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Review

Snakebite envenomings in the Republic of Korea from the 1970s to the 2020s: A review

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ABSTRACT

Snakebite envenomings remain a neglected disease across the globe causing severe injuries and death. An understanding of regional snakebite patterns is a necessary prerequisite for public health programs aimed at reducing snakebite risks. However, such regional knowledge is poorly documented or lacking in many countries where the risk of snakebite envenomings receive little medical attention, and the Republic of Korea is one of these countries. Here, we reviewed the literature on snakebites published between 1970 and 2020 as well as public healthcare data recorded between 2010 and 2019 to determine the patterns of snakebite envenomings in the Republic of Korea. Our results, based on literature data, show Gangwon province as a hotspot of snakebite occurrences and identify middle-aged males living in rural areas as the demographic group at highest risk of venomous snakebites. We also highlight major limitations for further understanding snakebite patterns in the country, most notably the lack of proper species identification for snakes and conflicting patterns of envenomings revealed by different sources of data. Our study provides baseline information on venomous snakebites occurring in the Republic of Korea, thereby filling a gap in the knowledge of snakebite trends in the country.

1. Introduction

Snakebite envenoming is a serious worldwide public health issue. Worldwide, approximately 5.4 million people are bitten by venomous snakes annually with up to 2.7. million envenomings and 138,000 fatalities (WHO, 2019). Even when treated, venomous snakebites may lead to permanent physical and psychological trauma (Habib and Brown, 2018; WHO, 2019). The widespread impact and threat raised by snakebite envenoming was reflected in the 2017 decision of the World Health Organization to re-include snakebite envenoming on the list of the Neglected Tropical Diseases (Chippaux, 2017).

Despite such medical importance, information on key patterns of snakebite envenomings is still limited or lacking for many countries, notably where snakebite envenomings have received little medical attention. For example, patterns of snakebites in northern Asian countries are relatively poorly documented compared to Southeast Asian countries where the annual rate of snakebite envenomings is much higher (Chippaux, 1998). Therefore, such countries with poor documentation represent "knowledge gaps" in snakebite envenoming, and accurate estimations of snakebite burden both at local and global scales are hindered by such knowledge gaps (Chippaux, 1998; Kasturiratne et al., 2008).

In this study, we highlight the Republic of Korea (hereafter South Korea) as one such knowledge gap. The country is home to nine species of venomous snakes (Orlov and Barabanov, 1999; Lee et al., 2012; The Korean Society of Herpetologists, 2018, Fig. 1). The venomous snake fauna includes three Pitvipers: *Gloydius brevicaudus, G. intermedius, G. ussuriensis* (Viperidae: Crotalinae); Tiger keelbacks, *Rhabdophis tigrinus* (Natricidae); and five marine species (Elapidae). Many of these species are considered medically important to humans because they are widespread, live close to human habitations, and their venoms are used widely in clinical research (Silva, 2013; WHO, 2016). However, no national census of snakebite envenomings has been made for the country, and research on snakebites in South Korea is largely limited to isolated case reports and retrospective clinical reviews of relatively short-term (<10 years) records. Moreover, as such studies are published by only a small number of medical institutions (Shin et al., 1984; Jin et al., 2008; Lee et al., 2011; Kang et al., 2014; Senek et al., 2019), generally written

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in Korean and published in Korean journals, information on snakebite envenomings in South Korea has not been widely disseminated to the global research community. In fact, South Korea is one of only two countries (the other being the Democratic People's Republic of Korea) in Northeast Asia where information on snakebites has not been readily available to researchers in other countries. This was made evident in studies of global snakebite epidemiology where South Korea appears as data deficient (Kasturiratne et al., 2008; Harrison et al., 2009). These factors combined have prevented a detailed understanding of snakebite trends in the country.

In order to better estimate the global snakebite burden in the future, it is important to incorporate information from countries where snakebite data has been under-represented. To this end, a review of the literature and the synthesis of information on snakebite patterns in South Korea are needed. In this study, we reviewed the literature and public health data published between 1970 and 2020, representing the broadest time span utilized for such study conducted in South Korea. We also present the broad patterns of snakebite envenomings in the country resulting from the review of the literature and a public health database, and provide a brief review of envenomings by major groups of venomous snakes in South Korea. By providing baseline information on snakebite envenomings in South Korea, our study aims to fill in the gap of knowledge that is critical for guiding future public health programs.

2. Methods

2.1. Literature search

We collected published literature on the epidemiology, case reports and clinical studies on snakebite envenomings in South Korea. Our search was conducted using Google Scholar and Kangwon National University library with the following key words (both in English and in Korean): 'venomous snakebite Korea', *'Gloydius', 'Agkistrodon', 'Gloydius ussuriensis', 'Gloydius brevicaudus', 'Gloydius intermedius', 'Gloydius saxatilis'*, 'mamushi bite', *'Rhabdophis tigrinus', 'Natrix tigrinus', 'Laticauda', 'Hydrophis', 'Pelamis'*, 'sea snake bite' 'snakebite antivenom', and 'snakebite epidemiology'. We used the last two keywords to incorporate a broader scope of information regarding snakebites in South Korea.

2.2. Literature review

Our literature search resulted in a total of 58 papers including case reports, clinical reviews, epidemiological and clinical research on snakebite envenomings in South Korea. We excluded some literature based on the following criteria: 1) studies that used potentially duplicate data from the same source (e.g. records from the same hospital), in which case we used the most recent one to extract the data as it encompasses all the previous records but also contained new ones; 2) studies with partially overlapping study periods, in which case, we chose

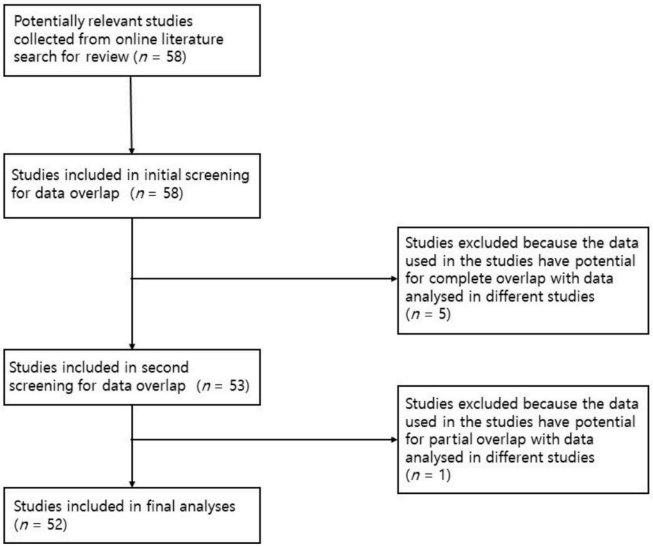

Fig. 2. Literature selection flow diagram. See Table 1 for the list publications used in the review. Literature search was conducted through Google Scholar and Kangwon National University Library.

