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Field sting reactions in patients receiving Hymenoptera venom immunotherapy: real-life experience

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Abstract

Background: Hymenoptera stings can cause systemic allergic reactions (SARs) that are prevented by venom immunotherapy (VIT). Sting challenge tests or field stings are used to evaluate the outcome of VIT.

Objective: The aim of the study was to investigate the consequences of field stings in patients during or after completion of VIT, and to identify patients at higher risk.

Methods: Patients treated with VIT between 1995 and 2018 were retrospectively evaluated. Contacted patients were invited to the clinic and a questionnaire was conducted regarding the history of field stings.

Results: A total of 115 patients (F/M: 45/70, mean age: 38.5 ± 12 years) treated with VIT were included; 74/115 were contacted and asked about field stings after VIT cessation. A history of 73 field stings was reported in 38 patients, 25 of whom were treated with honeybee venom and 13 with common wasp venom. Eighteen of the reactions were SARs [8 with honeybees (1 grade-I, 6 grade-II, 1 grade-III) and 10 with common wasps (1 grade-I, 5 grade-II, 4 grade-III)]. There was no association between the severity of index reactions and field stings with either the honeybee or common wasp. The median duration of VIT was longer in patients showing no reaction than in patients with an SAR. Of the 7 patients on ACE inhibitors or beta-blockers, 1 asthmatic patient developed grade-II SAR due to field stings in the first year of VIT.

Conclusion: This study confirms that VIT lasting at least 3 years is effective in preventing SARs after field stings.

Key words: honeybee venom, common wasp venom, insect allergy, immunotherapy, sting reactions, field sting, systemic allergic reaction, local allergic reaction, adverse effects, ACE inhibitor, severity of index reaction

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Introduction

Hymenoptera venom allergy in adults is one of the most common causes of anaphylaxis along with food and drug reactions. It has been reported that nearly half of the anaphylaxis seen in adults is secondary to venom allergy.[1] In fact, Hymenoptera stings can cause a wide variety of reactions, from mild to life-threatening anaphylaxis. Systemic allergic reactions (SARs) due to Hymenoptera stings affect up to 5% of the adult population.[1,2] Venom immunotherapy (VIT) has been proven both to protect most patients with IgE-mediated systemic sting reactions from the risk of future serious SAR and to improve quality of life.[3] However, how long VIT should be continued is still a controversial issue. Recent guidelines generally recommend a VIT duration of at least 3 to 5 years, although more than 5 years of lifetime therapy is recommended in some high-risk patients (e.g., in mastocytosis).[4,5]

The sting challenge test is known as the gold standard for demonstrating the efficacy of VIT. However, if this test is not possible, the result of natural field sting reactions may help to understand the efficacy of VIT.[3] There are very few reports in the literature describing the results of field stings in patients

during and after VIT treatment. In this study, our objective was to evaluate the safety and efficacy of honeybee and common wasp VIT based upon self-reported field stings; furthermore, we wanted to elucidate patients at higher risk for systemic sting reactions. The nature of symptoms after field stings and adverse reactions related to VIT were also analyzed.

Methods

Study design

This study was conducted as a prospective survey and a retrospective review of the files of patients treated between 1995 and 2018 in the Ankara University School of Medicine, Department of Chest Diseases, Division of Immunology and Allergy. Two physicians (RK and ZCS) reviewed the charts. This study protocol was reviewed and approved by the local ethics committee of Ankara University School of Medicine (Number: 13-806-17), and written informed consent was obtained from all participants.

Study population

A total of 125 patients treated with VIT were evaluated. Ten were excluded because they did not continue the maintenance phase of VIT. A total of 115 patients who underwent VIT between 1995 and 2018 were included. Patient records were reviewed for demographic characteristics, detailed history of insect sting reaction, co-morbid diseases, beta-blocker and/or angiotensin-converting enzyme inhibitor (ACEI) drug use, schedules of VIT, type of venom used for immunotherapy, severity of index sting reaction, number of adverse effects, and the number and severity of field sting reactions during the up-dosing and maintenance phases of VIT. Afterwards, all patients were called by phone and contacted patients were invited to the clinic and asked to complete a questionnaire on the field sting reactions after VIT cessation. In addition to the file records about field sting reactions during VIT, detailed information about field sting reactions such as the time of field sting, how many stings, type of insect and severity of the reaction were obtained after VIT was discontinued in 74 out of 115 patients.

