

Risk factor, monitoring, and treatment for snakebite induced coagulopathy: a multicenter retrospective study

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Background: Snakebite can cause various complications, including coagulopathy. The clinical features of snakebite-associated coagulopathy differ from those of disseminated intravascular coagulation (DIC) caused by other diseases and its treatment is controversial.

Methods: We retrospectively reviewed the medical records of patients hospitalized for snakebite between January 2006 and September 2018.

Results: A total of 226 patients were hospitalized due to snakebite. Their median hospital stay was 4.0 days (interquartile range, 2.0 to 7.0 days). Five patients arrived at hospital with shock and one patient died. Twenty-one patients had overt DIC according to the International Society of Thrombosis and Hemostasis scoring system. Two patients developed major bleeding complications. Initial lower cholesterol level at presentation was associated with the development of overt DIC. International normalization ratio (INR) exceeding the laboratory's measurement limit was recorded as late as 4 to 5 days after the bite. Higher antivenom doses ($\geq 18,000$ units) and transfusion of fresh frozen plasma (FFP) or cryoprecipitate did not affect prolonged INR duration or hospital stay in the overt DIC patients without bleeding.

Conclusions: Initial lower cholesterol level may be a risk factor for overt DIC following snakebite. Although patients lack apparent symptoms, the risk of coagulopathy should be assessed for at least 4 to 5 days following snakebite. Higher antivenom doses and transfusion of FFP or cryoprecipitate may be unbeneficial for coagulopathic patients without bleeding.

Key Words: antivenom; blood transfusion; consumption coagulopathies; disseminated intravascular coagulopathy; snakebite

INTRODUCTION

Snakebite is one of the most common causes of venomous animal bite in the world and in South Korea. There are 3,000 snake species worldwide [1]; about 15%–20% of species are venomous and are therefore medically important [2]. In South Korea, there are 14 species of snake, of which four are venomous [3].

Snake venom is one of the most complex natural toxins [4]. Although the taxonomies of snake venoms vary, the most important snake toxins from a clinical perspective include neurotoxins, hemorrhagins, coagulant toxins, nephrotoxins, myotoxins, and necrotoxins [5]. The composition of snake venom also varies between species and is influenced by the season, re-

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gion, and what the snake has ingested [3,6]. Therefore, victims of snakebite present with a variety of symptoms. Snakebites can cause local and systemic symptoms including coagulopathy [7].

Coagulopathy is a very common complication of snakebite that can cause serious sequelae and may be life-threatening. However, its clinical pattern and course differs from coagulopathy induced by other diseases [3]. Furthermore, there is some controversy regarding the treatment in patients without bleeding [2,3,5,8]. Therefore, at first, we introduced the clinical outcomes of 226 snakebite patients briefly. And then we evaluate risk factors of coagulopathy, its clinical feature and discuss its monitoring and treatment especially in case of no definite bleeding.

MATERIALS AND METHODS

We retrospectively reviewed the medical records of patients who were hospitalized for the treatment of snakebites between January 2006 and September 2018 at the six Hallym University affiliated hospitals. We included all snakebite cases regardless patients reported specific venomous species or not during the period. We excluded patients if it was unclear whether they were bitten by a snake, patients who refused hospitalized treatment and did not visit the hospital thereafter, and patients who were transferred to another hospital before finishing treatment.

To assess the severity of snakebite-associated coagulopathy, we used the disseminated intravascular coagulation (DIC) scoring system developed by the International Society on Thrombosis and Hemostasis (ISTH) as follows: normal (ISTH score, 0), simple coagulopathy (1 to 4), and overt DIC (≥ 5) [9].

We analyzed sex difference, age, body mass index, initial laboratory data at the first presentation to evaluate risk factors of coagulopathy, in particular the overt DIC. As previous studies suggested possibility that coagulopathy associated cholesterol level, leukocytosis, hemolysis and rhabdomyolysis [10,11], we chose variable of initial laboratory data based on them. Hospital stay and mortality were used to evaluate the prognosis. We also used international normalization ratio (INR) prolongation period and hospital stay to evaluate the effectiveness of each treatment option for the patients whose INR immeasurably high without bleeding.

