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Clinico-Epidemiological Profile of Immunocompetent Patients Diagnosed with Herpes Zoster: A Single-Center Retrospective Cohort Study from Sinop

Herpes Zoster Tanısı Alan İmmünkompetan Hastaların Epidemiyolojik ve Klinik Özellikleri: Sinop İlinden Tek Merkezli Retrospektif Kohort Çalışma

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ABSTRACT

Aim: Herpes zoster (HZ) mainly occurs in immunocompetent individuals, even though immunosuppression is a well-known risk factor. The aim of this study was to evaluate the demographic and clinical features of immunocompetent HZ patients and HZ-related complications with a special focus on possible contributing factors.

Material and Methods: This single-center, retrospective cohort study included 98 patients with no known immunosuppressive condition out of 103 patients diagnosed with HZ between September 2019 and August 2020. The patients were evaluated in terms of age, sex, medical history, clinical features, triggering factors, seasonality, complications, and neutrophil-to-lymphocyte ratio (NLR) as a marker of systemic inflammation.

Results: Ninetyeight immunocompetent patients (male:female ratio=1.1:1) were diagnosed with HZ, with a median age of 59 years (age range: 5-88). Thoracic dermatome was the leading dermatome (n=45). Trigeminal nerve was involved in 11 patients, eight of them presenting with ophthalmic HZ. HZ attacks were mainly detected in summer, while ophthalmic HZ cases were exclusively diagnosed during fall and winter. Two patients developed ophthalmic HZ following trauma. Eleven patients experienced postherpetic neuralgia (PHN) during follow-up with a male predominance (p=0.009). A higher mean NLR value was detected in PHN patients, although it was not statistically significant (p=0.136).

Conclusion: The findings of our study are compatible with the current literature regarding the main presentation pattern of HZ as unilateral thoracic dermatome involvement and the complications such as PHN and ophthalmic HZ occurring in a subgroup of patients. The high HZ incidence rate in our series is likely due to the high median age of the population in our region. The summer peak of HZ cases further supports the seasonal variability due to the ultraviolet effect, whereas mechanical trauma is another possible triggering factor. The predictive value of NLR for PHN should be evaluated in further studies.

Keywords: Herpes zoster, immunocompetent, postherpetic neuralgia, ophthalmic herpes zoster, neutrophil-to-lymphocyte ratio

ÖZ

Amaç: İmmünsupresyon herpes zoster (HZ) için iyi bilinen bir risk faktörü olsa da, bu tablo genellikle immünkompetan olgularda görülür. Bu çalışmada immünkompetan HZ olgularında demografik ve klinik özelliklerin, HZ gelişimine neden olan faktörlerin ve HZ ile ilişkili komplikasyonların değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Bu tek merkezli retrospektif kohort çalışmaya, Eylül 2019 ve Ağustos 2020 tarihleri arasında HZ tanısı alan 103 hasta arasından bilinen immünsupresif durumu olmayan 98 hasta dahil edilmiştir. Hastalar yaş, cinsiyet, tıbbi özgeçmiş, klinik bulgular, tetikleyici faktörler, tanı aldıkları mevsim, komplikasyonlar ve sistemik inflamasyon göstergesi olarak nötrofil lenfosit oranı (NLO) açısından değerlendirilmiştir.

Bulgular: Ortanca yaşı 59 olan (yaş aralığı: 5-88) 98 immünkompetan hasta (erkek:kadın oranı=1,1:1) HZ tanısı almıştı. En sık tutulan dermatom torakal dermatomdu (n=45). Trigeminal sinir tutulumu olan 11 hastanın sekizinde oftalmik HZ mevcuttu. HZ atakları sıklıkla yaz döneminde görülürken tüm oftalmik HZ olguları sonbahar ve kış mevsimlerinde tanı almıştı. İki olguda travma sonrası oftalmik HZ görülmüştü. Takipte erkek cinsiyet baskın olmak üzere 11 hastada postherpetik nevralji (PHN) gelişmişti (p=0,009). İstatistiksel olarak anlamlı olmamakla birlikte (p=0,136), PHN gelişen hastalarda ortalama NLO değeri daha yüksekti.