Measurements

Diagnosis of Hymenoptera venom hypersensitivity was based on clinical history, positive skin prick (SPT), and/or intradermal skin tests (IDT) and/or detection of sIgE antibody to the respective venom strain. First, SPTs (100 and 300 µg/mL) were performed on all patients with commercially available venom extracts including *Apis mellifera* and *Vespula vulgaris* (ALK-Abello, Madrid, Spain). Histamine dihydrochloride (10 mg/mL) was used for the positive control and saline was used for the negative control. A positive reaction was considered as a wheal diameter of 3 mm or more compared to the negative control after 20 minutes. IDTs were performed with the same venom extracts in patients whose SPT results were negative. The IDT started with a concentration of 0.001 µg/mL and then increased in 10-fold increments to a maximum of 1 µg/mL if the results were negative. IDTs were evaluated at 20-minute intervals and considered positive if at least ≥ 3 mm edema with erythema occurred.[6]

Specific IgE levels for whole venom (i1; *A. mellifera* and i3; *V. vulgaris*) of all patients were measured according to the manufacturer's instructions. Antibody concentrations higher than ≥ 0.35 kU_A/L were considered positive (Thermo Fisher, Phadia, Uppsala, Sweden).

Venom immunotherapy

In our clinic, all patients except 1 were treated with *A. mellifera* or *V. vulgaris* venom extracts using rush, clustered or conventional protocols. The rush VIT regimen was completed within 7 days in hospitalized patients.[7] Conventional VIT build-up was typically given as a weekly injection until the maintenance dose was reached. A weekly cluster regimen of 2 or more injections per visit was administered during the up-dosing phase over a 7-week period, followed by monthly maintenance injections of 100,000 SQ-U/mL. Biologically standardized extracts in depot (adsorbed in aluminum hydroxide) allergen product were administered for clustered and conventional protocols while aqueous formulation was administered for the rush schedule (ALK-Abello, Madrid, Spain). Trained nurses administered the subcutaneous injections. Full emergency resuscitation facilities were always available, and all patients stayed at the immunotherapy unit for at least 30 minutes after application of the dose. Allergen extract dosage, local and systemic reactions, and treatment of adverse effects were recorded. Adverse reactions were classified by their type and severity. Indurations larger than 10 cm in diameter were described as large local reaction (LLR). During the VIT course, patients were interviewed at every VIT administration visit during the up-dosing period and every 4 to 6 weeks in the maintenance period. Field sting events and possible reactions were also recorded during the VIT course. Immediate systemic reactions were classified from grade-I to grade-IV according to the method of Ring and Messmer.[8]

Statistical analysis

The statistical analysis was performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). Numeric values with normal dispersion are expressed as means ± SD, and non-normally distributed variables are given as median values (IQR). Categorical variables are given as n (percentage). The chi-square test was used for the comparison of 2 independent groups for categorical data. The importance of the difference according to the means between groups was examined using Student's t-test. The Mann–Whitney U test was used to determine the importance of the difference in medians between independent groups. All directional p values were 2-tailed, and significance was assigned to values lower than 0.05.

Results

Demographics

A total of 115 patients (45 F/70 M) with a mean age of 38.52 ± 12.67 years were included in the study. The severity of the index systemic reaction before VIT was grade-II in 18 patients, grade-III in 86 patients and grade-IV in 11 patients. Sixty-two patients were treated with honeybee venom (BV), 52 patients with common wasp venom (WV), and 1 patient with BV and WV. Patients were treated with either cluster (42.5%), rush (40.8%) or conventional (16.5%) VIT.

Table 1. Characteristics of study population.