Research Ethics

This study was approved by the Institutional Review Board of Hallym University Dongtan Sacred Heart Hospital (IRB No. 2009-01-004-001). Because of the retrospective nature of this

KEY MESSAGES

- Initial lower cholesterol level may be a risk factor for overt disseminated intravascular coagulation following snakebite.
- Even if patients do not have apparent symptoms, the risk of coagulopathy should be assessed for at least 4 to 5 days following snakebite.
- Higher antivenom doses and transfusion of fresh frozen plasma or cryoprecipitate may be unbeneficial for coagulopathic patients without bleeding.

study, the need for informed consent from enrolled subjects or their surrogates was waived. Therefore, this study did not impact on the patients' treatment.

Statistical Analysis

Independent t-test and analysis of variance were used for parametric tests, and the Mann-Whitney test, Kruskal-Wallis test, and chi-square test were used for nonparametric tests. Univariate and multivariable logistic regression was performed to assess associations with overt DIC. A P-value of <0.05 (two-tailed) was considered to be statistically significant. IBM SPSS ver. 24.0 (IBM Corp., Armonk, NY, USA) was used for all statistical analyses.

RESULTS

General Characteristics and Clinical Outcomes

Among 226 patients included in the study, 157 were male and 69 were female. The median and interquartile range (IQR) of age was 54.0 years (IQR, 43.0 to 63.0 years). The median and IQR of body mass index was 23.9 kg/m² (IQR, 21.0 to 25.7 kg/m²). Seventy-two patients had underlying diseases such as hypertension, diabetes mellitus, dyslipidemia, chronic lung disease, chronic liver disease, and neurologic disorders. The median and IQR of hospital stay was 4.0 days (2.0 to 7.0 days). Five patients arrived at the hospital in a state of shock. One patient suffered hypotension and cardiac arrest within 30 minutes after the snakebite and died 2 days later because of multi-organ failure (Table 1). Only 44 patients (19.5%) were able to identify species of venomous snake.

Comparison of Patients According to the Presence and Severity of DIC

We could assess the presence/severity of coagulopathy using the ISTH scoring system in 167 patients; coagulopathy could

Table 1. Patient demographics, initial laboratory data at first presentation, and clinical outcomes

Variable	Result
Demographics	
Total patients	226
Sex (male:female)	157:69 (69.47:30.53)
Age (yr)	54.0 (43.0–63.0)
BMI (kg/m ²)	23.9 (21.0–25.7)
Underlying disease	72 (31.86)
Initial laboratory data	
Hb (g/dl)	14.36 ± 1.61
WBC (×10 ³ /μl)	8.10 (6.40–10.55)
Platelet (×10 ³ /μl)	242.38 ± 74.53
Cr (mg/dl)	0.84 (0.70–1.00)
CPK (IU/L)	163.00 (107.00–248.00)
ALT (IU/L)	21.00 (15.00–29.00)
Albumin (g/dl)	4.30 (4.10–4.50)
Cholesterol (mg/dl)	172.40 ± 38.41
Clinical outcome	
Hospital stay (day)	4.0 (2.0–7.0)
Initial shock ^a	5 (2.21)
Death	1 (0.44)

Values are presented as number (%), median (interquartile range), or mean ± standard deviation.

BMI: body mass index; Hb: hemoglobin; WBC: white blood cell; Cr: creatinine; CPK: creatine phosphokinase; ALT: alanine aminotransferase.

^aDefined as systolic blood pressure < 80 mm Hg or administration of vasopressors prior to hospital admission or in the emergency department.

not be assessed in the other 59 patients (26.1%) due to incomplete examinations. Three subgroups were defined according to the ISTH scoring system: the normal group comprised 88 patients (52.7%), the simple coagulopathy group comprised 58 patients (34.7%), and the overt DIC group comprised 21 patients (12.6%). The one expired patient met the criteria of overt DIC. However, as we mentioned above, the overt DIC seemed to come from multiorgan failure after cardiac arrest, rather than direct effect from coagulopathic venom.

In statistical analysis of subgroups according to the ISTH scoring system, initial white blood cell (WBC) count, initial cholesterol level and hospital stay reached statistical significance (Table 2). Bleeding occurred in six patients, including major bleeding complications in two patients (diffuse alveolar hemorrhage and hemothorax) and minor bleeding in four patients (e.g., ecchymosis, petechiae, and hematoma in extremities). The two patients with major bleeding and two patients with minor bleeding met the criteria of overt DIC. The other two patients with minor bleeding met the criteria for simple coagulopathy. No definite thrombotic or embolic complications were identified in any patient.

