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ORIGINAL RESEARCH

Bee Sting Injuries in Thailand's High Apicultural Area: Outcome, Risk and Treatment Patterns

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Objective: This study aims to assess the clinical outcomes and risk factors associated with severe systemic reactions following bee stings, focusing on patients treated at Pa-Sang Community Hospital, located in Lamphun Province, Thailand, which is recognized as one of the country's largest apicultural areas.

Methods: A retrospective review was conducted, utilizing electronic medical records with ICD-10 coding, of patients treated for bee sting injuries at the Emergency Department of Pa-Sang Hospital from January 2015 to December 2019.

Results: This analysis included a total of 591 bee sting events involving 533 patients. The average incidence of bee sting injuries was 31.3 per 10,000 Emergency Department visits, with 55% being male. A significant majority (86%) of events occurred outside the patients' home area. Notably, the head or extremities (49%) were the most common anatomical sites stung. Systemic reactions were observed in 44% of cases, with 96 visits (16%) diagnosed as anaphylaxis. Epinephrine injection was administered in 77% of these cases, and fortunately, no fatal anaphylactic reactions were recorded. Protective factors for anaphylaxis and severe systemic reactions after bee stings included age less than 15 years old and stings on extremities. Conversely, having more than ten bee stings and seeking Emergency Department treatment within 60 minutes of being stung were identified as significant risk factors.

Conclusion: Bee sting injuries were a common presentation at the hospital situated in the high apicultural area, and severe systemic reactions were observed. This study highlights the need for comprehensive interventions to mitigate the increased risk of bee-related accidents in communities with thriving apicultural industries.

Keywords: bee sting, venom, anaphylaxis, bee keeping, Thailand

Introduction

Bees, among the most common insects responsible for venomous accidents in humans, can cause a range of reactions, from local pain and swelling to severe systemic manifestations. Bee stings are typically characterized by local pain, swelling, and redness. Some individuals experience reactions that extend beyond the immediate site of the sting, leading to systemic manifestations, including allergic responses and, in rare instances, severe anaphylaxis.[1–4] Moreover, a direct toxic reaction can occur following the multiple stings and may lead to renal failure, rhabdomyolysis, hepatic injury, and possibly death.[3,4] The clinical spectrum underscores the need for a nuanced understanding of individual variations in immune reactions, as well as the factors influencing the severity of clinical outcomes.

The introduction of honeybees, specifically *Apis mellifera*, to Thailand dates back to the 1940s, primarily for agricultural pollination and the production of honey and beeswax. Today, it stands as the most favored bee species for apiculture in Thailand.[5] Located in Lamphun Province, Northern Thailand, the Pa-sang District emerges as one of the largest longan and lychee orchard areas in the country. Here, the cultivation of these fruits is complemented by another facet of agricultural brilliance - apiculture. The diligent efforts of honeybees, as they pollinate the blossoms of longan and lychee, play a pivotal role in enhancing crop yields and fostering biodiversity. In early February, roughly two weeks before the longan trees bloom, approximately 285 beekeepers from northern Thailand relocate between 100,000 and 120,000 *A. mellifera* hives within the Chiang Mai and Lamphun regions. These hives are strategically placed around and

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beneath the longan trees. This seasonal migration allows the bees to capitalize on the longan blooms, typically generating a honey harvest of an annual yield of 3000–4200 metric tons.[6,7] An interesting contrast exists between beekeeping practices in Thailand and western countries. While western growers often rent beehives for pollination purposes, Thai beekeepers must rent or lease longan plantation space for their hives.[6] Due to this annual relocation of hives, obtaining precise data on the numbers of hives per unit area in Pa-sang, Lamphun, remains a challenge.

Despite the indispensable role of bees in agriculture, bee sting injuries pose a substantial risk to individuals living close to apicultural activities.[8] Unraveling the intricacies of bee stings within the fabric of community life is crucial, given the consequences they pose. A comprehensive understanding of the patterns, factors, and health implications of bee sting injuries in high apicultural areas is crucial. This knowledge not only ensures the safety of individuals but also promotes the harmonious cohabitation of communities and honeybee colonies. Therefore, this study aims to investigate the epidemiological characteristics, clinical outcomes, and contributing factors to anaphylaxis and severe systemic reactions (SSR) following bee stings. For this investigation, we analyzed data from the Emergency Department (ED) of a community hospital located in a high apicultural area.

