently extract the information for each article chosen into an excel sheet data. The data entered into the sheet include (a) Number, (b) Authors, (c) Study design, (d) Country involved, (e) Number of victims, (f) Number of deaths, (g) Determinants of mortality, (h) Snake species and (i) Comments.

2.5. Quality assessment tool

All the articles chosen were critically appraised for its quality using a mixed-method assessment tool (MMAT version 2018) by two independent reviewers. This tool has been shown to be useful in systematic review encompassing different study designs [9]. Any discrepancy about the quality was then reviewed by a third person.

3. Results

3.1. Study selection

The selection of articles to be included in the study is displayed in Fig. 1. There were a total of 38 articles found through all the three search engines. There were 6 duplicated articles and therefore were removed. After the screening of titles, abstracts and full-text assessment of selected articles, a total of 25 articles were excluded. The final number of articles selected for this study was 7 articles (Table 1).

The reasons for excluding all of the other 25 articles include outcome measures (15 articles), ineligible study population (1 article), studies not conducted in Asia (7 articles) and the remaining 2 articles were review articles.

3.2. Description of studies

A total of 7 studies were included in the analysis. They consisted of 3 cross-sectional studies, 2 case reports, 1 observation prospective study and 1 randomized control trial. The studies were conducted in India (2 articles) Sri Lanka (2 articles), Taiwan (1 article), Vietnam (1 article) and Nepal (1 article). The cases of snakebite victims were retrieved from the year 1987 until 2017. In total, there were 762 cases of snakebite victims recorded with 61 victims succumbed to death. In summary, 4 of the studies (57.1%) were due to delayed treatment access and 3 of the studies (42.9%) were due to suboptimal care. The snake species identified from all the seven studies were *Malayan Krait, Daboia Russelli Siamensis, Bungarus Caeruleus, Naja Naja, Bungarus Lividus* and *Hypnale*