Fig. 1. Terrestrial venomous snakes of South Korea. (A): Tiger keelback (*Rhabdophis tigrinus*) is generally inoffensive but has been known to be capable of inflicting fatal bites. (B): Ussuri pitviper (*Gloydius ussuriensis*). This species is commonly found throughout the country, including several offshore islands. (C): Rock pitviper (*Gloydius intermedius*). This species inhabits high altitude forests of South Korea and rarely comes into contact with people. (D): Short-tailed pitviper (*Gloydius brevicaudus*) is distinguished from *G. ussuriensis* by its black tongue. Photographs by Hyun-Tae Kim.

the papers with the broadest time span to utilize full data from institutions without causing redundancy (Fig. 2). These exclusions resulted in a total of 52 papers for subsequent literature review (Table 1).

We extracted the following information from the literature: 1) Geographical provinces, subdivided into nine provinces of South Korea. In order to have minimum provincial divisions without affecting data interpretation, we included Seoul and Incheon into Gyeonggi province, Sejong and Daejeon into South Chungcheong province, Daegu into North Gyeongsang province, Busan and Ulsan into South Gyeongsang province, and Gwangju into South Jeolla province. In cases where the exact locations were difficult to ascertain, we used the authors' institutions, where patients received treatment, to approximate provincial locations. We assumed that people who got bitten by venomous snakes would not travel great distances to receive treatment. 2) Age, divided into categories such as under 10, 10s, 20s, 30s, 40s, 50s, 60s, and over 70 years old. 3) Gender, divided into males, females, and unknown. 4) Body part bitten, divided into hand, foot, arm, leg and face categories. 5) Seasonal variation, we divided a year into three periods of equal length (January–April, May–August, September–December) and each datapoint was assigned to one period. A four month period was used as it enabled the use of the largest number of datapoints without being too general, although snakebites are unlikely to occur during winter months (November–February) when snakes hibernate. 6) Habitat, divided into five categories: agricultural area, mountain, residential area, and river, characterizing major habitat areas of venomous snakes. 7) Snake species, divided into three major groups of Korean venomous snakes (*Gloydius, Rhabdophis*, marine snakes), and an unknown category.

As a separate source of data, we extracted snakebite envenoming records from the Healthcare Bigdata Hub (healthcare database hereafter) of the Health Insurance Review & Assessment Service (https://opendata.hira.or.kr/home.do; accessed February 13, 2021). This is a national database providing various types of medical statistics and publicly available data. We searched for snakebite occurrence records using the code T631 (toxic effects of reptile venoms) under the Korean Standard Classification of Diseases. As all venomous reptiles native to South Korea are snakes, we treated all data entries as snakebite

Table 1
Summary of the literature used for each dataset used in the analyses (○ = literature included in analyses; X = literature excluded from analyses).

	Gender	Age	Species	Provinces	Body part	Habitat type	Seasons
Ahn et al. (2007)	○	○	○	○	○	○	○
Ari (2001)	○	○	○	○	○	○	○
Baek et al. (2017)	○	○	○	○	○	○	○
Cha et al. (2018)	○	○	○	○	○	○	○
Cho and Park (1996)	○	○	○	○	○	○	○
Cho et al. (2004)	○	○	○	○	○	○	○
Choi et al. (1991)	○	○	○	○	○	○	○
Han (1981)	○	○	○	○	○	○	○
Hwang et al. (1991)	X	X	○	○	○	○	○
Jang et al. (1996)	○	○	○	○	○	○	○
Jang et al. (2011)	○	○	○	○	○	○	○
Jin et al. (2008)	○	○	○	○	○	○	○
Kang et al. (2014)	○	○	○	○	○	○	○
Kang et al. (2016)	○	○	○	○	○	○	○
Kim and Choi (2000)	○	○	○	○	○	○	○
Kim and Kim (1986)	○	○	○	○	○	○	○
Kim and Kim (1989)	X	X	○	○	○	○	○
Kim et al. (1992)	X	X	○	○	○	○	○
Kim et al. (1994)	○	○	○	○	○	○	○
Kim et al. (1995)	○	○	○	○	○	○	○
Kim et al. (1995b)	○	○	○	○	○	○	○
Kim et al. (2006)	○	○	○	○	○	○	○
Kim et al. (2007)	○	○	○	○	○	○	○
Kim et al. (2008a)	○	○	○	○	○	○	○
Kim et al. (2008b)	○	○	○	○	○	○	○
Kim et al. (2009a)	○	○	○	○	○	○	○
Kim et al. (2009b)	○	○	○	○	○	○	○
Kim et al. (2009c)	○	○	○	○	○	○	○
Kwon et al. (1998)	○	○	○	○	○	○	○
Lee (2011)	○	○	○	○	○	○	○
Lee et al. (2001)	○	○	○	○	○	○	○
Lee et al. (2004)	○	○	○	○	○	○	○
Lee et al. (2006)	○	○	○	○	○	○	○
Lee et al. (2007)	○	○	○	○	○	○	○
Lee et al. (2009)	○	○	○	○	○	○	○
Lee et al. (2011)	○	○	○	○	○	○	○
Lim et al. (2004)	○	○	○	○	○	○	○
Moore (1977)	○	○	○	○	○	○	○
Nam et al. (1995)	○	○	○	○	○	○	○
Oh et al. (1982)	X	X	○	○	○	○	○
Paik and Son (1996)	○	○	○	○	○	○	○
Park et al. (2009a)	○	○	○	○	○	○	○
Park et al. (2009b)	○	X	X	○	X	X	X
Rha et al. (2015)	○	○	○	○	○	○	○
Lyu et al. (1991)	X	X	○	○	○	○	○
Ryu et al. (1996)	○	○	○	○	○	○	○
Senek et al. (2019)	X	X	X	○	X	X	X
Seo et al. (2014)	○	○	○	○	○	○	○
Shin et al. (1984)	○	○	○	○	○	○	○
Sohn et al. (2007)	○	○	○	○	○	○	○
Sung and Hah (1981)	○	○	○	○	○	○	○
Yoon et al. (1970)	○	○	○	○	○	○	○

envenomings. However, we could not rule out the possibility of envenomings inflicted by non-native venomous snakes and lizards (e.g., helodermatids) under captive settings, as detailed data on species identification and circumstantial context of envenomings were not provided by the database. We extracted data for monthly trends, yearly trends, geographical provinces, age, and gender collected from 2010 to 2019. We used the same geographical subdivisions, gender, and age classes as used for the data extracted from the literature. Data for snake species, affected body parts, and habitat were not available from this database. We treated literature and healthcare data separately because we were unable to determine the degree of overlap between these two datasets.

In addition, we accessed the World Health Organization mortality database (WHO Cause of Death Query online) to retrieve annual snakebite mortality records from South Korea. We used version 10 of the International Statistical Classification of Diseases and Health Problems (ICD10) only because there was no code specifying snakebite envenoming as a cause of death under ICD9. Therefore, the diagnosis code we used to extract data was X20 (contact with venomous snakes and lizards) under ICD10. Since there are no native venomous lizards in South Korea all mortalities were attributed to venomous snakes. We obtained country data for all age groups (0–95+ and unknown ages) and all genders (male, female, unknown) to fully incorporate archived data. This process returned records from 1995 to 2015.

