Cukurova Medical Journal
ÇUKUROVA ÜNİVERSİTESİ TIP FAKÜLTESİ

Cukurova Med J 2019;44(3):1040-1045
DOI: 10.17826/cumj.493805

ARAŞTIRMA / RESEARCH

The relationship between neutrophil lymphocyte ratio and clinical outcomes after snakebite in pediatric patients

Çocuk hastalarda yılan sokması sonrası nötröfil lenfosit oranının klinik sonuçlarla ilişkisi

Nagehan Aslan[1], Dincer Yıldızdaş[2], Özden Özgur Horoz[2], Faruk Ekinci[2], Didar Arslan[2], Sevcan Bilen[3], Hayri Levent Yilmaz[3]

[1]Cukurova University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Intensive Care, [2]Department of Pediatrics, Division of Pediatric Intensive Care, [3]Department of Pediatrics, Division of Pediatric Emergency, Adana, Turkey

Cukurova Medical Journal 2019;44(3):1040-1045.

Abstract

Purpose: Snake venom has serious cardiotoxic, neurotoxic, nephrotoxic effects. The neutrophil-to-lymphocyte ratio (NLR) is a new biomarker of inflammation and can be used as an indicator and prognositic marker of inflammation. In this study we aimed to analyze the association with clinical outcomes of pediatric patients with snakebite envenomation, and NLR.

Materials and Methods: A total of 61 pediatric patients with snakebite who admitted to a tertiary university hospital and a children's hospital between July 2012 and July 2017 were included in the study. Demographic features, clinical findings and complications of snakebite, length of stay in hospital, NLR at admission (NLR1), and NLR at the twelfth hour (NLR2) and NLR at the discharge (NLR3) and mean platelet volume (MPV) were retrospectively reviewed and recorded.

Results: There was a positive correlation between NLR1 and the length of hospital stay. We found that as the level of NLR1 increased, the length of hospitalization was prolonged. NLR1 level increased as the disease stage progressed, but it was not statistically significant. Our study showed that when the severity of the illness increased, the length of hospital stay was significantly prolonged.

Conclusion: The study revealed a positive correlation with NLR and severity of the illness. We claim that NLR at admission can be a useful marker for predicting severe clinical course and prolonged hospital length of stay for pediatric patients with snake envenomation.

Keywords: Pediatric, snake, envenomation, the neutrophil-to-lymphocyte ratio.

Öz

Amaç: Yılan zehirinin ciddi kardiyotoksik, nörotoksik, nefrotoksik etkileri mevcuttur. Nötrofil-lenfosit oranı inflamasyonun tanınmasında ve progresyonunda kullanılabilen yeni bir biyomarkerdır. Biz burada yılan sokması nedeni ile izlediğimiz hastaların klinik sonuçları ve nötrofil-lenfosit oranları (NLO) arasındaki ilişkiyi incelemek istedik.

Gereç ve Yönetem: Üçüncü basamak üniversite hastanesi ve bir çocuk hastanesinin çocuk acil ve çocuk yoğun bakım birimlerine, Temmuz 2012-Temmuz 2017 yılları arasında başvuran toplam 61 hastanın demografik özellikleri, klinik bulguları ve komplikasyonları, hastanede yatış süreleri retrospektif olarak tarandı. Başvurudaki (NLO1), 12.saatteki (NLO2), taburculuktaki (NLO3) nötrofil-lenfosit oranı ve mean platelet volüme (MPV) değerleri kaydedildi.

Bulgular: Hastanede yatış süresi ile NLO1 arasında pozitif korelasyon saptandı. NLO1 arttıkça hastanede yatışın uzadığını ve yılan sokmasının evresinin arttığını saptadık. Yılan sokmasının evresi arttıkça hastanede yatış süresinin uzadığını görülmüştür.

Sonuç: Çalışmamız NLO ile hastalık ciddiyeti arasında pozitif korelasyon tespit etmiştir. Buradan yola çıkarak biz, başvuruda yüksek NLO değerleri olan yılan sokmalarında kötü klinik gidiş ve uzamış hastane yatışının öngörülebileceğini düşünmekteyiz.