Materials and Methods

Study Design

This was a retrospective cohort study using data from electronic medical records of patients who attended the ED at Pa-Sang Hospital due to bee sting injuries from January 2015 to December 2019. Pa-sang Hospital is a community hospital equipped with 75 beds. It is the emergency and health care center for 55,573 people living in the nearby area. Approximately 150,000 outpatients visit the hospital each year.

This study adheres to the principles outlined in the Declaration of Helsinki and was conducted with prior approval from an ethics committee. This approval was granted by the Research Ethics Committee of the Faculty of Medicine, Chiang Mai University (Reference Number: 107/2020, Date: March 20, 2020). Due to the retrospective nature of the study, informed consent was not required from participants. Access to the data was restricted to authorized investigators who are bound by anonymization, confidentiality, and data processing regulations.

Inclusion Criteria and Methods

We conducted a review of electronic medical records for patients who visited the ED, utilizing the International Statistical Classification of Diseases and Related Health Problems, 10th version (ICD-10) codes.: T782 (Anaphylactic shock, unspecified), T784 (Allergy, unspecified), T788 (Other adverse effect, not elsewhere classified), L500 (Urticaria-Allergic urticaria), X23 (Contact with hornets, wasps, and bees), T634 (Toxic effect with contact with venomous animals - Toxic effect of contact with other Venomous animals), T638 (Toxic effect with contact with venomous animals-Venoms of other arthropods toxic effect).

The inclusion criteria for the study required a confirmed history of bee stings through documented medical records of the culprit bee and/or the presence of sting marks during physical examination. Exclusion criteria encompassed patients stung by insects other than bees, reactions from routes other than stings (eg, bee product ingestion), and those with insufficient information. Data was collected for patients meeting the inclusion criteria.

Demographic information, underlying diseases, atopic status, previous allergic reactions, number of stings, body parts affected, locations of stings, clinical presentations, the time lapse between exposure and symptom onset, treatment details, and outcomes were systematically collected using a record form. Large local reactions were identified by swelling and redness extending from the sting site, exceeding 10 cm in diameter. Anaphylaxis diagnosis was established for patients meeting at least one of the three clinical diagnostic criteria outlined in the 2006 National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID-FAAN) symposium.[9] Severe systemic reactions (SSR) were defined by the presence of at least one of the following: loss of consciousness, hypotension, cardiovascular collapse, respiratory failure, or cyanosis observed at ED arrival or as treatment outcomes. Severe anaphylactic reactions (grade III and IV, according to Ring and Messer[10,11]) were considered to fall under both the categories of SSR and anaphylaxis.

Statistical Analysis

Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS), version 23.0 for Windows. Descriptive analysis presented continuous variables as the mean with standard deviation (SD) and categorical variables as percentages or ratios, as appropriate. Group comparisons between anaphylactic and non-anaphylactic groups were conducted using *t*-tests for continuous variables and chi-squared or Fisher's exact tests for categorical variables, as appropriate. Odds ratios (OR) with corresponding 95% confidence intervals (95% CI) were calculated to analyze factors associated with anaphylaxis and severe systemic reactions (SSR). Covariates with a p-value < 0.05 in univariate analysis were included in the multivariate analysis. Statistical significance was set at a p-value < 0.05 for a two-sided test.

Results

Over the five-year study period, there were 188,306 ED visits. A total of 2612 ED visits from electronic medical records with included ICD-10 codes were reviewed. Six hundred and four events were reported as bee sting injuries. Thirteen events were excluded from the analysis: seven with reactions from bee product ingestion, four with insufficient data on the culprit insect, and two involving repeated follow-up visits. A total of 591 events, involving 533 patients, were included in the evaluation. Among these, 46 patients had multiple ED visits due to repeated bee stings. This group includes eight patients who experienced multiple ED visits (≥ 3 times) during the five-year study period. The average incidence of bee sting injuries was calculated as 31.3 per 10,000 ED visits.