Sonuç: Çalışmamızdaki bulgular, HZ'nin ana prezentasyon paterni olan tek taraflı torakal dermatom tutulumu ve bir grup hastada ortaya çıkan PHN ve oftalmik HZ gibi komplikasyonlar açısından mevcut literatür ile uyumludur. Serimizdeki yüksek HZ insidans oranı, muhtemelen bölgemizdeki popülasyonun ortanca yaşının yüksek olmasından kaynaklanmaktadır. HZ olgularının yaz döneminde artış göstermesi ultraviyole ışınlarına bağlı mevsimsel etkiyi desteklerken, mekanik travma başka bir olası tetikleyici faktördür. NLO'nun PHN açısından prediktif değeri ileri çalışmalarla değerlendirilmelidir.

Anahtar Sözcükler: Herpes zoster, immünkompetan, postherpetik nevralji, oftalmik herpes zoster, nötrofil lenfosit oranı

INTRODUCTION

Herpes zoster (HZ) is a neurocutaneous disease presenting with painful vesicular eruption confined to specific dermatomes in a majority of patients (1,2). It appears as a result of the reactivation of latent varicella zoster virus (VZV) (1). The probable lifetime HZ risk was considered 30%, increasing with advancing age (3). Chronic debilitating pain, namely postherpetic neuralgia (PHN) and ocular involvement in the setting of ophthalmic HZ are among the major complications that might cause significant morbidity in affected individuals (4-6).

Immunosuppressive conditions and age-related immunosenescence are well-known risk factors for HZ (1,5,6). History of solid organ or bone marrow transplantation, hematological or solid organ malignancies, HIV infection and immunosuppressive medications such as biological agents, high dose corticosteroid or chemotherapy agents are the main immunosuppressive conditions (1,5).

Determinants facilitating HZ in immunocompetent patients are still a matter of debate. To date, several population-based studies have been conducted to elucidate these factors, target high-risk patient groups, and provide guidance for better vaccination and preventive strategies (5,7). Several chronic diseases, such as chronic obstructive pulmonary disease (COPD), chronic kidney disease, diabetes and mood disorders, were found to be associated with increased HZ risk (1,5,7). Autoimmune disorders such as rheumatoid arthritis, systemic lupus erythematosus and inflammatory bowel disease were likewise speculated to increase the risk of HZ (1,5). However, the latter may partly result from immunosuppressive medications employed during disease management (1).

Only a few studies are present in the literature regarding the demographic and clinical characteristics of HZ patients from different regions of Turkey (8-10). This study aimed to investigate the epidemiological profile and clinical presentations of immunocompetent patients diagnosed with HZ, the predisposing factors and HZ complications.

MATERIAL and METHODS

In this single-center, retrospective cohort study, 103 patients were included who were diagnosed with HZ among 9215 patients (32.6% older than 50 years and 16.9% older than 65 years) admitted to the dermatology outpatient clinic for any dermatological complaint (1.1%) between September 2019 and August 2020 in a secondary healthcare center in Sinop, a city in Northern Turkey region. The study was approved by the Sinop University Ethics Committee (approval number: 2020/10) and conducted in accordance with the Declaration of Helsinki.

The HZ diagnosis was established based on clinical findings. In ophthalmic HZ cases, the patients were evaluated in terms of ocular involvement. Persistent pain for at least three months after the resolution of the lesions was evaluated as PHN.

Of these, 98 patients who had no known immunosuppressive medical condition (history of solid organ/bone marrow transplantation, hematological or solid organ malignancy, HIV infection or use of any immunosuppressive medication) comprised the main study group, while five patients on immunosuppressive therapy (methotrexate [n=3], adalimumab [n=2]) for rheumatoid arthritis were excluded. The medical files of patients were evaluated regarding the demographic variables [age, sex (male:female ratio)], medical history [comorbidities (hypertension, diabetes, COPD, hyperlipidemia, hypothyroidism, depression, other), immunization profile], habits (smoking status), lesion localization [distribution pattern (as single dermatome or involvement of non-contiguous dermatomes), affected dermatome (cranial nerve, cervical, thoracic, lumbar, sacral)], presence of trauma history related to involved dermatome, time of admis-

sion (month and season), HZ complications (presence of ophthalmic involvement and involvement pattern, occurrence of PHN) and neutrophil-to-lymphocyte ratio (NLR) as a laboratory parameter for assessing inflammation. The presence of PHN was further evaluated with regard to age, sex, depression and NLR.

Statistical Analyses

IBM SPSS® Statistics Version 22 was used to store and analyze the data. Shapiro-Wilk test was used to evaluate the normality of variable distribution. Descriptive statistics were calculated as mean ± standard deviation and median [minimum-maximum] values for continuous variables, and as frequency and percentage for categorical variables. The differences in the distribution of categorical variables between independent groups were assessed by the Fisher's exact test. The Mann-Whitney U test was used for the comparison of non-normally distributed groups. The p-value less than 0.05 was considered statistically significant.