Anahtar kelimeler: Çocuk, nötrofil-lenfosit oranı, yılan, zehirlenme

Yazışma Adresi/Address for Correspondence: Dr. Nagehan Aslan, Cukurova University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Intensive Care, Adana, Turkey E-mail: nagehan_aslan@hotmail.com
Geliş tarihi/Received: 07.12.2018 Kabul tarihi/Accepted: 24.02.2019 Çevrimiçi yayın/Published online: 08.09.2019

INTRODUCTION

Snake bite is a very serious health problem, especially in tropical regions. Toxic snake bite is a condition that requires urgent intervention and causes significant mortality and morbidity[1]. In Turkey snake bites are more common in warm regions like Mediterranean, south and southeastern regions. *Viperidae* are the most common species however our country contains approximately 40 species of snakes[2]. Çukurova region is also one of the regions where snake poisonings are frequent due to the warm climate[3]. Snake bites cause local and systemic complications ranging from simple extremity oedema up to compartment syndrome and amputation, but often heals without sequelae[4].

The neutrophil-to-lymphocyte ratio (NLR) is an easily available method that can be used in the diagnosis of many rheumatological, dermatological, cardiac, endocrinological disease with an inflammatory component. It is a new biomarker of inflammation and can be used as an indicator and prognostic marker of inflammation. The neutrophil-to-lymphocyte ratio (NLR) is a useful marker that predicts disease progression and mortality in inflammatory disease[5-10].

In this study, we aimed to evaluate the association with clinical outcomes such as hospitalization time and disease severity of pediatric patients who applied for snake envenomation, and NLR in complete blood count.

MATERIALS AND METHODS

A total of 61 patients who were admitted to the emergency department of Çukurova University Balcalı Hospital and Meydan Children's Hospital between July 2012 and July 2017 with snake bite and followed up in the pediatric emergengy and intensive care departments were included in the study. The medical reports of the cases were evaluated retrospectively. Age, gender, season when the snake bite occured, site of bite, clinical findings, local and systemic complications, length of stay in hospital were recorded. The absolute neutrophil count was divided by the absolute lymphocyte count to calculate the NLR. The NLR at admission (NLR1), NLR at the twelfth hour (NLR2), NLR on the day when the patient was discharged (NLR3) and mean platelet volume (MPV) were recorded. All patients were evaluated, and antivenom therapy was administered according to clinical stage. Other treatment approaches (antihistamine, steroid) and antibiotherapy needs and tetanus immunizations were evaluated.

The patients were assessed as having grade 0, 1, 2, 3 according to the severity of poisoning. In grade 0 only puncture wounds can be seen and there are no local or systemic findings. In grade 1 mild tissue swelling and ecchymosis can be detected with no systemic symptoms. In grade 2 pain and ecchymosis can be seen and it is accompanied by prolonged PTT, thrombocytopenia. In grade 3 advanced swelling, pain, necrosis and bullouse lesions can be seen and severe systemic symptoms and coagulopathies. Patients with grade 0 and 1 were considered mild poisoning group, and patients with grade 2 and 3 were considered to be severe poisoning group. The study protocol was approved by the Çukurova University Medical School Ethics Committee (April 2018;76).

Statistical analysis

All analyses were performed using IBM SPSS Statistics Version 20.0 statistical software package. Categorical variables were expressed as numbers and percentages, whereas continuous variables were summarized as mean and standard deviation and as median and minimum-maximum where appropriate. Chi-square test was used to compare categorical variables between the groups. The normality of distribution of continuous variables was confirmed with the Kolmogorov-Smirnov test. For comparison of continuous variables between two groups the Mann Whitney U and for more than two groups the Kruskal Wallis test was applied. To evaluate the correlations between measurements, The Spearman Rank Correlation Coefficient was used. The statistical level of significance for all tests was considered to be 0.05.

RESULTS

Sixty one patients who admitted to pediatric emergency care unit and hospitalized to pediatric intensive care unit because of snake bites were included in the study. Fourty six of the patients were male (75.4%) and the mean age was 128.5±58.7 months (min: 12-max: 210). The site of 20 (32.8%) bites was an upper extremity, the site of 40 (65.5%)

bites was a lower extremity, the site of 1 (1.7%) was on the neck. Mean length of stay in hospital time was 3.5±2.6 day. Mean NLR1 was 12.4±8.8, mean NLR2 7.1±4.9, mean NLR3 2.3±1.1, mean MPV was 8±1.5 fL. Forty one (67.2%) patients with grade 0 and 1 were considered mild poisoning group, and twenty (32.8%) patients with grade 2 and 3 were considered to be severe poisoning group. The NLR, MPV levels and hospitalization days of these two groups seen in Table 1.