		Honeybee venom N (%) N: 62	Common Wasp venom N (%) N: 52	Honeybee + Common wasp N (%) N: 1	TOTAL N: 115
Gender	Female	21 (33.9)	24 (46.2)		45
	Male	41 (66.1)	28 (53.8)	1 (100)	70
Mean age ± SD (years)		39.02 ± 13.2	38.33 ± 11.9	18	38.52 ± 12.67
Mean duration of VIT (months)		40.39 ± 18.82	39.72 ± 20.93	38.79	40.07 ± 19.64
Schedule of VIT	Clustered	27 (43.5)	22 (42.3)		49 (42.6)
	Rush	29 (46.8)	18 (34.6)		47 (40.8)
	Conventional	6 (9.7)	12 (23.1)	1	19 (16.5)
Duration of VIT	5 years or more	15 (24.2)	15 (28.8)		30 (26)
	Continuing on maintenance phase	14 (22.6)	6 (11.6)		20 (17.3)
	1 to 3 years	18 (29)	18 (34.6)	1	37 (32.1)
	3 to 4 years	15 (24.2)	13 (25)		28 (24.3)
Field sting history (N: 38)	No reaction	20 (80)	7 (53.8)		27 (71)
	SAR	3 (12)	5 (38.4)		8 (21)
	LLR	2 (8)	1 (7.6)		3 (7.9)
Index reaction	Grade-II	14 (22.6)	4 (7.7)		18 (16)
	Grade-III	46 (74.2)	39 (75)	1 (100)	86 (75)
	Grade-IV	2 (3.2)	9 (17.3)		11 (9)

VIT: venom immunotherapy, SAR: systemic allergic reaction, LLR: large local reaction.

Mean duration of VIT was 40.07 ± 19.67 months. Ninety-five patients completed their maintenance treatment and VIT was stopped. Twenty patients were still on the maintenance dose of VIT (**Table 1**).

Adverse effects during venom immunotherapy administration

Adverse reactions occurred in 38 patients during VIT administration, of which 28 were SAR (18 BV, 9 WV and 1 BV + WV) and the remaining 10 were LLR (4 BV and 6 WV) (**Figure 1**). The rate of SAR for all patients undergoing VIT was 29.47% (28/95). The severity of SAR in the patients was grade-I (n: 13), grade-II (n: 11) or grade-III (n: 4). The timing of adverse reactions was mostly during the up-dosing phase (n: 16, 57.1%) and the first year of the maintenance phase of VIT (n: 12, 42.8%). Recurrent systemic reactions were seen in 5 patients treated with BV during the up-dosing phase. Recurrent reactions occurred no more than twice in the same patient, and all were similar in severity to the patient's initial adverse reaction. The frequency of adverse reactions during VIT administration was higher in asthmatic patients. The rate of SAR in asthmatic patients was 66% (4/6).

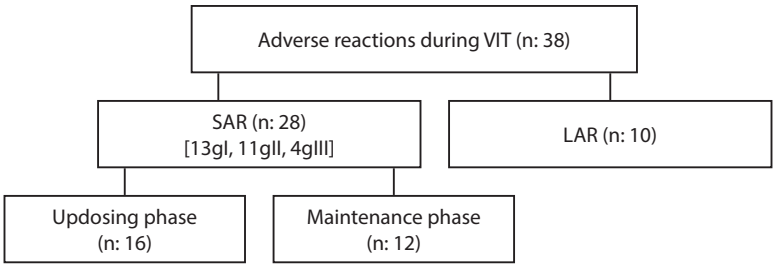

Figure 1. Frequency and severity of VIT-associated reactions.
SAR: systemic allergic reaction, LAR: local allergic reaction, g: grade