2.3. Statistical analyses

We conducted separate statistical analyses for the data extracted from the literature and healthcare database to generate broad patterns of snakebite envenomings in South Korea. However, due to the lack of traceability of these data, we created independent datasets for each data category and data source. Because the data was not normally distributed, we conducted Chi-square tests for every dataset except for snake species, for which we used a one-sample Binomial test.

Geographical variation. Data for geographical distribution of snakebite envenomings were extracted from 52 publications, resulting in a total of 3179 cases. There was only one datapoint for which provincial information was missing. The same category of data extracted from the healthcare database comprised of 1735 cases. *Age*. The data for age distributions were extracted from 45 publications, and the sample size was 929 cases. The same category of data extracted from the healthcare database comprised of 1832 cases. *Gender*. The data for gender were extracted from 46 publications for a total of 2078 cases, although excluding the number of unrecorded gender data brought down the final sample size down to 1903. The same category of data extracted from the healthcare database comprised of 1832 cases. *Body part*. The dataset was comprised of 1473 datapoints extracted from 50 publications. *Seasonal variation*. To assess seasonal variation of snakebite envenomings, we extracted data from 50 publications which resulted in 1195 datapoints. Also, using 1832 cases extracted from the healthcare database, we plotted monthly and annual trends of snakebite envenomings from 2010 to 2019. *Habitat*. To determine if snakebite envenomings were more prevalent in a specific type of habitat, we extracted 808 datapoints from 50 publications. *Snake species*. For this dataset, we initially extracted 3009 datapoints from 50 publications. Here, we only included two terrestrial venomous snake genera as no envenomings from marine species were identified during data collection. Species data was incomplete or lacking for the majority of available literature, and the genus-level identification was provided in 179 cases only. *Mortality*. Here, we analysed gender and age distribution of snakebite mortalities by extracting datapoints from the WHO mortality data. This dataset was composed of 101 datapoints. We also plotted the number of mortalities over time to visualize the annual trend of snakebite mortality. All statistical analyses and plotting were conducted in software R version 3.6.3 (R Core Team, 2020).

3. Results

Geographical variation. The analysis of regional variations using literature data showed that the majority of envenomings were recorded in eastern South Korea (968 in Gangwon, 632 in North Gyeongsang), followed by northern regions (485 in Gyeonggi, 408 in South Chungcheong), and followed by South Jeolla ($n = 562$), North Chungcheong ($n = 97$), Jeju ($n = 47$), and South Gyeongsang ($n = 26$) provinces. No envenomings were recorded in North Jeolla province. The number of envenomings was significantly different among regions (Chi-square test: $n = 3179$, $\chi^2 = 2015.3$, df = 7, $p < 0.001$; Fig. 3A). The analysis based on the healthcare database, however, showed a considerably different pattern from the analysis based on the literature data. While the number of envenomings was significantly different between regions (Chi-square test: $n = 1735$, $\chi2 = 1848$, df = 8, $p < 0.001$; Fig. 3B), the highest number of envenomings was recorded in Gyeonggi ($n = 693$), followed by South Jeolla ($n = 340$), North Gyeongsang ($n = 209$), South Gyeongsang ($n = 164$), Gangwon ($n = 105$), North Chungcheong ($n = 74$), South Chungcheong ($n = 64$), North Jeolla ($n = 43$), and Jeju ($n = 43$).

Age. The distribution of envenomings by age group for the 929 cases extracted from the literature was such that $n = 28$ for 0–10 years old, 72 for 10s, 90 for 20s, 103 for 30s, 180 for 40s, 226 for 50s, 168 for 60s and 62 for 70+ years old. The number of envenomings was significantly different between age groups, and the age group 50s received the highest number of bites (Chi-square test; $n = 929$, $\chi^2 = 278.50$, df = 7. $p < 0.001$; Fig. 4A). The age distribution of envenomings based on 1832 cases extracted from the healthcare database is as follows: $n = 393$ for 0–10 years old, 108 for 10s, 75 for 20s, 136 for 30s, 201 for 40s, 275 for 50s, 309 for 60s and 335 for 70+ years old. The number of envenomings was significantly different between age groups, and the age group 0–10 years old received the highest number of bites (Chi-square test; $\chi^2 = 412.39$, df = 7. $p < 0.001$; Fig. 7A).

Gender. For gender distribution among the 2078 cases of snakebite envenomings compiled from the literature, 720 were women (35%), 1183 were men (57%) and 175 were of unrecorded gender (8%). Men were bitten significantly more frequently than women (Chi-square test; $n = 1903$, $\chi^2 = 112.65$, df = 1, $p < 0.001$; Fig. 4B). In contrast, the number of envenomings between men ($n = 959$) and women ($n = 873$) was only slightly different among 1832 cases extracted from the healthcare database ($\chi2 = 4.0371$, df = 1, $p = 0.04$; Fig. 7C).

Body part. Out of the 3059 cases included in the analysis, 1586 cases were not assigned to a specific body part. For cases where bitten body parts were recorded, hands were bitten the most frequently ($n = 817$), followed by feet ($n = 381$), legs ($n = 164$), arms ($n = 107$) and faces ($n = 4$). The number of bites was significantly different among body parts (Chi-square test: $n = 1473$, $\chi^2 = 1415.7$, df = 4, $p < 0.001$; Fig. 4C).

Seasonal variation. Based on the data compiled from the literature, the highest number of envenomings was recorded between May and August (n = 942), followed by the period between September and December (n = 243) and the period between January and April (n = 10). The number of envenomings was significantly different between seasons (Chi-square test: $n = 1195$, $\chi2 = 1181.2$, df = 2, $p < 0.001$; Fig. 4D). In addition, the number of envenomings was also significantly different between months for 1832 cases extracted from the healthcare database (Chi-square test: $\chi2 = 2103.2$, df = 119, $p < 0.001$). Also, there were prominent peaks of envenoming cases between June and August (Fig. 6), coinciding with the active season of venomous snakes. The annual number of envenomings was also significantly different for the same number of cases extracted from the healthcare database (Chi-square test: $\chi2 = 214.53$, df = 9, $p < 0.001$ Fig. 7B). Both monthly and annual patterns of snakebite envenomings showed overall decreasing trends.