Out of the 591 ED visits, 96 visits (16.2%) in 87 patients met the criteria for anaphylaxis, while 37 visits (6.3%) were classified as SSR. Four patients with a history of loss of consciousness and/or hypotension after bee stings were classified in both the anaphylaxis and SSR groups. Common clinical presentations among patients who visited the ED after bee stings included systemic reactions such as generalized urticaria, anaphylaxis, and SSR, surpassing local reactions (66.2% vs 33.7%). Interestingly, bee stings were reported as elicitors of anaphylaxis in 47% of all patients diagnosed with anaphylaxis at the hospital's ED during the study period. A majority of the events (66%) occurred outside residential areas, with common activities during daily routines (32.7%), including religious activities in temples, walking, riding motorcycles, and gardening. Only 14% of the events were related to occupational activities. The occurrence of bee stings and clinical outcomes are shown in Table 1.

Table 2 illustrates the demographic characteristics of patients and compares those who presented with anaphylaxis to those without. The mean age of the patients was 30.7 years (SD=21.0), with 55% being male. Patients with anaphylaxis were significantly older than those without (mean age 40.5 vs 28.7 years, p-value < 0.001). There was no significant difference in the proportion of patients with underlying diseases (allergic and cardiovascular diseases) and current cardiovascular medicine usage (beta-blocker or angiotensin-converting enzyme inhibitor) between the anaphylactic and non-anaphylactic groups.

Table 3 presents the results of logistic regression analysis identifying factors associated with the occurrences of anaphylaxis and SSR. The age of less than 15 years old was only the significant baseline demographic protective factor (n=533) associated with anaphylaxis and SSR (OR 0.164, 95% CI 0.070–0.384). Regarding the factors during the incidents (n= 591 events) in the multivariate regression model (n= 591 events) by multivariate regression model, the body area of sting at extremities was the protective factor (OR 0.626, 95% CI 0.393–0.998), whereas number of stings more than ten, and duration of an ED visit within 60 minutes of being stung were the significant risk factor (3.186, 95% CI 1.626–6.243 and OR 2.630, 95% CI 1.523–4.545, respectively). There was no statistically significant association between severe reactions and factors such as underlying cardiovascular diseases, current beta-blocker use, history of previous systemic reactions to bee stings, and the locations of injuries.

Information on the treatment after bee sting injuries is shown in Table 4. Eighty-one patients (13.7%) were admitted to the hospital. Patients diagnosed with anaphylaxis had a significantly higher rate of hospitalization (63.5% vs 4.0%, p-value < 0.001). Although epinephrine was administered only in 74 (77.1%) anaphylactic events, there was no report of severe, protracted, or biphasic anaphylaxis. H1 antihistamines were the predominant medication prescribed, accounting for 93% of all events. No cardiopulmonary resuscitation, intubation, or fatality was documented. Only five of 87 patients with anaphylaxis were given self-injectable epinephrine to prevent future anaphylactic reactions. Among these five patients, there was a history of recurrent anaphylaxis due to bee stings. The majority of patients received treatment at the

Table 1 Occurrence of Bee Stings and Outcomes (N=591 Events)

	N(%)
Bee sting reactions:	
Local reactions	199 (33.7)
• Large local reactions	34 (5.8)
Systemic reactions	391 (66.2)
• Generalized urticaria	262 (44.3)
• Anaphylaxis*	96 (16.2)
• Severe systemic reactions*	37 (6.3)
Geographic location	
• Residential area	101 (17.1)
• Public area	329 (55.6)
• Occupational area	56 (9.5)
• Not available	105 (17.8)
Type of activity at the time of stings	
• Daily activities	193 (32.7)
• Occupational activities	85 (14.4)
• Leisure activities	63 (10.7)
• Not available	250 (42.3)

Notes: *Four events were classified as both severe systemic reactions and anaphylaxis.

Table 2 Demographic Characteristics of Patients and Comparison Between Anaphylactic and Non-Anaphylactic Group (n (%))[a]

	Total (n=533)	Anaphylaxis (n=87)	Non-anaphylaxis (n=446)	*p-value*[b]
Sex: male	295 (55.3)	52 (59.8)	243 (54.5)	0.410
Age (years±SD)	30.7±21.0	40.5±18.7	28.7±20.9	<0.001
• < 15 years	145 (27.2)	6 (6.9)	139 (31.2)	<0.001
• > 60 years	55 (10.3)	12 (13.8)	43 (9.6)	0.244
Underlying diseases				
• Allergic diseases[c]	12 (2.3)	2 (2.3)	10 (2.2)	0.974
• Cardiovascular diseases	56 (10.5)	11 (12.6)	45 (10.1)	0.477
Current medications				
• Beta-blocker	15 (2.8)	4 (4.6)	11 (2.5)	0.272
• Angiotensin-converting enzyme inhibitors	29 (5.4)	3 (3.4)	26 (5.8)	0.370