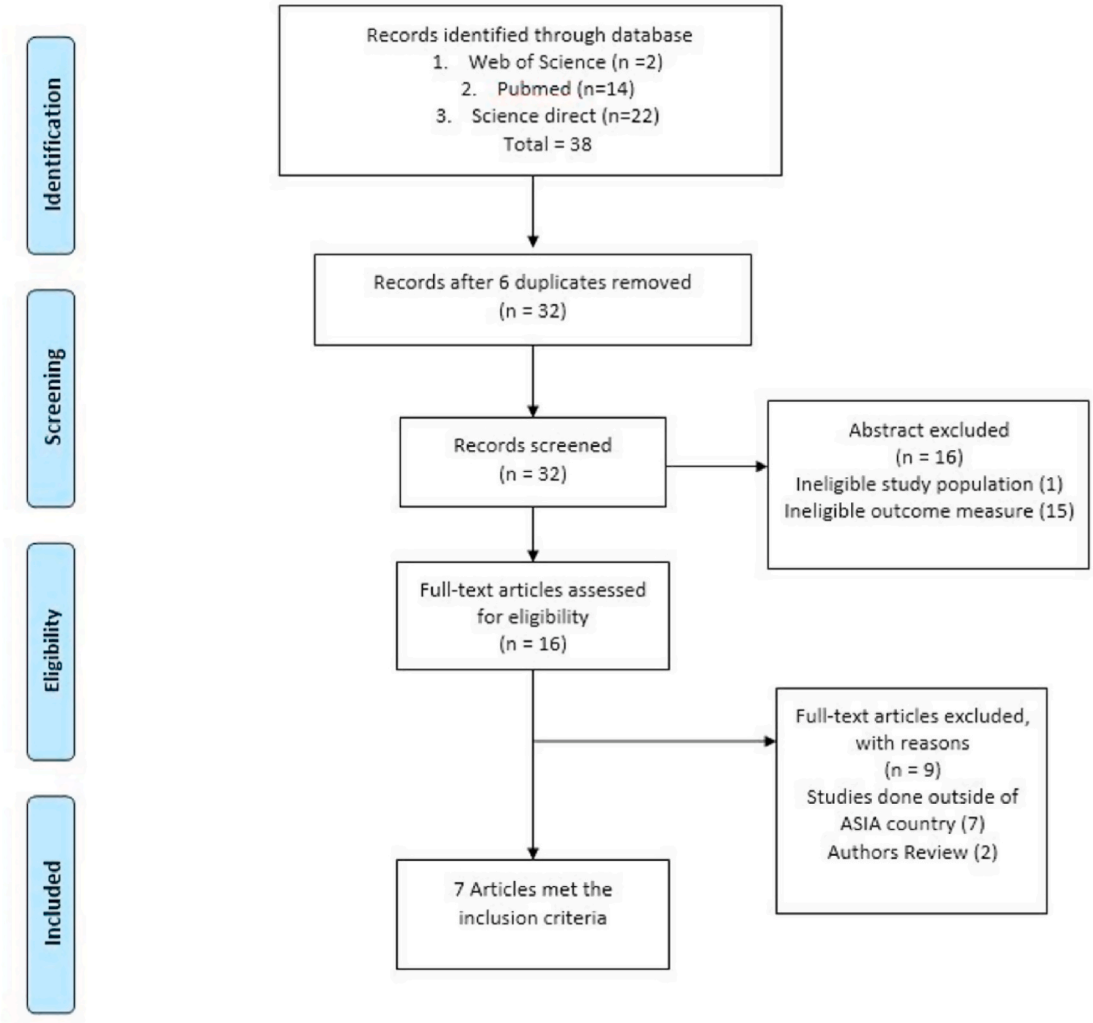

Fig. 1. PRISMA diagram flow.

Table 1
Determinants of snakebite mortality in selected Asian countries.

Countries	Years	Study designs	No of victims	No of deaths	Snake species	Determinants of mortality	References
Vietnam	2017	Cross Sectional	31	1	*Malayan Krait*	Delayed Treatment Access	Blessman et al., 2018
Taiwan	1987–1999	Cross Sectional (Retrospective clinical case analysis)	18	3	*Daboia russelli siamensis*	Delayed Treatment Access	Hung et al., 2002
India	2001	Observational Prospective Study	37	12	*Bungarus caeruleus, Naja naja*	Delayed Treatment Access	Bawaksar et al., 2004
India	1997–2007	Retrospective chart review/cross sectional	533	40	*Daboia russelii, Naja naja and Bungarus caeruleus*	Delayed Treatment Access	David et al., 2012
Nepal	2004	Case Report	1	1	*Bungarus Lividus*	Suboptimal Care	Kuch et al., 2011
Sri Lanka	2008	Case Report	1	1	*Hypnale zara*	Suboptimal Care	Maduwage et al., 2016
Sri Lanka	2012–2015	Randomized Control Trails	141	3	*Daboia russelli siamensis*	Suboptimal Care	Isbister et al., 2017

Zara.

3.3. Delayed treatment access

A study done in three different regions in Thua Thien Hue Province in Central Vietnam regarding the incidence of snakebites envenomation showed out of 31 victims of snakebite, one victim died [10]. The victim was a 2 years old child bitten by *Malayan Krait* snake in a mountain. Due to the geographic location of which the child was bitten in the mountain where the child lives, it took quite some time to reach the hospital to get proper treatment. The same situation also occurred in India in which the victim died on the way to the hospital due to poor access to nearest hospital [11].

A study done in Taiwan showed out of 18 victims of snakebite envenomation, 3 of them died [12]. The reason for the mortality was due to delayed treatment access which includes lacking medical facilities

and inadequate antivenom. The author mentioned that the region in Taiwan is indeed lacking medical facilities. A retrospective chart review was done in 533 victims of snakebite in India, showed that pre-hospital delay for more than 24 h has caused 18% of mortality compared to those who were hospitalized within a specified period with just 5% of mortality [13].

3.4. Suboptimal care

A randomized control trial was done in Sri Lanka among snakebite victims in which the experimental group was given high dose antivenom compared to the control group which was given low dose antivenom [14]. Among 141 victims enrolled, 3 victims from low dose antivenom group died and it was due to suboptimal care in which all the patients developed complication post envenomation.