Habitat. Among 808 datapoints, most of the envenomings ($n = 524$) were recorded in agricultural areas, followed by mountains ($n = 228$), residential areas ($n = 53$) and rivers ($n = 3$). The difference among landscape types was significantly different (Chi-square test: $\chi^2 = 822.58$,

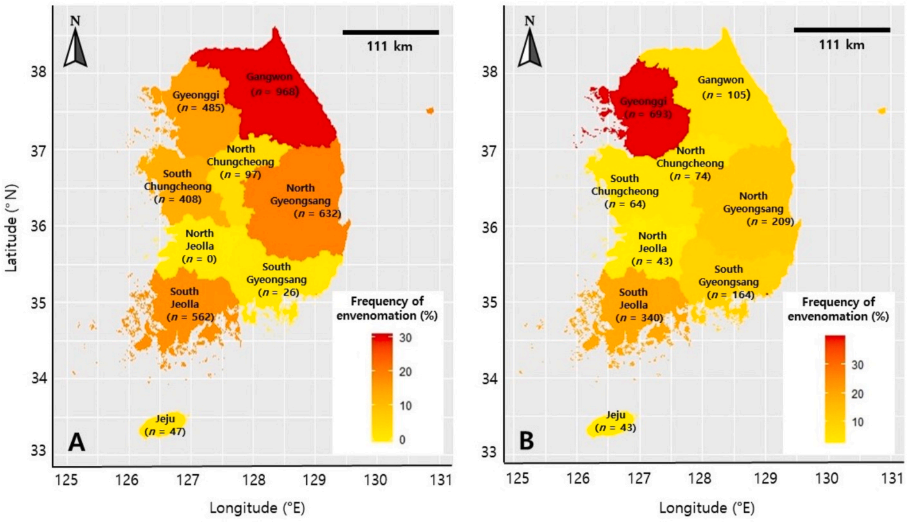

Fig. 3. Heatmap of snakebite frequency of South Korea between 1970 and 2020. Note the significant regional bias in snakebite occurrences. While the literature data (A) suggest Gangwon province (n = 968; in red) as a hotspot of snakebite envenomings, the healthcare data (B) suggest Gyeonggi province as a hotspot. This demonstrates conflicting results between datasets used to determine the patterns of snakebite envenomings in the country. Baekryeong island is omitted from the map but the omission does not affect data interpretation. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

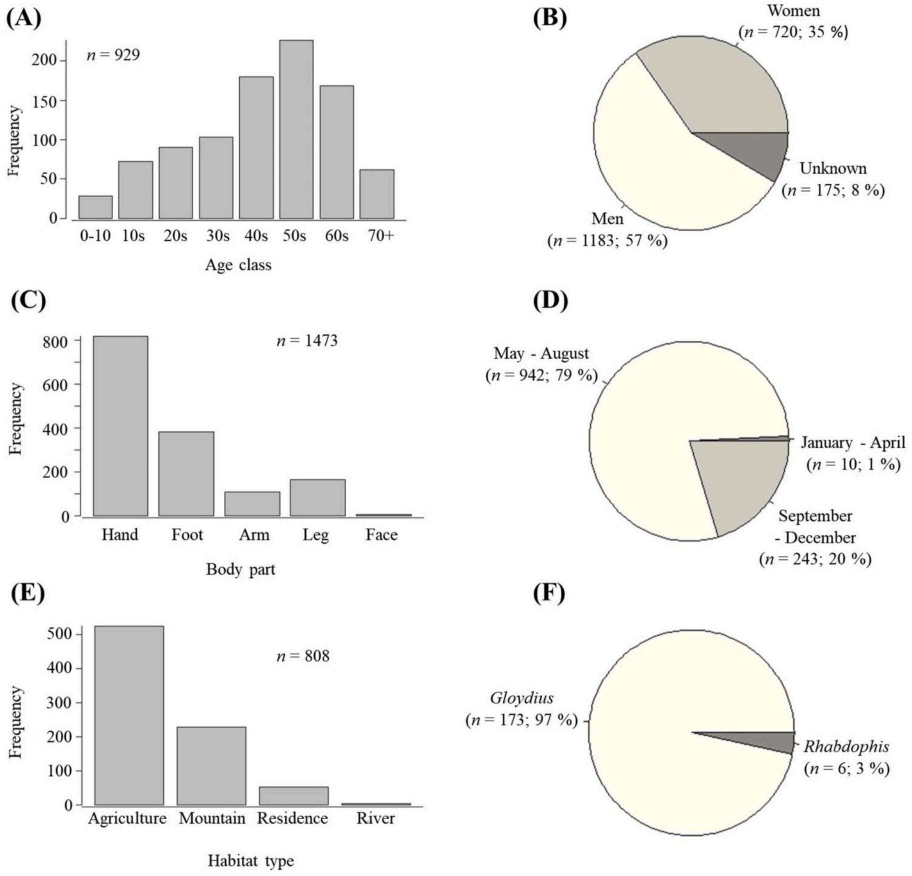

Fig. 4. General patterns of snakebite envenomings in South Korea between 1970 and 2020, based on literature data. (A): The number of people bitten was significantly different between age groups, and people in their 50s (n = 226) were bitten the most. (B): Gender distribution of snakebite. Men (n = 1183) were bitten significantly more than women (n = 720). (C): Body parts bitten by venomous snakes. Hands (n = 817) and feet (n = 381) were bitten significantly more than other body parts. (D): Occurrence of snakebites were significantly different between seasons. Most bites were recorded between May and August (n = 942). (E) Habitat types where snakebites occurred. Most bites were recorded in agricultural areas (n = 524) and mountains (n = 228). (F): Snake species responsible for envenomings. *Gloydius* (n = 173) were mostly responsible for bites in cases where snake species were identified.

df = 3, $p < 0.001$; Fig. 4E).

Snake species. Among the 179 cases for which genus-level identifications were available, 173 bites were assigned to *Gloydius* and six were assigned to *Rhabdophis tigrinus*. There was a significant difference between genera of venomous snakes involved in snakebite incidents (Binomial test rejecting the null hypothesis of an equal number of bites for each genus; $n = 179$, t = 173.00, SE = 6.69, $p < 0.001$; Fig. 4F).

Mortality. Among 101 people who died from snakebite envenomings during the 20-year period (1995–2015), 62 were men (61.4%) and 39 were women (38.6%; Chi-square test: $\chi^2 = 5.2376$, df = 1, $p < 0.05$; Fig. 5C). For age classes, the highest number of deaths was recorded in people aged 70+ ($n = 35$), followed by age classes 60s ($n = 24$), 50s ($n = 18$), 40s ($n = 13$), under 10 ($n = 6$), 10s ($n = 2$), 20s ($n = 2$), and 30s ($n = 1$). The number of deaths was significantly different among age classes (Chi-square test: $\chi^2 = 84.267$, df = 7, $p < 0.001$; Fig. 5A). Also, the number of snakebite mortalities showed a clear decreasing trend over the 20-year period (Fig. 5B).