RESULTS

Ninetyeight immunocompetent patients were diagnosed with HZ. The demographic and clinical characteristics of the patients are shown in Table 1. Of these 98, 69.4% (n=68) were older than 50 years, while 42.9% (n=42) were older than 65 years. Ten patients comprised the pediatric age group with a median age of 11 years (age range: 5-17 years).

Various comorbidities were identified in 49% of the study group (n=48), with hypertension being the leading disorder (n=33) (Table 1). None of the COPD patients (n=6) were receiving long-term systemic corticosteroid therapy, but using inhaler corticosteroids. Five patients had been diagnosed with depression by a psychiatrist and were using antidepressant treatment. History for immunization against VZV was present in only three pediatric patients aged 5, 7, and 8 years old, respectively, while none of the patients in the study had received the HZ vaccine.

The main distribution pattern was the involvement of one or two adjacent dermatomes (96.9%, n=95). In three patients (3.1%), two non-contiguous dermatomes were involved (bilateral in one patient, unilateral in two patients). The most commonly affected dermatomes were thoracic dermatomes (45.9%, n=45), followed by cervical (20.4%, n=20) and lumbar dermatomes (15.3%, n=15). Similarly, thoracic dermatomes (n=5) were the most commonly involved dermatomes in pediatric patients, while concomitant involvement of ipsilateral sacral and contralateral lumbar dermatomes was observed in two of these cases who were aged 7 and 16 years old, respectively.

Among cranial nerves, the trigeminal nerve was exclusively affected in 11 cases (11.2%), eight of them presenting

Table 1: Demographic and clinical characteristics of immunocompetent herpes zoster patients.

	Immunocompetent patients diagnosed with herpes zoster (n=98)
Age, year	5-88 (median:59)
Sex, male:female (ratio)	52:46 (1.1:1)
Comorbidity (present), n (%)	48 (49.0)
Comorbidity, n (%)	
Hypertension	33 (33.7)
Diabetes	14 (14.3)
Chronic obstructive pulmonary disease	6 (6.1)
Hyperlipidemia	6 (6.1)
Hypothyroidism	5 (5.1)
Depression	5 (5.1)
Other	5 (5.1)
Active smoker, n (%)	23 (23.5)
Distribution pattern, n (%)	
Single dermatome*	80 (81.6)
Single dermatome* crossing midline	15 (15.3)
Two non-contiguous dermatomes	3 (3.1)
Dermatome, n (%)**	
Cranial nerves***	11 (11.2)
Cervical	20 (20.4)
Thoracic	45 (45.9)
Lumbar	15 (15.3)
Sacral	10 (10.2)
Ophthalmic involvement (present), n (%)	8 (8.2)
Ophthalmic involvement pattern, n (%)	
Vesicular lesion on eyelid	7 (7.1)
Blepharitis	3 (3.1)
Follicular conjunctivitis	1 (1.0)
Dendritic ulcer	1 (1.0)
Marginal keratitis	1 (1.0)
Endothelitis	1 (1.0)
Iridocyclitis	1 (1.0)
Postherpetic neuralgia (present), n (%)	11 (11.2)
Season at admission, n (%)	
Summer	35 (35.7)
Fall	26 (26.5)
Winter	21 (21.4)
Spring	16 (16.3)
Neutrophil-to-lymphocyte ratio, mean±SD	2.73±2.13

SD: Standard deviation. *with/without adjacent dermatome. **The total number does not correspond to the number of patients, since more than one dermatome was involved in three patients. ***Eight patients presented with ophthalmic herpes zoster.

with ophthalmic HZ (8.2%). Vesicular lesions were present on the eyelid in seven patients. The leading ocular finding observed in ophthalmic HZ cases was blepharitis (n=3) (Table 1).

Two patients had a recent history of ophthalmic surgery (cataract surgery [n=1] and abscess drainage [n=1]) one month prior to HZ occurrence and both of them presented with ophthalmic HZ of the affected eye.

When the distribution of HZ occurrence was examined concerning seasons and months, the peak incidence was detected during summer (n=35, 35.7%) and August (n=23, 23.5%), respectively. On the contrary, all ophthalmic HZ cases were observed during the fall (n=6, 75%) and winter seasons (n=2, 25%) (Figure 1).