Notes: [a]Values are presented as mean ± standard deviation, number (%). [b]*P-value* compared between anaphylaxis and non-anaphylaxis groups. [c]Allergic diseases consist of asthma, allergic rhinitis, and atopic dermatitis. Cardiovascular diseases consist of myocardial infarction, heart failure, arrhythmia, hypertension, and dyslipidemia.

Table 3 Factors Associated with Anaphylaxis and SSR (n=591 Events)

	OR (95% CI)	Adjusted OR (95% CI)
Age: < 15 years old (n=533)	0.164 (0.070–0.384)	
> 60 years old (n=533)	1.500 (0.755–2.977)	
Underlying cardiovascular diseases (n=533)	1.290 (0.638–2.606)	
Current use of beta-blocker	1.906 (0.593–6.129)	
Previous history of anaphylaxis to bee stings	2.629 (0.646–10.699)	
Previous history of SSR due to bee stings	1.177 (0.503–2.757)	
Number of stings >10	3.825 (2.051–7.133)	3.186 (1.626–6.243)
Time-lapse between bee stung and ED visits < 1 hour	2.865 (1.681–4.882)	2.630 (1.523–4.545)
Locations: residential area	0.984 (0.520–1.862)	
Body site: head and neck	1.299 (0.837–2.015)	
Trunks	1.896 (1.069–3.363)	0.979 (0.514–1.867)
Extremities	0.576 (0.368–0.901)	0.626 (0.393–0.998)

Table 4 Treatments and Outcomes of Bee Stings Injuries (N=591 Events)

	Total (591 Events)	Anaphylactic Events (96 Events)	Non-Anaphylactic Events (495 Events)	P-value*
Hospitalization	81 (13.7)	61 (63.5)	20 (4)	<0.001
Intubation/ CPR	0	0	0	0
Death	0	0	0	0
Treatments				
• Epinephrine injection	82 (13.9)	74 (77.1)	8 (1.6)	<0.001
• Antihistamine	548 (92.7)	92 (95.8)	456 (92.1)	0.29
• Systemic steroids	359 (60.7)	90 (93.7)	269 (54.1)	0.009
• IV fluid	29 (4.9)	25 (26)	4 (0.8)	<0.001
• Oxygen supplement	40 (6.8)	38 (39.6)	2 (0.4)	<0.001

Notes: **P-value* compared between anaphylactic and non-anaphylactic events.

community hospital. However, a 63-year-old man with underlying chronic renal failure, injured by multiple bee stings, was referred to the provincial hospital due to SSR.

Discussion

This retrospective cohort study explored the incidence, clinical characteristics, and treatment outcomes of bee sting injuries among patients treated in the ED of a community hospital situated in a high apicultural area in Thailand. Over the five years from 2015 to 2019, the incidence of ED visits due to bee stings averaged 31.3 per 10,000 ED visits. Sixty-six percent of them presented at the ED with systemic reactions, including generalized urticaria, anaphylaxis, and SSR. Fortunately, no fatal reactions were recorded. Factors protecting against severe reactions included age less than 15 years

and stings on extremities. Conversely, significant risk factors were associated with more than 10 stings and a time-lapse exceeding 60 minutes between being stung and arriving at the ED.

Pa-sang Hospital, a community hospital, is situated amidst vast agricultural lands, predominantly filled with longan and lychee orchards. Apiculture or beekeeping has an essential role in the agricultural pollination of fruit blossoms. The by-products of apiculture such as honey, beeswax, propolis, and royal jelly also have a huge economic impact on the community. However, previous studies have revealed that beekeepers are not the only individuals at risk of bee sting reactions; their family members also experience a high incidence of reactions, likely due to the proximity of bee hives to their homes.[5,8] The study reveals that the common location where patients were afflicted was in public areas. This highlights that residents in a community with high apicultural activities are at risk of bee-related accidents in various places. The remarkably high rate of ED visits due to bee stings, when compared to other areas in Thailand,[12] underscores the urgent need for further investigation and community-based interventions. Additionally, the majority of patients in this study sustained injuries during their routine daily activities, such as walking or riding on transportation. Furthermore, community residents have expressed complaints about numerous minor, unreported accidents involving motorcycles and bicycles, all linked to the nuisance of bee stings. It confirms that every resident of a high apiculture community is at risk of adverse impacts on their health even for those who are not involved in the apicultural industry.