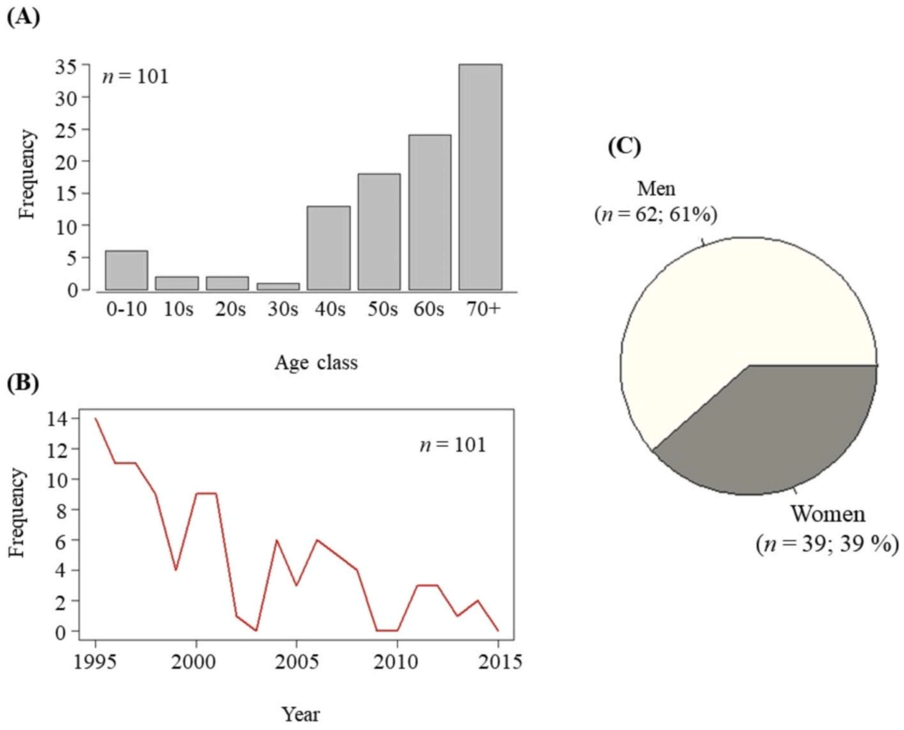

Fig. 5. Patterns of snakebite mortality in South Korea between 1995 and 2015 (n = 101), based on WHO mortality data. (A): Snakebite mortality was significantly different between age groups, with 70+ age group recording the highest number of deaths (n = 35). (B): Snakebite mortality trends in South Korea show a clear decreasing trend between 1995 and 2015. (C): Gender distribution of snakebite mortality. Men (n = 62) died significantly more from snake envenomings than women (n = 39).

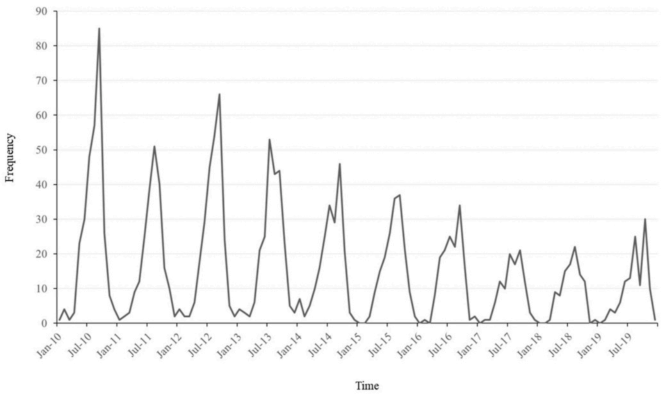

Fig. 6. Monthly patterns of snakebite envenomings in South Korea recorded from 2010 to 2019, based on healthcare data (n = 1832). The number of recorded envenomings differed significantly between months. The peaks of envenoming cases largely coincide with the active season of venomous snakes (May–September). The monthly patterns show an overall decreasing trend of snakebite envenomings.

4. Discussion

4.1. Broad patterns of snake envenomings in South Korea

4.1.1. Literature data

Geographical variations in snakebite envenomings based on literature data tentatively identify Gangwon province as the area with the highest occurrence of snakebites in South Korea (Fig. 3A), accounting for 30% of all cases compiled (but see section 4.1.2). This may be due to widespread rural areas in the province bringing humans and snakes into contact. Our results also show significant regional bias of snakebite occurrences in the country. The drastic differences in the number of snakebite cases in two adjacent provinces (especially between South and North Chungcheong, South and North Jeolla, and South and North Gyeongsang) are likely the result of unreported cases rather than actual demographic factors or population density of venomous snakes. The distribution map of Korean herpetofauna is also in line with this argument, which shows that the three most common venomous snake species (*G. ussuriensis, G. brevicaudus, and R. tigrinus*) have similarly widespread distributions throughout the mainland (Jang et al., 2016).

Regarding age groups, people in their 50s were affected the most, a pattern that is in contrast with that of the rural tropics where most victims are between 10 and 40 years old (Alirol et al., 2010; Kasturiratne et al., 2008). We attribute the age distribution patterns of victims in South Korea to the aging of rural communities (Nam et al., 1995; Kim and Choi, 2000). Our result shows that, for people over 40 years of age, there is a positive correlation between increasing age and the number of recorded mortalities. Meanwhile, there is a negative correlation between increasing age and the number of mortalities for people younger than 40 years old. This is a different pattern from the age distribution of overall snakebite occurrences, in which people in their 50s were bitten most frequently and people over 70 years old and people younger than ten were the least affected age groups. Our explanation for these patterns are the general differences in health conditions and subsequent reactions to snake venom and treatment in different age groups. Patients with poor previous health conditions are more likely to develop severe systemic symptoms which can lead to fatal outcomes (Feitosa et al., 2015). Thus, considering that people are more likely to suffer from chronic diseases as they age, people in their 40s and above are more likely to experience severe symptoms and mortality (Nam et al., 1995). Meanwhile, people under ten years old showed the highest mortality among people under 40 years old. This may be due to smaller body size relative to the amount of venom injected (Nam et al., 1995; Feitosa et al., 2015).

Our results demonstrate that men were bitten significantly more frequently by venomous snakes compared to women. This is likely because of men spending more time outdoors than women in rural areas of South Korea (e.g. plantation workers, collecting herbs, or hiking; Senek et al., 2019). The snakebite data from other countries also show that large number of victims were men bitten while involved in outdoor activities (Chang et al., 2007; Alirol et al., 2010; Rahman et al., 2010; Feitosa et al., 2015).