Comparison between Patients without Overt DIC and Patients with Overt DIC

We divided the patients into two groups, as patients without overt DIC (normal group plus simple coagulopathy group) and patients with overt DIC. Univariate analyses showed that

Table 2. Characteristics of patients without coagulopathy, patients with simple coagulopathy, and patients with overt DIC

Variable	Normal (n=88)	Simple coagulopathy (n=58)	Overt DIC (n=21)	P-value
Sex (male:female)	68:20 (77.27:22.73)	34:24 (58.62:41.38)	15:6 (71.43:28.57)	0.054
Age (yr)	54.0 (43.00–60.00)	55.5 (47.00–69.00)	54.0 (45.00–71.00)	0.347 ^a
BMI (kg/m ²)	24.50 (21.72–26.19)	24.12 (21.48–26.41)	22.86 (21.12–25.60)	0.380 ^a
Underlying disease	32 (36.36)	17 (29.07)	9 (42.86)	0.480
Hb (g/dl)	14.40 ± 1.42	14.42 ± 1.63	14.90 ± 1.95	0.409 ^b
WBC (×10 ³ /μl)	7.25 (5.65–8.93)	8.86 (7.10–11.58)	8.75 (7.11–15.06)	0.003 ^a
Platelet (×10 ³ /μl)	240.50 (205.50–299.50)	237.50 (186.00–280.00)	190.00 (163.00–277.00)	0.140 ^a
Cr (mg/dl)	0.90 (0.70–1.00)	0.80 (0.63–1.00)	0.90 (0.70–1.20)	0.181 ^a
CPK (IU/L)	149.00 (105.00–205.00)	163.50 (102.00–276.00)	199.00 (112.50–317.50)	0.706 ^a
ALT (IU/L)	20.00 (15.50–28.00)	21.00 (14.00–28.00)	23.00 (15.00–31.00)	0.507 ^a
Albumin (g/dl)	4.40 (4.20–4.60)	4.30 (4.10–4.50)	4.10 (3.90–4.45)	0.094 ^a
Cholesterol (mg/dl)	178.00 (150.00–195.00)	185.00 (155.00–201.00)	145.00 (124.00–162.00)	0.002 ^a
Hospital stay (day)	3.00 (2.00–5.00)	5.00 (3.00–8.00)	8.50 (7.00–11.50)	<0.001 ^a

Values are presented as number (%), median (interquartile range), or mean ± standard deviation. Presence of coagulopathy could not be assessed in 59 patients due to incomplete examinations. The laboratory data are initial results at the first presentation.

DIC: disseminated intravascular coagulopathy; BMI: body mass index; Hb: hemoglobin; WBC: white blood cell; Cr: creatinine; CPK: creatine phosphokinase; ALT: alanine aminotransferase.

^aAnalysis by Kruskal-Wallis test; ^bCalculated by analysis of variance.

initial higher WBC count, initial lower albumin level and initial lower cholesterol level were associated with the development of overt DIC. However, in multivariable logistic regression using the variables of which P-value less than 0.100 in the univariate analysis, only the initial lower cholesterol was independently associated with the development of overt DIC (Table 3).

The receiver operation characteristic curve of initial cholesterol level and overt DIC shows that the area under the curve is 0.785 (95% confidence interval, 0.703 to 0.853; $P < 0.001$). The optimal cutoff value is 163 mg/dl by Youden index. Its sensitivity and specificity are 0.85 and 0.62, respectively at the cutoff value (Figure 1).

INR Prolongation in Patients with Overt DIC

Among 21 patients with overt DIC, INR was immeasurably high in 19 patients (values exceeding the laboratory’s measurement limits of 8.93, 13, and 25 depending on machine used). For the other two patients, the INR did not increase above 1.5 in one patient and the other patient died before the INR exceeded the maximum measurable value. The median time from snakebite to an INR > 1.5 was 2 days, ranging from 0 to 4 days. The median time from snakebite to immeasurably

high INR was 3 days, ranging from 0 to 4 days. In 15 patients, an immeasurably high INR was recorded on the same day as INR > 1.5 . The maximum interval between INR > 1.5 and immeasurably high INR was 2 days (Table 4).