Bee stings can elicit a spectrum of reactions, ranging from mild to severe, including local irritation, allergic responses, urticaria, anaphylaxis, and systemic toxic reactions.[1,2] Local reactions, often mild, can be effectively managed with local or oral analgesic agents. These mild local reactions are the most common presentations in ED visits following insect envenoming. Previous epidemiological studies conducted in national poison control or emergency care centers across various countries, including Thailand, Taiwan, South Korea, and Brazil,[13–17] have consistently shown that local reactions to insect stings are more commonly reported than systemic reactions. In our study, nearly 70% of ED patients due to bee stings reported systemic reactions, encompassing generalized urticaria, anaphylaxis, and SSR. This finding raises the possibility of underreporting bee sting incidents within the community. Mild reactions, although common, might often go unnoticed as they are typically self-limited and managed through self-treatment.

Systemic reactions from bee stings may result from either immunologic hypersensitivity or the direct toxicity of bee venom. Common signs of anaphylaxis include urticarial rash, wheezing, and hypotension. However, respiratory symptoms, large local reactions, and hypotension can also stem from the direct toxic effects of bee venom. Phospholipase A2, a primary venom component, can directly induce vasodilation, acute lung injury, and alveolar edema.[4,18] These effects mimic the presentation of IgE-mediated anaphylaxis. At present, no clinical sign possesses sufficient capacity to discriminate between direct toxic effects and anaphylaxis.[14] Even a systemic cutaneous reaction can also be seen in non-allergic reactions. While serum tryptase level serves as a useful biomarker for confirming the diagnosis of insect sting anaphylaxis,[19] its availability is limited in resource-limited settings or community care practices. Therefore, we analyzed factors associated with SSR and anaphylaxis together, revealing that several stings >10 were a predictor of poor outcomes. It was in line with the previous studies that a greater number of stings results in the injection of a higher amount of venom.[13–16] Each sting of a bee delivers a relatively constant volume of venom. In the case of direct toxicity, the number of stings appears to be correlated with the degree of clinical severity,[14,15] which may also be seen in anaphylaxis in a previous report.[13] However, the reason why a higher number of stings is correlated with a higher rate of allergic reactions remains unknown.

Bee sting injuries were the most prevalent type of stinging insect injury reported in our study. This finding contrasts with a previous study from central Thailand, where wasp sting injuries were more common.[14] The previous studies also suggested that wasp stings might lead to more severe outcomes compared to bee stings.[14,15,20] This could be explained by the higher potency of wasp venom, more aggressive behavior, and their ability to sting repeatedly. Unlike bees, which have barbed stingers that lodge in the skin upon stinging, often resulting in their death, wasps have smooth stingers, allowing them to deliver multiple stings.

In our study, patients with SSR and anaphylaxis tended to visit the ED earlier than those with less severe reactions. Furthermore, a duration of less than 60 minutes between bee sting and ED arrival emerged as another predictor of poor outcomes. This observation may be explained by the tendency of individuals with severe symptoms to seek medical treatment earlier. Similar findings were reported in another study, where the majority of patients with severe reactions visited an ED within one hour of being stung.[13,21]

Severe reactions are more likely with stings on the head, as this area includes the nose and mouth - the anatomical entry points of the airway. Stings in this area may cause tissue swelling leading to airway obstruction.[16,22] Interestingly, our recent study did not establish a correlation between stings on the head and neck and severe reactions. However, stings on the extremities were found to be less severe. In our study, no correlation was found between severe reactions and age group, underlying cardiovascular or allergic diseases, or the concomitant use of beta-blockers or angiotensin-converting enzyme inhibitors (ACEIs).