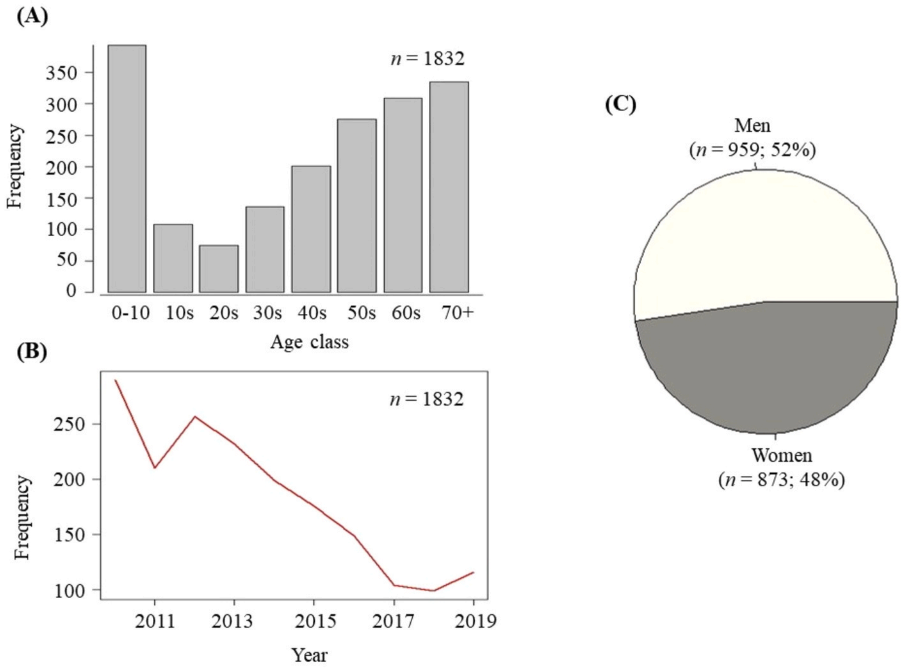

Fig. 7. Patterns of snakebite envenomings in South Korea based on healthcare data recorded from 2010 to 2019. (A) The number of envenomings was significantly different between age groups, and people under 10 years of age were bitten the most. (B) The number of recorded envenomings differed significantly between years, with a clear decreasing trend towards 2019. (C) The number of envenomings recorded for each gender class differed only slightly, with men bitten more frequently than women.

Considering that bite victims are people involved in outdoor activities, the pattern of bitten body parts is also explained in this context. Farmers and hikers can get bitten by snakes on hands and legs while doing manual work (e.g. cutting weeds), walking through bushes, and putting hands in or on crevices where snakes hide.

Seasonally, people were bitten most frequently between May and September, followed by October to December, and then January to April. Snakes are most active in the months between May and September because these are the warmest months in South Korea (Shim et al., 1998; Lee et al., 2012). Meanwhile, snakes start to search for hibernacula from early October, and in doing so they may come closer to agricultural and residential areas (Lee et al., 2012). Snakes emerge from hibernation in late March to early April and bask frequently to raise their body temperatures with increasing amounts of diurnal activities (Lee et al., 2012). Therefore, the ecology of venomous snakes may bring snakes in close contact with people during certain periods of the year, and this is consistent with seasonal patterns of snakebite occurrences in South Korea.

Most recorded bites have occurred in agricultural areas and mountains where victims were bitten while harvesting crops or hiking (Kwon et al., 1998; Kang et al., 2014). Species such as *Gloydius ussuriensis, G. brevicaudus, and Rhabdophis tigrinus* utilize rice paddies and areas adjacent to agricultural lands for foraging (Shim et al., 1998; Lee et al., 2012). Also, venomous snakes and farmers or hikers can come into contact in mountains as these are natural habitats of venomous snakes.

4.1.2. Healthcare data

Our analyses on the healthcare data are largely conflicting with the literature data, and we focus on discussing such conflicts between the datasets. The geographical variation of snakebite envenomings based on the healthcare data highlighted Gyeonggi province as a hotspot of envenomings instead of Gangwon province (Fig. 3B). This may result from the considerably shorter temporal coverage of the healthcare data (2010–2019) compared to the literature data (1970–2019). However, shorter time coverage alone cannot explain the conflicting patterns between the two datasets, as the number of envenomings for some provinces recorded by the healthcare data is comparable to (e.g., South Chungcheong and Jeju) or exceeding (e.g., North Jeolla and South Gyeongsang) the number recorded by the literature data. It is therefore possible that the hotspot of envenomation has shifted over time, between the 1970's and 2010's, supported by the sharp in increase in human population in Gyeonggi province, and a resulting higher probability of encountering wildlife.

Some possible reasons for such conflicting results between the two datasets are regional differences in human population densities, snake population densities, and regional bias in access to medical treatment following snakebite envenomings. However, these conflicting results can only be reconciled with additional data.

Regarding the temporal variations in snakebite envenomings, the healthcare data provided both monthly and annual trends. Such temporal resolutions were not available for the literature data. The peaks of envenoming cases largely coincided with the active season of venomous snakes (May–September). However, the healthcare dataset recorded a small number ($n < 5$) of envenomings in January and February as well, the months when native venomous snakes are hibernating. While we cannot rule out the possibility of envenomings inflicted by non-native species under captive settings or from disturbance in hibernaculum, this is difficult to explain without having circumstantial information on envenomings and identification of species. Therefore, comparing healthcare data with the literature data revealed considerable conflicts and uncertainties between different sources of data to determine the patterns of snakebite envenomings in South Korea (see section 4.2).

4.1.3. WHO mortality data

The WHO mortality database shows 101 records of mortality in South Korea caused by snakebites from 1995 to 2015. The number of mortalities during this period shows a clear decreasing trend (Fig. 5B), potentially resulting from multiple factors such as the improvement of snakebite treatments, a general decrease of rural populations, and a decline of venomous snake populations (Shim et al., 1998). As it was impossible to trace the species of snakes that caused mortalities based on WHO database alone, we looked at ten additional mortalities recorded in the literature. Among these records, only one case of mortality was tied to a specific species (*Gloydius ussuriensis*; Paik and Son, 1996). We were unable to determine the overlap between WHO and literature records.

4.2. Major limitations for understanding snakebite envenomings in South Korea

One of the most significant and prevalent limitations in the literature and healthcare data was the lack of proper identification of snake species responsible for envenomings. For healthcare data, information on species was completely lacking. Among the 3009 cases of snakebites we analysed from the literature, identification at the genus-level and below were available for only 179 cases, all of which were associated with terrestrial species (173 associated with *Gloydius* and six with *Rhabdophis*). As *R. tigrinus* is distinctly different from *Gloydius* in overall body shape and coloration, we consider the identification of this species by victims or doctors to be reasonably reliable. However, proper species-level identification of *Gloydius* can be obscured by the general use of common names. In South Korea, the word 'doksa' (literally meaning 'venomous snake' in English) is generally used by people to refer to any kind of venomous snake. Also, the word 'salmosa' (meaning 'viper' in English) is used for any viper species found in the country, but incidentally the word is also a Korean common name for *G. brevicaudus* (Lee et al., 2012). Thus, there are high possibilities of making incorrect identifications, or correct identifications with an inadequate name. The difficulty of proper identification is also evident in clinical studies, in which alleged vipers were variously referred to by their common names, regional dialects, and other dubious names (e.g. Han et al., 1981). Such unreliability of species identification can lead to difficulties in identifying possible species-specific clinical symptoms and further clinical decisions.