In addition, there were three patients who reach immeasurably high INR in the simple coagulopathy group. They reached the immeasurably high INR in 3 days, 4 days, and 5 days (but less than 120 hours) after the snakebite, respectively. Those days were same day of INR above 1.5. The highest INR was 1.43 in the patients who did not reach immeasurably high INR and who could assess ISTH scoring system except for the one dead patient.

Table 3. Univariate and multivariable logistic regression analyses of factors associated with overt DIC

Variable	Univariate		Multivariable	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Female sex	0.93 (0.34–2.55)	1.000		
Age	1.00 (0.98–1.03)	0.963		
BMI	0.89 (0.78–1.03)	0.112		
Underlying disease	1.49 (0.59–3.76)	0.554		
Hb	1.22 (0.91–1.63)	0.182		
WBC	1.00 (1.00–1.00)	0.008	NS	NS
Platelet	1.00 (1.00–1.00)	0.082	NS	NS
Cr	0.98 (0.62–1.55)	0.925		
CPK	1.00 (1.00–1.00)	0.792		
ALT	1.00 (1.00–1.01)	0.297		
Albumin	0.21 (0.07–0.64)	0.006	NS	NS
Cholesterol	0.97 (0.96–0.99)	0.003	0.97 (0.96–0.99)	0.006

The laboratory data are initial results at the first presentation. In multivariable logistic regression, the variables of which P-value less than 0.100 in the univariate analysis were used.

DIC: disseminated intravascular coagulopathy; OR: odds ratio; CI: confidence interval; BMI: body mass index; Hb: hemoglobin; WBC: white blood cell; NS: not significant; Cr: creatinine; CPK: creatine phosphokinase; ALT: alanine aminotransferase.

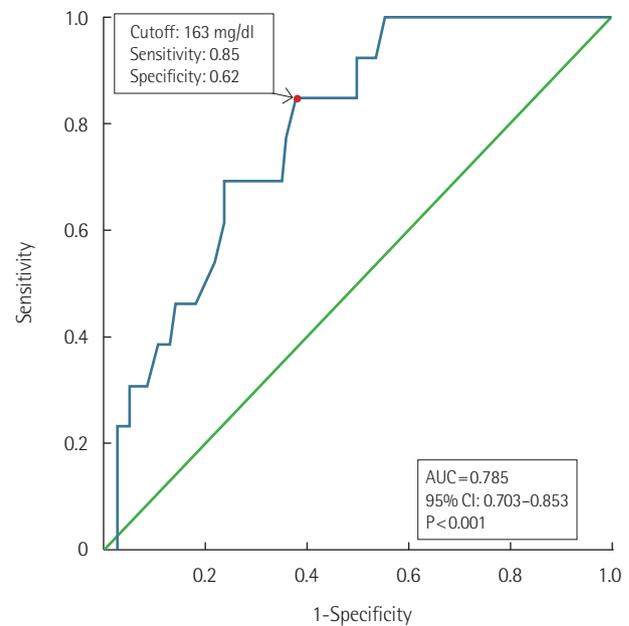


Figure 1. The receiver operation characteristic curve of initial cholesterol level and overt disseminated intravascular coagulation. AUC: area under the curve; CI: confidence interval.

Table 4. Timing of elevated INR in patients with overt DIC (n = 19)

Variable	Min-max (day) ^a	Median (IQR) (day) ^a
Timing of INR > 1.5	0.0–4.0	2.00 (1.00–3.00)
Timing of INR immeasurably high	0.0–4.0	3.00 (1.00–3.50)
Interval between INR > 1.5 and INR immeasurably high	0.0–2.0	0.00 (0.00–0.00)

Two patients were excluded: in one patient, INR did not increase above 1.5; the other patient died before reaching immeasurably high INR.

INR: international normalization ratio; DIC: disseminated intravascular coagulation; IQR: interquartile range.

^aFrom the day of the snakebite.

Table 5. Effects of antivenom dose on duration of immeasurably high INR and hospital stay in patients with overt DIC without bleeding

Variable	Antivenom dose < 18,000 units (n=8)	Antivenom dose ≥ 18,000 units (n=7)	P-value
Duration of INR >3 (day)	4.00 (2.00–5.50)	2.00 (1.50–3.00)	0.195
Hospital stay (day)	9.00 (7.00–10.00)	8.00 (6.50–10.00)	0.598

Values are presented as median (interquartile range). One patient was excluded because INR was not increased.