Another concern is the prompt treatment of epinephrine in patients diagnosed with anaphylaxis. Every patient with suspected anaphylaxis must receive an intramuscular epinephrine injection.[1,9,23] In this study, among the population meeting the criteria for anaphylaxis at ED arrival, only 77% received epinephrine. The consequences of delayed anaphylaxis treatment are associated with increased morbidity and mortality.[23,24] The underuse of epinephrine at the ED may be due to a misdiagnosis, and lack of knowledge. There is a need to enhance awareness regarding the use of epinephrine for anaphylaxis, particularly in the emergency care setting. A recent 23-year epidemiological study (1994–2016) investigating fatalities from Hymenopteran sting in Europe found a total of 1691 deaths recorded. This translates to an average of 0.26 fatalities per million inhabitants annually.[25] Notably, male adults between the ages of 25 and 64 were the most frequent victims, which likely reflects higher risk from occupational and outdoor activities.[20,25] Fortunately, the outcomes of bee sting reactions reported in our study were favorable. No instances of cardiopulmonary resuscitation, intubation, or fatality were documented, even in cases involving multiple stings. Only an elderly patient with chronic renal failure who experienced more than 10 bee stings and developed rhabdomyolysis was transferred to a higher medical care center.

Adding to the concerns is the low rate of prescribed self-injectable epinephrine among individuals with a history of anaphylactic reactions. A mere 6% (five out of 87) of patients with anaphylaxis were prescribed self-injectable epinephrine. These prescriptions were made exclusively in cases of recurrent sting-induced anaphylaxis. Current recommendations emphasize that patients with a history of systemic hypersensitivity to insect stings, at risk of recurrent severe reactions, should carry epinephrine for emergency self-treatment and be familiar with its appropriate use.[1,9,23,24] There is a need to encourage physicians and patients to proactively prescribe and use self-injectable epinephrine for the prevention of sting anaphylaxis, particularly in cases of severe systemic reactions and anaphylaxis. Because living near the beekeeping area may be unavoidable, strong consideration should be given to referring individuals to allergy specialists for bee venom immunotherapy, a highly effective treatment offering protection against reactions after being restung.[1,2] Although access to medical service is sufficient in the Pa-Sang District, most events may be treated by general practitioners at the Primary Care Unit. Referral for allergy specialist evaluation seems to be challenging. Regrettably, none of the cases in this report were referred for immunotherapy. In light of these findings, urgent action is required, necessitating the development and implementation of community awareness programs, safety measures, and educational initiatives. This comprehensive approach should ensure access to self-medication, specifically self-injectable epinephrine, while emphasizing the critical importance of repeated education - particularly for patients with a history of sting reactions.

Several limitations are noteworthy in this study. Firstly, the retrospective nature of the study resulted in incomplete information on certain variables, particularly geographical location, and activities during the incidents. Secondly, the confirmed identity of the culprit insect was absent in some cases. The presence of bee stingers was typically documented or reported by patients in most instances. Only four patients were reported to have injuries from insects other than bee stings during the five-year study. Consequently, we can assert that almost all the reported cases involved stings from honeybees. Thirdly, the severity of envenomation was assessed based on documentation in the ED medical records. It is essential to note that patients who sought medical attention due to late reactions on subsequent days might not have been included. Lastly, it is crucial to highlight that the study was conducted in a community hospital located in a high apicultural area in Northern Thailand. As a result, caution is warranted when attempting to generalize the findings to populations in different settings.

Conclusions

The hospital in the high apicultural area frequently witnessed bee sting injuries, which often resulted in SSR and anaphylaxis during ED presentations. These severe reactions are notably associated with a higher number of stings and a shorter duration between being stung and ED arrival. In conclusion, the increased risk of bee-related accidents in

communities with thriving apicultural industries emphasizes the imperative for comprehensive interventions. To mitigate this risk, essential measures include community awareness programs, safety initiatives, and targeted educational programs. Additionally, ensuring accessible self-medication, particularly self-injectable epinephrine, coupled with recurrent education, is paramount, especially for individuals with a history of sting reactions.

Data Sharing Statement

The datasets generated during the current study are available from the corresponding author upon reasonable request.

Ethics and Consent Statements

This study adheres to the principles outlined in the Declaration of Helsinki and was conducted with prior approval from an ethics committee. This approval was granted by the Research Ethics Committee of the Faculty of Medicine, Chiang Mai University (Reference Number: 107/2020, Date: March 20, 2020). Due to the retrospective nature of the study, informed consent was not required from participants. Access to the data was restricted to authorized investigators who are bound by anonymization, confidentiality, and data processing regulations.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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