Another limitation is the difficulty of extracting detailed clinical symptoms and associated clinical outcomes from the literature and healthcare data. Factors including time to antivenom treatment, delta-neutrophil index, local effect score, and serum amylase concentration have been highlighted as predictors of severe symptoms (Jun et al., 2004; Jin et al., 2008; Jeon et al., 2009). However, such information was either unavailable for the healthcare data or was rarely available for most of the studies examined in this review and could not be generalized across all studies. Similarly, we were unable to extract clinical symptoms and detailed causes associated with snakebite mortalities. Thus, studies utilizing the full scope of information from long term data are needed to fully understand the correlated factors of snakebite severity.

The literature and healthcare data included in this review were based on clinical data from a small number of medical institutions in the country (e.g., <30 out of 353 general hospitals for the literature data; Korean Hospital Association, 2019). These clinical data are inherently limited and are an unreliable source to estimate the true magnitude of snakebite envenomings in the country because both literature and healthcare datasets were exclusively based on hospital admissions. It is likely that many patients do not seek medical attention after receiving bites when the symptoms are not severe. This is more likely to happen in rural areas far from hospitals and where traditional medicine is still prevalent (Cho and Park, 1996; Shim et al., 1998).

In addition, extracting hospital-based data was made difficult by the lack of standardization for reporting snakebite envenomings between medical institutions. While healthcare data was largely free from this problem by having a data entry format, the lack of standardized reporting was evident in the literature data. For example, studies published by different hospitals use different age, body parts, temporal, and habitat categorizations. Although the categories used in the different studies overlap to some degree, such inconsistencies may compromise the traceability of data. Considering these factors, we argue that hospital-based data are not representative of the true picture of snakebite envenomings in the country.

The conflicting patterns of snakebite envenomings revealed by different sources of data are yet another limitation to understand snakebite envenomings in South Korea. Regarding the literature data, the omission of envenoming records from reporting could be a source of discrepancies. For example, our study compiled 3179 cases spanning the past 50 years from the literature. However, a study using data from the nationwide clinical database compiled 1335 cases spanning just six years (from 2011 to 2016) with an average 223 cases annually (Senek et al., 2019). Similarly, the healthcare data based on health insurance registrations recorded 1823 cases of snakebite envenomings spanning ten years (from 2010 to 2019). This potentially indicates a significant under-reporting of snakebite envenomings in the literature. A study by Shim et al. (1998) also showed huge discrepancies between estimations of nationwide snakebite occurrences. An estimation based on published reports was calculated to be 409.6 cases per year. However, when the authors calculated the actual number of annual occurrences based on the average annual number of snakebite patients admitted to three general hospitals and assuming there are two general hospitals per province, the estimation was 2706 cases per year (Shim et al., 1998). In addition to the total number of envenomings, age and regional patterns show similar kinds of conflicts between datasets used. Therefore, additional studies using more detailed and comprehensive data are needed to reconcile such conflicting patterns.

Symptoms of venomous snakebite are complex effects of venom components and patient's reactions to snake venom. As snake venoms are known to vary at different levels (e.g. ontogenic, population, and species levels), different symptoms can develop in different regions (Chippaux et al., 1991). In South Korea, at least one clinical study noted a difference in the rate of coagulopathy in victims from six provinces, and noted differences in snake species or venom variations between regions as potential causes (Park et al., 2009a). Anecdotal personal communication with people leaving on isolated islands (>50 km from the mainland) also suggests contrasting patterns associated with snakebites (likely *Gloydius* sp.), ranging from the general absence of pain on some islands, to the risk of death even for healthy individuals on other islands. However, this has not been tested and may only be perceived differences, and the variation of venom components and its role in clinical outcomes have not been investigated for Korean venomous snakes.

4.3. Snakebites by gloydius pitvipers

Gloydius species were shown to be responsible for most snakebites in South Korea (59.3%; 40.7% unidentified species of snake; Shim et al., 1998). In our result, *Gloydius* vipers were responsible for 96.6% of snakebite cases where the species was identified. In Japan, the closely related *G. blomhoffi* is responsible for 2000 to 3000 snakebite cases and at least 10 mortalities annually (Okamoto et al., 2017).

Among the three species of *Gloydius* present in South Korea (Fig. 1; Table 2), *G. intermedius* comes into contact with people relatively less frequently due to its preference for high altitude mountainous habitats (Lee et al., 2012). On the other hand, *G. ussuriensis* and *G. brevicaudus* utilize broader types of habitats ranging from mountain forests to rice paddies. Therefore, these two species are likely to be responsible for the majority of snakebites in the country.

Among the three South Korean *Gloydius* species, *G. ussuriensis* was recorded to have the highest venom toxicity measured by lethal dose 50 (LD_{50}) and minimum lethal dose (MLD), followed by *G. intermedius* and *G. brevicaudus* (Yoo et al., 1999). Also, the venom of *G. ussuriensis* was recorded to have the highest haemorrhagic effects measured by the minimum haemorrhagic dose (MHD), followed by *G. brevicaudus* and *G. intermedius* (Yoo et al., 1999).

In South Korea, *Gloydius* envenoming causes a range of symptoms including lethargy, vomiting, oedema, ptosis, tissue necrosis, ophthalmic disorders, brain infarction, internal bleeding and coagulopathy (Moore, 1977; Kwon et al., 1998; Ari, 2001; Lee et al., 2001, 2011; Cho et al., 2004; Lim et al., 2004). Most patients treated for *Gloydius* envenoming recover from bites within several weeks (Kim et al., 2008b; Park et al., 2009b; Kang et al., 2014). However, at least ten snakebite mortalities in the past 48 years were associated with *Gloydius*, with at least one of those cases specifically attributed to *G. ussuriensis*.

Table 2
Brief identification keys to Korean terrestrial venomous snakes (Based on Lee et al., 2012 and Uetz et al., 2019; also see Fig. 1 for images).

Family	Species	Synonyms	Characteristics
Viperidae	*Gloydius ussuriensis*	*Ancistrodon blomhoffi ussuriensis, Agkistrodon caliginosus, Agkistrodon ussuriensis, Agkistrodon halys ussuriensis*	Total length 25–50 cm. Body coloration range from reddish brown to reddish grey. Body pattern consists of irregular dark brown bands or circular patterns. Tongue is pink or red in colour.
	Gloydius brevicaudus	*Ancistrodon halys brevicaudus, Agkistrodon blomhoffi brevicaudus*	Total length 30–55 cm. Body coloration range from greyish brown to dark brown. Body pattern consists of circular blotches with dark brown margin and light brown interior. Tongue coloration black.
	Gloydius intermedius	*Ancistrodon halys intermedius, Ancistrodon blomhoffi intermedius, Ancistrodon intermedius, Agkistrodon saxatilis, Gloydius saxatilis*	Total length 40–70 cm. Body coloration is yellowish brown with irregular black or dark brown crossbands. Dark stripe behind the eyes are much narrower compared to G. *ussuriensis* or *G. brevicaudus*.
Natricidae	*Rhabdophis tigrinus*	*Natrix tigrina, Natrix tigrina lateralis, Rhabdophis tigrinus lateralis*	Total length 60–100 cm. Body coloration is pale green. Body pattern consists of black bands or blotches. There are reddish blotches on the anterior part of body. These blotches fade away towards the posterior part of body.