A case report was conducted in Sri Lanka showed a 47-year-old farmer died post snakebite envenomation due to suboptimal care [15]. In this case, he was initially not given any antivenom because the doctor was mistaken this case as for a harmless snake. Inadequate knowledge of snakebite management led to this death. Another similar case report reported in Sri Lanka showed inadequate knowledge of snakebite management has led to a case of mortality [16].

4. Discussion

In Asia, it is documented that up to 2 million victims were envenomed by snakes each year; most of them were women, children, and farmers of poor rural communities in low- and middle-income countries. Of which, these countries have poor health systems and medical resources were scarce. Compared to other serious diseases worldwide, snakebite envenomation has a highly effective treatment. Therefore, deaths and other serious complications following snakebites envenomation are highly preventable should we have safe and effective antivenom which are readily available and accessible [4].

Delayed treatment access is the highest cause of death, especially in India [13]. It is known that the most vulnerable community to the exposure often live far from reliable and effective medical service that treats snakebites [17]. Apart from the issue of distance, travelling cost is also a factor that causes delays in treatment [18]. Cultural and religious beliefs also contribute to the reason for the delay in treatment. A significant number of cases in remote areas did not seek medical attention due to the perception that the bite is a manifestation of witchcraft or deity displeasure and medical treatment won't resolve the problem [19]. Practise of seeking treatment from traditional healers might also contribute to mortality. Popular traditional treatments include chanting, incisions, attempts to suck venom from the bite site, and the application of herbal medicine or snake stones [19].

The practice of seeking treatment from traditional healers will lead to suboptimal care and eventually death. Victims were usually left in agony for days before being sent to the medical facility and often arrived in the state of neuroparalytic [20]. However, if patients did receive early medical attention from qualified professionals, it was reported that many doctors were unable to recognize systemic signs of envenoming. Snakebite victims seeking treatment at primary health centres ended up receiving inadequate doses of antivenom [19]. This suggests that improving the knowledge of caregivers at all levels of the health system is a challenge of paramount importance and great urgency in both rural and urban hospitals.

Antivenoms used in the treatment of snakebite are not free from scrutiny. Although they have been proven in scientific studies, their effectiveness very much depending on the region that they were developed. Antivenoms widely used in India, are mostly produced from the snakes in the state of Tamil Nadu. This antivenom is less potent for the treatment of Russell's viper in Sri Lanka [21]. It was reported that the commonly used antivenoms in South Asia had never undergone any independent clinical trial [19]. Cases of adverse effect from the usage such as anaphylactoid or pyrogenic reactions, or late serum sickness were reported in up to 80% of the patients treated [19]. Most of the time, snakebite happened in the most rural area among the poorest of poor people [22]. The reason for the shortage of antivenoms in the specific area was due to the fact that the antivenoms manufactured did not bring profit to the manufacturer and proved to be costly [23].

There are a few limitations identified in this study. Firstly, the searched articles only yielded 32 articles despite extensive search done within the Asia countries. Of all 48 Asian countries, only 5 countries were included. The result might not be able to capture all the cases of mortality snakebite envenomation that happened in the region. Another limitation is that the keywords used in the searching method might not capture the bigger picture of mortality due to snakebite envenomation.

In conclusion, mortality following snakebite envenomation could be prevented and complication post envenomation could be significantly reduced if access to treatment is improved and optimal care provided to the victims. Health practitioners should be well equipped regarding information of snakebite so that efficient and effective treatment could be delivered in reducing mortality and morbidity post-snakebite envenomation. In future, large, representative, community-based epidemiological studies should be conducted to estimate the true burden of snakebite morbidity and mortality. In addition to that, well-designed clinical trials to establish safety, efficacy, and optimal dose of antivenom should be conducted to provide the best treatment outcome for patients.

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Provenance and peer review

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Declaration of competing interest

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Ethical approval

Ethical approval is not required.

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Author contribution

WAHWI wrote the manuscript.
MFA involved in data collection.
MIA analysed the data.
SSSAR supervised the study progress.
MSJ provided the expert opinion.
ZIA provided the study concept.
FH became the correspondence and dealt with the journal matters.
MRH provided the study design and final review.

Registration of research studies

Not related.

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Consent

Consents are not required.

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Appendix A. Supplementary data

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