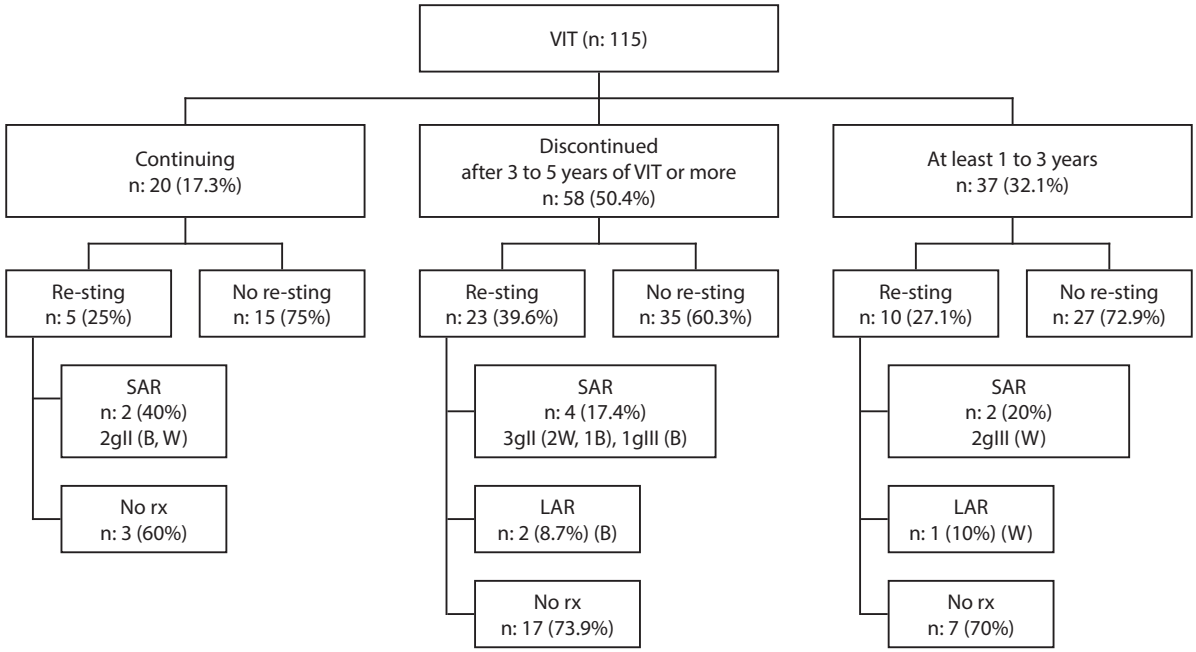

Figure 2. Patients reacting systemically to field stings during or after VIT.
VIT: venom immunotherapy, SAR: systemic allergic reaction, LAR: local allergic reaction, no rx: no reaction, B: honeybee, W: wasp, g: grade

Reactions due to field stings

Field sting reactions during VIT were recorded from the patient files. Seventy-four out of 115 patients (64.3%) were contacted and asked about field stings after VIT cessation. Thirty-eight (51.4%) of 74 patients reported a history of field sting. Among them, 25 (65.8%) were treated with BV and 13 (34.2%) with WV. Of the 38 patients reporting a field sting, systemic reactions developed in 3 patients on BV and 5 patients on WV. Of these 8 patients, 4 had VIT for at least 3 to 5 years [3 grade-II, 1 grade-III]; 2 continued VIT for less than 3 years [2 grade-III]; and 2 were still receiving treatment [2 grade-II] (p = 0.57) (**Figure 2**).

In terms of the number of field stings, these 38 patients had 73 field sting reactions with honeybees or common wasps at various times during the VIT schedule (1 field sting in 19 patients, 2 field stings in 7 patients, 3 field stings in 9 patients, 4 field stings in 2 patients and 5 field stings in 1 patient) (Figure 3). Importantly, the vast majority of field stings were LLR (4%) or were asymptomatic (71.2%). Eighteen (24.6%) of the field stings resulted in 8 SARs (1 grade-I, 6 grade-II, 1 grade-III) with honeybees and 10 SARs (1 grade-I, 5 grade-II, 4 grade-III) with common wasps.