Table 1. Comparison of NLR, MPV levels and hospitalization time of mild (Grade 0 and 1) and severe (Grade 2 and 3) poisoning groups

Mean±SD Median (min-max)	**Mild poisoning group**	**Severe poisoning group**	***p* value**
Number (%)	41 (67.2%)	20 (32.8%)	
NLR1	11.04±8.16 9.3 (1.4-39.1)	15.4±9.7 16.2 (2.5-34.4)	0.080
NLR2	6.6±4.2 5.4 (1.1-22)	8.2±6.1 6.9(2.1-29.8)	0.341
NLR3	2.1±1.1 1.9 (0.6-6)	2.8±1 2.7 (1-4.4)	**0.010**
MPV (fL)	8±1.5 7.4 (6.4-13)	7.9±1.4 7.7 (6-12)	0.930
Hospitalization days	2.4±1.6 2 (1-8)	5.9±2.6 5 (1-11)	**<0.001**

Local findings were detected in 49 (80.3%) and systemic findings were detected in 17 (27.8%) patients. Swelling was the most common local complication, tachycardia was the most common systemic complication. Snake exposure in the cases was found to be the most common in July (24.5%) and September (22.9%).

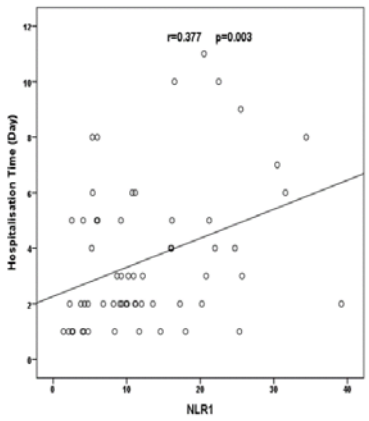

Figure 1. Positive correlation between NLR1 and hospitalization day

All the patients were immunized with tetanus. Antivenom therapy was administered according to clinical stage. A total of 44 patients (72.1%) were treated with antivenom. European viper antiserum provided by Turkey's Health Ministry was used (10 mL flacon) and administered intravenously. No complications related to antivenom occurred in any of our patients. Antibiotherapy was administered to 23 patients (37.7%) who developed cellulitis or thrombophlebitis. Fifty five (90.1%) patients came from the rural area of Çukurova.

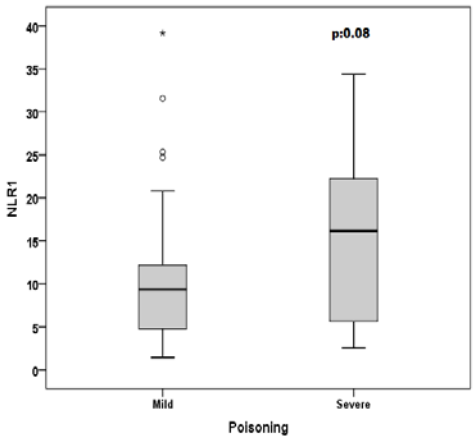

Figure 2. NLR1 level increased in severe poisoning group

There was a positive correlation between NLR1 and the length of hospital stay. We found that as the level of NLR1 increased, the length of hospitalization was prolonged (r:0.377, p:0.003) (Figure 1). We found that the NLR1 level was higher as the disease stage

was progressed, but it was not statistically significant (p:0.08) (Figure 2). We detected when the severity of the illness increased, the length of hospital stay was significantly prolonged (p<0.001). NLR3 was significantly lower in the middle poisoning group compared to the severe poisoning group (p:0.01).

Compartment syndrome developed in one patient's arm and fasciotomy applied (1.6%). The admission NLR value of the patient with clinically suspected compartment syndrome was 39.1 and this is the highest value of study group. No mortality was detected in our patients.

DISCUSSION

Although not fully known, approximately 2,500-3,000 species of snakes living in the world. About one-third of these are venomous at a dangerous level to humans. Snake bites cause serious mortality and morbidity, especially in tropical regions[11]. There are approximately 40 species snakes in Turkey and snake bites are common in the south and southeastern region. In the region of Çukurova there are especially venomous snakes of the species *Vipera ammodytes* and *Vipera lebetina*[2,4]. The poisons of these kinds often have hematotoxic, rarely neurotoxic effects. Snake venom includes toxic enzymes and proteins and cause severe inflammatory response and tissue damage. Snake bites can cause various clinical manifestations, ranging from mild local symptoms such as swelling, edema, hematoma to systemic complications such as fever, vomiting, circulatory collapse, delirium, convulsions, coma, disseminated intravascular coagulopathy, compartment syndrome, acute renal insufficiency, intracranial hemorrhage and death[4]. In our study group the most common systemic and local symptoms were tachycardia and swelling. In one patient who had the highest NLR1 in the group, compartment syndrome developed and fasciotomy applied. Death was not detected of none of the patients.