Eleven patients (11.2%) had persistent, debilitating pain due to PHN lasting more than three months, necessitating analgesic therapy. The median age of the patients presenting with PHN was 80 years (age range: 56 - 88), with ten patients being older than 65 years, while the median age of patients without PHN was 57 years. Thoracic dermatome was involved in more than half of these cases (n=6), as only one patient had ophthalmic HZ. Males were found to experience PHN more frequently (P=0.009). The patients with PHN had a higher mean NLR value, although it was not statistically significant (P=0.136) (Table 2).

DISCUSSION

HZ poses a great health burden with its debilitating complications (5). Epidemiological research mainly belongs to specific geographical regions, while a scant number of reports is present in the literature from Asia, South America, and Africa (3). The incidence rate of HZ was reported between 3-5 per 1000 person-years in the general population based on the reports from North America, Europe, and Asia-Pacific, with an increased risk after the age of 50 (3). When the incidence rate was examined in terms of age groups, an increasing pattern was observed as 6-8 per 1000 person-years and 8-12 per 1000 person-years at 60 and 80 years of age, respectively (3). In our study, the incidence rate of HZ was calculated as 11 per 1000 person-years (1.1%). This relatively higher incidence rate

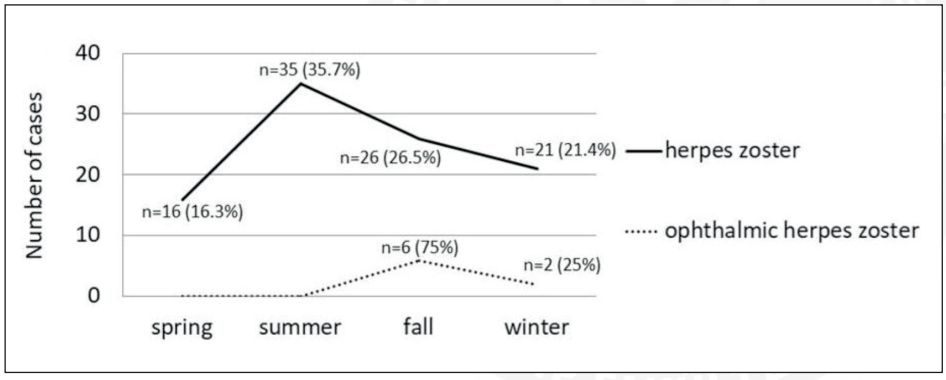

Figure 1: The distribution of herpes zoster (solid line) and ophthalmic herpes zoster (dotted line) cases with regard to seasons.

Table 2: Presence of postherpetic neuralgia with regard to demographic characteristics (age, sex), depression and neutrophil-to-lymphocyte ratio.

	Postherpetic neuralgia present	Postherpetic neuralgia not present	*p*-value*
Age groups, n (%)			
5-49 years	0 (0)	30 (34.5)	**0.017****
50-88 years	11 (100)	57 (65.5)	
Gender, n (%)			
Male	10 (90.9)	42 (48.3)	**0.009****
Female	1 (9.1)	45 (51.7)	
Depression, n (%)			
Yes	0 (0)	5 (5.7)	1.00**
No	11 (100)	82 (94.3)	
Neutrophil-to-lymphocyte ratio, mean±SD	4.19 ± 4.18	2.55 ± 1.66	0.136***

SD: Standard deviation

*Statistically significant values are highlighted in bold. ***p*-value was calculated with Fisher's exact test. ****p*-value was calculated with Mann-Whitney U test.

compared to previous general population data could be attributed to the higher percentage of the elderly population in the rural geographical region in which our study had been conducted, with 32.6% of the patients admitted to dermatology outpatient clinic during the study period being older than 50 years and 16.9% older than 65 years. The rates of HZ reported from our country ranging between 0.43-0.68% were comparable with the literature (8-10), but lower than our series. This difference may likewise be attributed to the lower mean/median age of patients in these studies (8-10). Moreover, Sinop, the city where our study was conducted, was reported to have the highest median age of residents among all cities in Turkey, according to the latest population registration data (11).

In a recent systematic review, the female sex was found to be a risk factor for HZ attributed to possible immunologic, hormonal, and/or healthcare-seeking attitude differences (5). However, the numbers of female and male patients were similar in our study, in line with some former studies showing no statistically significant difference between females and males (12,13).