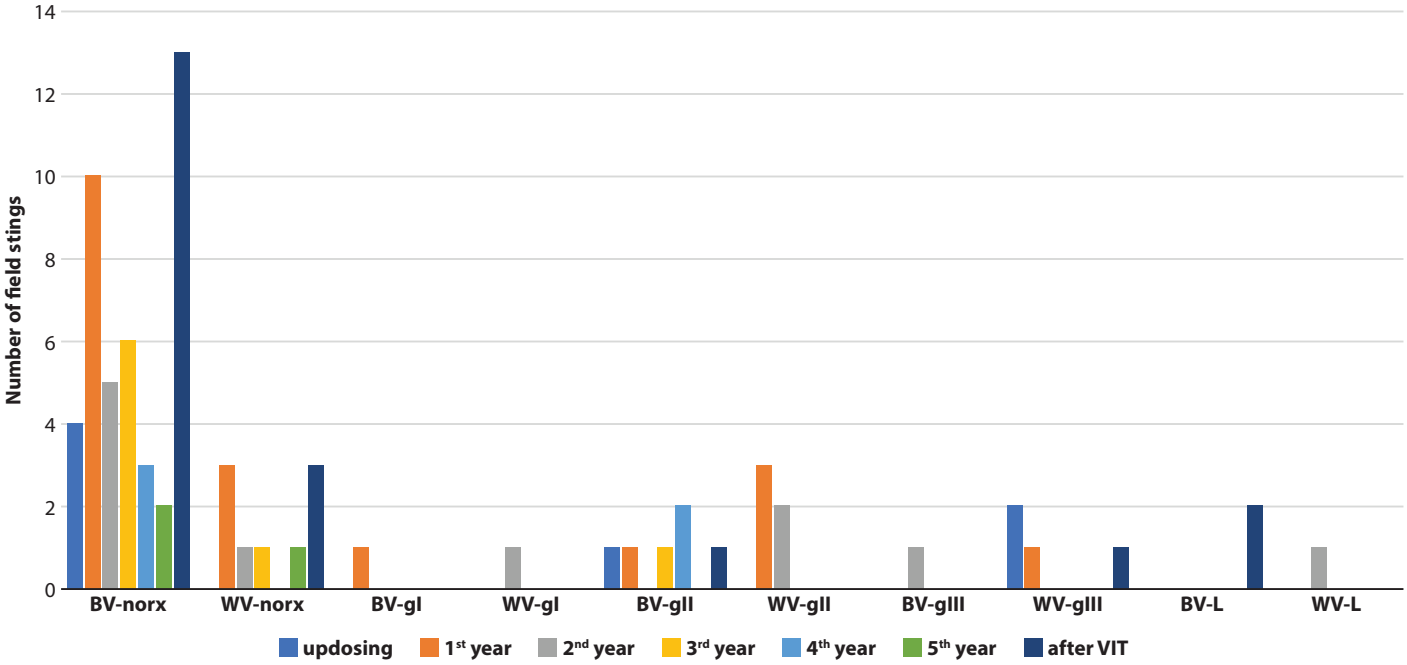

Figure 3. Number of honeybee or common wasp field stings and grade of reactions in 38 patients, 73 events.
WV: wasp venom, BV: honeybee venom, g-I: grade-I, g-II: grade-II, g-III: grade-III, L: local reaction, no rx: no reaction.

There was no difference in the severity of the index reaction or field sting reactions with either honeybee or common wasp. An important finding of the study was that median duration (IQR) of VIT was longer in patients showing no reaction than in patients with SAR after field stings [56.61 (27.02) vs 38.30 (31.82) months, respectively] ($p = 0.44$). On the other hand, it was found that patient's age, gender, kind of bee, duration of VIT and the severity of the index reaction did not increase the risk of the field sting SARs.

Seven patients used ACEIs or beta-blockers. An asthmatic patient on ACEI therapy developed grade-III SAR after VIT injection during up-dosing as well as the maintenance phase. In the same patient, 2 grade-II SARs occurred in the first year of VIT due to sting re-exposure.

Discussion

In this retrospective cohort study, we reported 38 patients who experienced 73 field stings following discontinuation of honeybee or common wasp VIT or during maintenance. Eighteen field stings occurring in 8 patients were categorized as systemic reactions. Contrary to other epidemiologic studies, the number of patients with BV allergy was higher than that of those allergic to WV in our group. We can explain this situation by the presence of allergic honey beekeepers in the study. There is general agreement in current guidelines that a duration of VIT of at least 3 years or more provides a high rate of protection while this protection sometimes occurs early, at the end of the VIT up-dosing period or in the first year of the maintenance phase.[3,9] A meta-analysis of 6 studies reported that only 2.7% of patients who underwent VIT experienced SAR following a sting, compared to 39.8% of untreated patients.[10] As is well known, the results of VIT with WV are somewhat more favorable than those with BV. But, unlike other studies, common wasp field stings caused more SARs than honeybee stings in our study group.