The reported snake bite incidence is higher in male gender similar to our study[11]. The incidence of snake bite is common in months of July to September[12,13]. In accordance with the literature snake bites were detected most frequently in July and September in our study. The site of snake bite has been reported to be on the extremities and especially on the lower extremities[14]. Similar to the literature, 65.5% of our patients were bitten on the lower extremity.

Antivenom is the main therapy and essential for patients with snake envenomation[15]. With an effective and timely antivenom treatment snake bite mortality and morbidity decreases. Anaphylactic reactions and serum sickness are important complications of antivenom treatment[16,17]. There were no complications detected due to antivenom in our study group.

MPV and NLR are measured as part of routine blood counts in many laboratories. Recent reports have suggested that increased MPV and NLR are associated with inflammation[18-20]. NLR is useful in diagnosis of inflammation and can be calculated simply by dividing neutrophil count to lymphocyte count. It has been reported as an indicator of systemic inflammation in various conditions such as obesity, metabolic syndrome, coronary artery disease, most of the rheumatic diseases or postoperative complications[21-25]. NLR increases in inflammatory diseases but there is not a defined cut-off value or upper limit of NLR for pediatric patients in the literature. Forget et al. reported the normal value for NLR in healty adults between 0.78 and 3.53[26]. In the recent literature there are some studies about snake envenomation and NLR. Elbey et al. have shown that higher NLR levels are associated with prolonged hospital admission and complicated clinical course in adult patients with snake bite[27]. In another study which includes pediatric patients Aktar et al. found no relationship between MPV, NLR and severity of snake bite[28]. In our study, we aimed to analyze the relationship between NLR with the severity of envenomation and hospitalization time in pediatric patients with snake bites. Our study showed a statistically significant positive correlation between NLR at admission and the length of hospital stay. We found that as the severity and grade of the snake bite increased, the NLR value at admission increased. It can be thought that; snake venom may increase NLR value secondary to inflammation.

MPV is an easily available and economical test and associated with thrombocyte activation in inflammatory conditions, however, contradictory results for MPV have been reported[29-31,7]. In the present study there was no relationship between MPV and severity of snake envenomation.

To the best of author's knowledge this is the first pediatric study which found a positive correlation with the application NLR and severity of the illness and the length of hospital stay in pediatric patients with snake envenomation. Our results show that NLR at admission can be a useful marker for

estimating severe clinical course and prolonged hospitalization period of patients. However; we think that prospective studies with larger patient groups may be more beneficial in terms of clarifying these relationships in NLR and severity of snake bite in children.

Yazar Katkıları: Çalışma konsepti/Tasarımı: NA, DY, DA; Veri toplama: NA, FE, SB; Veri analizi ve yorumlama: NA, DY; Yazı taslağı: NA, DY; İçeriğin eleştirel incelenmesi: DY, ÖÖH, HLY; Son onay ve sorumluluk: NA, DY, ÖÖH, FE, DA, SB, HLY; Teknik ve malzeme desteği: NA. FE, SB; Süpervizyon: DY, ÖÖH; Fon sağlama (mevcut ise): yok.
Bilgilendirilmiş Onam: Katılımcılardan yazılı onam alınmıştır.
Hakem Değerlendirmesi: Dış bağımsız.
Çıkar Çatışması: Yazarlar çıkar çatışması beyan etmemişlerdir.
Finansal Destek: Yazarlar finansal destek beyan etmemişlerdir.

Author Contributions: Concept/Design : NA, DY, DA; Data acquisition: NA, FE, SB; Data analysis and interpretation: NA, DY; Drafting manuscript: NA, DY; Critical revision of manuscript: DY, ÖÖH, HLY; Final approval and accountability: NA, DY, ÖÖH, FE, DA, SB, HLY; Technical or material support: NA. FE, SB; Supervision: DY, ÖÖH; Securing funding (if available): n/a.
Informed Consent: Written consent was obtained from the participants.
Peer-review: Externally peer-reviewed.
Conflict of Interest: Authors declared no conflict of interest.
Financial Disclosure: Authors declared no financial support

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