The immunocompromised individuals constitute only the minority of the HZ cases in the published literature (6), although the disease course is more severe in the presence of immunosuppression (14). Thus, several population-based studies were conducted on the additional possible risk factors for HZ (1,7,15) in addition to well-known ones, aging and immunosuppressive conditions (5). Forbes et al. reported various disorders associated with increased HZ risk in their case-control study, especially in younger age groups (1). In our study, diabetes was the second leading comorbidity, present in nearly 15% of the patients. Some previous studies demonstrated the relation between HZ and diabetes with a variable strength of association (5). However, the low number of our HZ patients diagnosed with diabetes could not be used to support this relationship. COPD diagnosis, present in six patients who were on inhaler steroid therapy, was also mentioned as a risk factor in former reports. On the other hand, the risk was increased, particularly in patients receiving oral corticosteroid therapy (5).

Patients with psychiatric disorders were found to have an elevated risk of HZ (16). Impaired immune response was observed in animal models due to stress and anxiety which made mice susceptible to infection (17). Moreover, reduced VZV-specific cellular immunity was detected in the peripheral blood of patients with major depression (18). In the case-control study by Forbes et al., depression was found to be associated with increased HZ risk (1). In our study, patients diagnosed with depression comprised less than 10% of the cases.

Interestingly, active smoking was demonstrated to be associated with reduced HZ risk, despite the possible negative impact of smoking on cell-mediated immunity (5,6). The number of non-smokers was greater than the current smokers in our cohort, which further supported the existing data.

HZ mainly presents unilaterally in immunocompetent individuals, affecting a single dermatome (mainly thoracic) with/without adjacent dermatomes (2,19), which was also the main clinical scenario in the majority of our patients. Rarely, the lesions may involve two non-contiguous dermatomes unilaterally or bilaterally. These presentations, mainly encountered in immunocompromised or elderly patients, are named HZ duplex unilateralis and bilateralis, respectively (19,20). Surprisingly, two of the patients presenting with HZ duplex unilateralis/bilateralis were belonging to the pediatric age group in our series.

The epidemiological characteristics of the immunocompetent pediatric age group diagnosed with HZ have not been widely investigated compared to adults (21). The thoracic dermatome was the leading dermatome involved in pediatric patients in general, as seen in our study (21). VZV infection in early childhood, especially younger than the age of one year, was accused of increased incidence of HZ (21,22). The relationship between VZV vaccination and HZ incidence in children has been a popular topic in recent years. The vaccine was introduced in Turkey in 2013 for children aged 12 months (23). In the literature, there are conflicting results on whether vaccination has increased or decreased the incidence of HZ (21). The dermatomes corresponding to vaccination sites (cervical or lumbar) were reported to be more frequently involved in children who had received the VZV vaccine (22). In our series, only one previously vaccinated child presented with cervical involvement, while the other two with thoracic dermatome. However, due to the limited number of pediatric patients (n=10), most of whom were not vaccinated, no further comments could be made.

Ophthalmic HZ results from the involvement of the ophthalmic branch of the trigeminal nerve and constitutes 10-20% of HZ cases (24), while a quite lower rate of ophthalmic HZ (8.2%) was observed in our study. The ophthalmic branch is divided into the frontal, lacrimal, and nasociliary nerves. The innervation field of the nasociliary nerve involves the tip of the nose and ocular structures (eyelid, sclera, conjunctiva, cornea, iris, and choroid). Thus the involvement of this nerve may result in ocular complications (25). However, in most studies, the incidence rates were calculated without clearly identifying whether ocular involvement was present or not in ophthalmic HZ cases (26). Clinical manifestations of ophthalmic HZ include vesicular dermatitis, blepharitis, conjunctivitis, keratitis, corneal ulceration, uveitis, retinitis, and optic neuritis (26-28). Among our patients with ophthalmic HZ, more than 80% had vesicular dermatitis on eyelids, as expected. Keratitis, uveitis, and conjunctivitis were

reported to be the leading ocular findings of ophthalmic HZ (26,29,30), whereas the most common ocular involvement in our series was blepharitis (37.5%).

Recent mechanical trauma was held responsible for HZ episodes in the literature (31), similar to the reactivation seen in the context of herpes simplex virus (HSV) infection (32). In a case-control study, 14 immunocompetent adult patients were found to present with HZ lesions at the site of recent trauma within one month (31). Authors suggested that trauma served as a stimulant for viral reactivation (31). Later on, a more comprehensive case-control study further supported the previous findings (32). Moreover, a greater association between trauma and HZ was reported in the cranial region and especially in the first week after the trauma (32). Accordingly, we had two patients presenting with ophthalmic HZ following mechanical trauma by means of ophthalmic surgical intervention at the same site.