Based on the severity of symptoms, treatment of *Gloydius* envenomings may involve administration of antivenom (Lim et al., 2013; Rha et al., 2015). The antivenom used for the treatment of *Gloydius* envenoming in South Korea is the Kovax freeze dried antivenom (Korea Vaccine, Korea; Lim et al., 2013). This is an equine origin antivenom that uses whole IgG antibody, made from '*Agkistrodon halys* (= *Gloydius halys*)' venom from the People's Republic of China (hereafter China; Lim et al., 2013). The exact *Gloydius* species used to manufacture this antivenom is difficult to determine as the taxonomy of *G. halys* complex is complicated (Wüster et al., 1997; Orlov and Barabanov, 1999). Also, it is possible that the venoms used for antivenom production were pooled from several different species of *Gloydius* (Chippaux et al., 1991). The Kovax antivenom is a polyvalent antivenom for all three *Gloydius* in the country. Although the need for monovalent antivenom for each species has been suggested to increase the effectiveness and safety of antivenom therapy (Yoo et al., 1999), the use of polyvalent antivenom for the genus may be safer given the general unreliability of species-level identification for clinicians and broad sympatry of the three species. Nevertheless, the venom composition of *G. intermedius* may be notably different from the other two species given the phylogeny of the genus (Xu et al., 2012). Whether such differences are large enough to affect antivenom therapy are yet to be investigated.

4.4. *Snakebites by Tiger keelback (Rhabdophis)*

Envenomings by *R. tigrinus* is known to cause headache, nausea, swelling, coagulopathy and severe and extensive haemorrhage (Mittleman and Goris, 1978; Hifumi et al., 2014a). Also, Mittleman and Goris (1974) noted acute kidney injury as a characteristic symptom of *R. tigrinus* envenomings, and they reported a death caused by *R. tigrinus* envenoming in captive settings in Japan, suggesting that this species is capable of inflicting fatal envenoming in humans. In Japan, 34 cases of envenoming were recorded in 43 years, with an 11.8% mortality rate (Hifumi et al., 2014b).

In South Korea, six cases of envenoming by *R. tigrinus* were recorded in the past 50 years with no fatal cases recorded (Kim et al., 1994; Rha et al., 2015). Among these records, only one case described the symptoms in detail (Kim et al., 1994). In this case, the patient developed acute kidney injury, which is consistent with characteristic of *R. tigrinus* envenoming noted by Mittleman and Goris (1978).

Considering that severe symptoms and mortality have been associated with this species since the 1970s, it is surprising that clinical literature from South Korea published between 1970 and 2007 did not list *R. tigrinus* as a venomous species (Han, 1981; Choi et al., 1991; Han et al., 1996; Cho et al., 2004). Therefore, envenoming by *R. tigrinus* in the country is likely underestimated because clinicians may have pre-emptively excluded possibilities of envenoming by this species when patients were admitted for treatment.

In Japan, experimental antivenoms have been manufactured by immunization of goats, rabbits, and horses (Morokuma et al., 2011). This antivenom showed positive results in treating patients bitten by *R. tigrinus* (Hifumi et al., 2014b). However, there is no antivenom available for treatment of *R. tigrinus* envenoming in South Korea, and a patient reported by Kim et al. (1994) was treated by a combination of dialysis and blood transfusion. Although *R. tigrinus* is usually not inclined to bite people, and envenoming by this species may therefore not be a common medical issue (Minton, 1990), all *Rhabdophis* species should be considered medically important.

4.5. *Snakebites by marine snakes (Laticauda and Hydrophis)*

No cases of envenoming by marine snakes are known from South Korea because marine snakes are rarely recorded in Korean seas. However, due to the increase of water temperatures, the number of marine snake records may increase in the future (Park et al., 2017). Thus, envenoming by marine snakes are likely to occur in the future.

Records of marine snakebite envenomings are rare and scattered in general (Reid, 1956a; Toriba, 1994; Li et al., 2015). In Japan, fishermen collect *Laticauda* sp. for food and they handle them with bare hands, suggesting this species are not inclined to bite (Toriba, 1994; Warrell, 1994). However, there are six identified cases of marine snakebite envenoming in Japan between the 1930s and 1990 (Toriba, 1994). Five among these cases were fatal, with one case attributed to *Laticauda* sp. and others to *Hydrophis* spp. (Toriba, 1994). All victims were bitten while handling the snakes and died within 24 h (Toriba, 1994). In China, one case is known of a patient bitten by an unidentified marine snake (Li et al., 2015). The patient entered a deep coma but recovered after treatment (Li et al., 2015).

Most records of marine snakebite envenomings come from coastal Southeast Asia (Warrell, 1994). This is likely because the region is a diversity hotspot of marine snakes (Sanders et al., 2010). Most detailed accounts of marine snakebite envenomings come from Malaysia (Reid, 1956a, 1975; Reid et al., 1956b; Reid and Lim, 1957). Most victims were fishermen and were bitten while handling fish and nets (Reid, 1956a). One hundred and forty-four cases, including 41 fatal incidents, were recorded up until 1955 in Malaysia (Reid and Lim, 1957).

The bites of marine snakes are known to be painless or only cause mild pain and no necrosis or swelling occur around the site of the bite (Warrell, 1994). Bite symptoms include general pains and weakness of muscles, vomiting, muscle spasms, excessive sweating, ptosis, trismus, and coma (Reid and Lim, 1957; Warrell, 1994; Li et al., 2015).

5. Conclusion

With this study, we provide baseline information on the characteristics of venomous snakebites in South Korea. Based on literature data, we have identified middle aged males living in rural areas as the demographic group at highest risk of snakebite envenoming, which is consistent with a previous study of snakebite epidemiology in South Korea (Senek et al., 2019). We have also tentatively identified Gangwon province as a hotspot of snakebite occurrences based on literature data. *Gloydius ussuriensis* and *G. brevicaudus*, especially the former, are the two species likely responsible for most snakebite cases in the country. Snakebite envenomings remain an important public health problem in the country (Senek et al., 2019). However, snakebite envenomings in South Korea are still poorly documented and not well represented in studies of global snakebite burden. Although our study aims to provide a synthesis of information on snakebite envenomings occurring in South Korea, this does not represent the national statistics of snakebites for the country. Our study, along with other similar studies, can be utilized to design future public health programs in the country. Meanwhile, a systematic national census is needed to properly inform such management plans while better understanding the burden of snakebite envenomings in South Korea. We also argue for the need of further studies using more detailed and comprehensive data to reconcile conflicts between datasets and overcome major limitations to understand the patterns of snakebite envenomings in South Korea.

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