INR: international normalization ratio; DIC: disseminated intravascular coagulation.

Effect of Antivenom Dose and Transfusion in Patients with Overt DIC without Bleeding

Among the 21 patients with overt DIC, 16 patients did not experience bleeding (five patients were excluded; four patients had bleeding, the other one patient died before determining clinical result such as bleeding from overt DIC). All of these patients were administered antivenom (*Agkistrodon halys* antivenom injection; 6,000 units/vial; the only antivenom in South Korea). In 15 of the patients, the first dose was administered within 3 hours after the snakebite. The other one patient was administered the first dose of antivenom more than 9 hours after the snakebite.

INR was immeasurably high in 15 patients, and did not increase above 1.5 in the other one patient in the 16 overt DIC patients without bleeding. Among 15 patients with immeasurably high INR, the duration of INR above 3 and hospital stay were not significantly different between patients whose antivenom dose was ≥ 18,000 units and patients whose antivenom dose was < 18,000 units (Table 5). Eleven patients had fresh frozen plasma (FFP) or cryoprecipitate transfusion. All the eleven patients had FFP transfusion (mean, 9.2 pints from 320 ml or 400 ml of whole blood) and two patients had cryoprecipitate transfusion (mean, 26.5 pints). Likewise, transfusion of FFP or cryoprecipitate was not associated with significant differences in the duration of INR above 3 or hospital stay in the 15 patients with immeasurably high INR (Table 6).

DISCUSSION

Epidemiology of Venomous Snakebites

The World Health Organization estimated that there are more than 421,000 cases of venomous snakebites per year, with 20,000 deaths [12]. In a prior study in South Korea, it was reported that between 142 and 621 cases of snakebite occurred per year, with five deaths [3]. In previous studies in South Korea, there were

Table 6. Effects of transfusion of FFP or cryoprecipitate on duration of immeasurably high INR and hospital stay in patients with overt DIC without bleeding

Variable	Non-transfusion (n=4)	Transfusion (n=11)	P-value
Duration of INR >3 (day)	4.00 (1.50–6.50)	3.00 (1.50–4.50)	0.465
Hospital stay (day)	7.00 (6.00–11.00)	8.00 (7.00–10.00)	0.597

Values are presented as the median (interquartile range). One patient was excluded because INR was not increased.

FFP: fresh frozen plasma; INR: international normalization ratio; DIC: disseminated intravascular coagulation.

more snakebites in men than in women, and most people were in their 40s or 50s [7,13]. In our study, all snakebites occurred between April and November because snakes in South Korea typically emerge in April and hibernate in November [13].

Coagulopathy Caused by Snake Venom

As described above, coagulopathy is one of the most common complications of snakebites. Kim et al. [11] reported that the cholesterol level was lower in patients with DIC. Winkler et al. [10] reported that the serum total cholesterol level on admission may indicate the severity of envenomation in patients bitten by snakes belonging to the *Vipera* family before the clinical syndrome fully develops. In our study, multivariable logistic regression showed that initial lower cholesterol level was associated with the development of overt DIC.

Snake venoms that cause coagulopathy can be classified as procoagulant toxins, anticoagulant toxins, platelet activity toxins, and vessel wall interactive toxins [2,14–16]. Coagulopathy manifested as prolonged INR, hypofibrinogenemia, thrombocytopenia, and increased fibrin degradation products in laboratory studies. In our study, 19 patients had immeasurably high INR among the 21 overt DIC patients, which could be explained as venom-induced consumption coagulopathy (VICC).