VIT is associated with an increased risk of adverse events during the up-dosing and maintenance phases in some patients and the range of adverse events reported in the literature varies from 17.9% to 45%.[11] Fortunately, in our cohort, we observed that the adverse effects which developed during VIT were mostly mild SARs and LLRs, and the treatment response was good. It was found that patients who are allergic to BV have a higher risk of developing SAR during VIT injections. This is consistent with the reports published to date.[12] As reported in several previous studies, most of the systemic adverse reactions in our study occurred during the up-dosing phase and in patients with asthma.[7,13]

While most SARs that occur in response to a field sting during VIT are mild, serious SAR fatalities have been reported following completion of the recommended maintenance years of VIT, even at times following previously tolerated field stings.[14] Unfortunately, data on sustained unresponsiveness after stopping VIT are much more limited. In patients receiving BV or WV immunotherapy for at least 3 to 5 years, sustained unresponsiveness to systemic reaction by culprit insect or sting challenge test varies between 80% and 95%, respectively.[15,16] In our population, 21% (8/38) of the patients exposed to field stings developed SAR. In the studies by Golden et al, the SAR rate was reported to be 9.5% in a group exposed to field stings at 1-to-2-year intervals for up to 5 years after at least 5 years of maintenance therapy. In their long-term observational study which included 51 more patients, they reported 26% of SARs developed in field stings 5–10 years after VIT was stopped.[17,18] These authors concluded that more than 80% of patients can discontinue VIT after 5 to 6 years, and the risk of an SAR to a sting is relatively low. Another study reported a 10.1% SAR in subjects with field sting over an observation period of up to 7 years after stopping VIT.[19] Finally, Lerch et al reported that this rate was 12.5% in at least 3 years of follow-up after VIT was discontinued.[20] It was thought that the lower SAR rates in these studies compared to our study were due to the fact that all patients in these studies completed the VIT in a sufficient time. Based on most of the findings in the literature, VIT duration appears to be a principal factor for efficacy.[19,20] In line with the literature, the median (IQR) duration of VIT in our study, although not significant, was longer in patients who remained unresponsive than in patients who developed SAR after field stings. In a recent study, Pickert et al reported that of 54 patients followed up to 29 years, 23 (79%) who had at least one field sting after VIT was discontinued had no systemic reaction, indicating that VIT was succesful.[21] This rate is quite similar to the success rate of 71.2% in our study.

The number of patients using anti-hypertensive drugs with systemic reactions in our study should be considered too small to draw meaningful observational conclusions in terms of increased risk of adverse effects or failure of VIT. In a recent multicenter study, it was shown that taking beta-blockers or ACEIs did not increase the frequency of systemic adverse events during VIT and did not reduce the efficacy of VIT.[22]

Some limitations of the study should be highlighted. First, the study was designed retrospectively. Second, although the study group was not homogeneous and included individuals who had received VIT for less than 3 years, making it difficult to evaluate the efficacy of immunotherapy, the proportion of these individuals to the entire group was low. Third, there might be a recall bias of field sting reactions as some of them were asked retrospectively. Fourth, we did not evaluate any other biomarkers (e.g., serum tryptase, IgG4 level) in all patients, and therefore could not include these parameters in our analysis. However, current guidelines also do not recommend measurement of any other biomarkers, such as specific IgE or skin test reactivity in the follow-up of patients undergoing VIT.[3]

Conclusion

This study confirms that VIT is highly effective and safe, as most of the side effects during the induction phase are mild. Furthermore, most patients tolerated field sting events, and an important aspect of this study is that patients who did not experience field sting reactions received longer duration of VIT. On the other hand, it seems that at least 3 years of VIT is needed to prevent serious systemic reactions after field stings. We hope that our results will mimic the situation observed in daily clinical practice.

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Statement of Ethics

This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The study protocol was approved by the local ethics committee of Ankara University, Ankara, Turkey (Number: 13-806-17), and written informed consent was obtained from all participants.

Conflict of Interest

The authors declare that they have no conflict of interest.

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The authors did not receive any funding.

Author Contributions

- BAS: made contributions to the study concept and design, collecting and analysis of data, manuscript drafting and revision.
- ZCS: made substantial contributions to the design, collecting and analysis of data, manuscript drafting and revision.
- RK: made contributions to data collection and analysis.
- PÇ: made contributions to data collection and analysis.
- ÖA, DM, SB, YSD, ZM: were involved in revising the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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