Seasonal variation as a contributing factor was discussed in the setting of HZ with no conclusion (28,33), while some reports revealed summer predominance (33,34). Increased ultraviolet exposure and intensity were suggested as triggering factors for HZ, similar to HSV reactivation (33). Similarly, a peak was detected during the summer months, especially in August, in our series. On the other hand, no common result was exhibited by previous studies from different regions of Turkey with variable peaks in different seasons (8-10). Seasonality of ophthalmic HZ was also evaluated previously (33), but no annual trend was observed. In contrast, all ophthalmic HZ patients presented in fall and winter in our study. In a former report, HSV-related ocular attacks were likewise found to exhibit an annual pattern with an increasing incidence rate in winter (35). The authors attributed this seasonality to the changes in the local and systemic immune responses in winter (35).

The rate of PHN evaluated in our patient group (11.2%) corresponded to the range reported in the literature, which was between 5 and 30% (3). The discrepancy between the PHN rates was attributed to the varying definitions of PHN in terms of pain duration and severity (3). In our study, PHN was defined as persistent pain lasting at least three months. The association between increased PHN risk and older age was supported by prospective studies (36). The age group (ranging from 56 to 88 years) experiencing PHN in our cohort was also compatible with these studies. Conflicting results were present about the effect of sex on PHN rates, while female sex was found to be a protective factor in studies in which the mean age of patients was ≥ 60 years (36). A significantly higher number of male patients presented with PHN, even though the median age of our patient group was 59 years.

An interesting finding was the higher mean NLR value in patients experiencing PHN, even though it was not statistically significant. The NLR has been widely used as a marker of systemic inflammation in various inflammatory conditions in the last few years (37). Higher levels of NLR have been reported to point out active disease in inflammatory disorders, worse prognosis in various malignancies, and higher mortality rates in cardiac events (37,38). In a recent study, the normal range of NLR has been reported in a healthy, adult population between 0.78 and 3.53 (38). In another study evaluating cost-effective inflammatory markers in terms of predictive value for PHN in HZ patients, no significant correlation between NLR and PHN has been observed (39). On the other hand, elevated NLR has been associated with a worse prognosis of facial palsy in Ramsay Hunt syndrome, another complication of HZ resulting from the reactivation of VZV in the geniculate ganglion (37). It has been recommended as a useful tool for determining the prognosis of the affected individuals (37). Based on our results, we think the role of NLR in the active phase of HZ for estimating the prognosis of PHN should be investigated in further large-scale studies.

The limited number of patients was the main limitation of this study. Moreover, statistical evaluation of the role of risk factors was not possible due to the absence of a control group. Likewise, the lack of a control group due to the study's design prevented the interpretation of the mean NLR in a healthy control group and the comparison of this value with the mean NLR of patients with HZ. The assessment of the patients by the same physicians was the main strength of this study compared to studies conducted with the information gathered from database systems.

In line with the literature, HZ was detected mainly as unilateral single thoracic dermatome involvement in patients with no immunosuppressive condition and resulting in complications such as PHN and ophthalmic HZ in a subgroup of patients. On the other hand, the higher HZ incidence rate compared to other series from different regions of Turkey and other countries might be due to the higher median age of the population in our region. Our data concerning seasonal variability further supported the reports showing an increased incidence rate of HZ during summer. Mechanical trauma was another triggering factor in our series, also highlighted in previous reports. Moreover, we believe that the predictive value of NLR for PHN should be evaluated in further studies.

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Author Contributions

Concept: **Zeynep Keskinkaya, Ayna Sariyeva İsmayilov, Özge Aydın Güçlü,** Design: **Zeynep Keskinkaya, Ayna Sariyeva İsmayilov, Özge Aydın Güçlü,** Data Collection or Processing: **Zeynep Keskinkaya, Ayna Sariyeva İsmayilov,** Analysis or

Interpretation: **Zeynep Keskinkaya, Ayna Sariyeva İsmayilov, Özge Aydın Güçlü,** Literature search: **Zeynep Keskinkaya, Ayna Sariyeva İsmayilov, Özge Aydın Güçlü,** Writing: **Zeynep Keskinkaya, Ayna Sariyeva İsmayilov, Özge Aydın Güçlü,** Approval: **Zeynep Keskinkaya, Ayna Sariyeva İsmayilov, Özge Aydın Güçlü.**

Conflicts of Interest

The authors have no conflict of interest to declare.

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Ethical Approval

The study has been approved by Sinop University Ethics Committee (approval number: 2020/10).

Review Process

Extremely peer-reviewed and accepted.

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