Venom-Induced Consumption Coagulopathy

VICC describes any coagulopathy resulting from the consumption of clotting factors by procoagulant toxins present in snake venom [5]. It is caused by venom from various snake species, including members of the Viperid, Elapidae, and some Colubridae families [17]. DIC results from activation of clotting pathway and has a very high mortality. By contrast, VICC involves a different pathogenic process (specific enzyme activation) and needs to be treated differently, but has a more benign course than DIC [2]. Procoagulant toxins cause rapid clot formation *in vitro*, but, *in vivo*, they cause consumption of severe clotting

factors therefore increase the risk of bleeding. Different snakes have different kinds of toxins, and the toxins activate various components in the clotting pathway [2]. The toxins in venom that cause VICC are classified by where they effect in the clotting pathway, with the important ones being thrombin-like enzymes (also known as fibrinogenase), prothrombin activators, factor V and X activators [14]. Lee et al. [7] reported abrupt prolongation of prothrombin time (PT) and activated partial thromboplastin time (APTT) on days 2 and 4 of hospitalization. In our study, we found the peak INR occurred as late as 4 days after the snakebite in the overt DIC group, as late as 5 days (less than 120 hours) in the simple coagulopathy group as well. We also noted that INR prolongation showed an abrupt pattern rather than gradual pattern because INR increased rapidly from 1.5 to immeasurably high on the same day in 15 of 19 patients with an immeasurably high INR in the overt DIC group, three of three patients with an immeasurably high INR in the simple coagulopathy group as well. Therefore, we suggest that coagulopathy should be monitored for at least 4 to 5 days after a snakebite, even in patients without apparent symptoms. Clinicians should also consider the possibility of VICC if their patient's INR rises above 1.5 within that period of time. The type of toxin and the administration of antivenom determine the duration of VICC. It took 24–48 hours to resolve VICC in Australian elapid envenoming regardless of antivenom treatment, and the rate of recovery was found to depend entirely on the production of new clotting factors [15]. On the other hand, Echis-induced VICC continued for days without antivenom treatment [18]. However, the patients recovered within 24–48 hours with antivenom treatment in Echis-induced VICC. This suggests that once the toxin is neutralized, the clotting factors recover normally. In the study by Lee et al. [7], it took a mean of 11.5 ± 2.4 days for INR to fall below 1.2.

Treatment of Coagulopathy Caused by Snake Envenomation

The aim of treating snakebite-induced coagulopathy is to prevent major bleeding and associated complications [2]. This is primarily achieved by neutralization of the procoagulant toxins followed by recovery of clotting factors up to a level where minor injury does not cause major bleeding.

Antivenom is the standard treatment for snake envenoming [19], and is highly effective for binding toxins and neutralizing their effects [20]. After the toxins have been neutralized, the patient's clotting function should recover within 24–48 hours [21]. However, the clinical benefit of antivenom in VICC may differ for different snakes [22,23]. The antivenom avail-

able in South Korea neutralizes venom from three of four venomous snakes in the region [3]. However, there are no specific guidelines regarding its indications and optimal dosage [3].

Clotting factor replacement for VICC without bleeding is controversial because this strategy may worsen VICC by increasing the supply of clotting factors (substrates) to procoagulant toxins, and hence this may “add fuel to the fire” [24,25]. In an Australian study, ongoing reductions in fibrinogen was shown in patients with FFP given within 6 hours of a snakebite, despite prior neutralization with antivenom [25]. However, one study suggested that early use of FFP may allow quicker recovery from VICC [22]. In our study, transfusion of FFP or cryoprecipitate did not influence the duration of increased INR or hospital stay in patients without bleeding. However, patients have active bleeding, clotting factor replacement may expedite the recovery of VICC [2].

Limitations

This study has several limitations to discuss. First, because this was a retrospective observational study, the admission, examination, treatment, and discharge of patients were at the attending doctor's preference rather than a predetermined protocol. Second, this study focused on hospitalized patients, not outpatients. Therefore, the patients included in this study may have had more severe snakebites than those treated in outpatient settings. Third, total number of the overt DIC patients was small. Larger number of patients are required to get more definite conclusion.

Conclusion

Snakebites can cause a broad spectrum of symptoms with variable severity; coagulopathy is one of these symptoms. Initial lower cholesterol level could be a risk factor of developing overt DIC. The risk of coagulopathy should be assessed for at least 4 to 5 days following snakebite. Higher doses of antivenom and transfusion with FFP or cryoprecipitate may be unbeneficial for patients without bleeding.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Conceptualization: YJJ. Data curation: YJJ, JWK. Formal analysis: YJJ. Methodology: YJJ, SGP, DWS. Project administration, Visualization, & Writing - original draft: YJJ. Writing - review & editing: YJJ, JWK.

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