



# Evaluation of bone marrow functions and new inflammatory markers in patients with immunocompetent herpes zoster

*Immünokompetan herpes zoster hastalarında kemik iliği fonksiyonları ve yeni enflamasyon belirteçlerinin değerlendirilmesi*

✉ Esma İnan Yüksel, Ⓣ Demet Çiçek\*, Ⓣ Betül Demir\*, Ⓣ Ozan Erdem\*\*

Biruni University Faculty of Medicine, Department of Dermatology, İstanbul, Turkey

\*Fırat University Faculty of Medicine, Department of Dermatology, Elazığ, Turkey

\*\*İstanbul Medeniyet University Faculty of Medicine, Göztepe Prof. Dr. Süleyman Yalçın City Hospital, Clinic of Dermatology, İstanbul, Turkey

## Abstract

**Background and Design:** Herpes zoster (HZ) is a viral infection characterized by dermatomal vesicles caused by the reactivation of the latent varicella-zoster virus (VZV). There are conflicting reports regarding the effects of VZV on bone marrow functions. In this study, we aimed to evaluate bone marrow function and systemic inflammation in immunocompetent HZ patients.

**Materials and Methods:** This study included patients aged  $\geq 18$  yr diagnosed with HZ and admitted to a dermatology outpatient clinic between June 2011 and June 2021. Hematological parameters in routine hemogram tests of patients with HZ and new inflammatory markers, such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune inflammation index, and platelet-neutrophil ratio (PNR), were determined and compared with healthy control groups.

**Results:** Thrombocytopenia was observed in 6.1% and lymphopenia in 8% of 461 HZ patients. The mean leukocyte (white blood cell), lymphocyte, neutrophil, eosinophil, and platelet (PLT) counts in HZ patients were statistically significantly lower than in the control group ( $p < 0.05$ ). NLR and PLR values were statistically significantly higher in HZ patients than in the control group ( $p < 0.05$ ). PLT, eosinophil count, and PNR values were statistically lower in HZ patients aged  $\geq 65$  yr than in patients aged  $< 65$  yr, whereas mean platelet volume and NLR values were higher ( $p < 0.05$ ).

**Conclusion:** Thrombocytopenia and lymphopenia may occur in immunocompetent HZ patients. NLR and PLR values increase in HZ patients. The increase in inflammatory markers and decrease in platelet count are more evident in HZ patients aged  $\geq 65$  yr.

**Keywords:** Herpes zoster, inflammation, Bone marrow, thrombocytopenia

## Öz

**Amaç:** Herpes zoster (HZ), latent varicella-zoster virus' (VZV) reaktivasyonuyla ortaya çıkan dermatomal vezikülerle karakterize bir viral enfeksiyonudur. VZV'nin kemik iliği fonksiyonları üzerindeki etkilerine ilişkin gelişkili yazılar bulunmaktadır. Bu çalışmada, immünokompetan HZ hastalarında kemik iliği fonksiyonları ve sistemik enflamasyon düzeyini ortaya koymak amaçlanmıştır.

**Gereç ve Yöntem:** Haziran 2011-2021 yılları arasında, dermatoloji polikliniğine başvuran, HZ tanısı almış  $\geq 18$  yaş hastalar çalışmaya dahil edildi. Hastaların rutin hemogram tespitlerindeki hematolojik parametreler ve yeni enfiamasyon belirteçlerinden olan nötrofil/lenfosit oranı (NLO), platelet/lenfosit oranı (PLO), sistemik immün-enflamasyon indeksi ve platelet nötrofil oranları (PNO) belirlenerek sağlıklı kontrol gruplarıyla karşılaştırıldı.

**Bulgular:** Toplam 461 HZ hastasının %6,1'inde trombositopeni, %8'inde lenfopeni izlendi. HZ'li hastalarda ortalama lökosit sayısı, lenfosit, nötrofil, eozinofil ve platelet (PLT) sayısı kontrol grubundan istatistiksel açıdan anlamlı şekilde düşüktü ( $p < 0,05$ ). HZ'li hastalarda NLO ve PLO değerleri kontrol grubundan istatistiksel açıdan anlamlı şekilde yükseltti ( $p < 0,05$ ).  $\geq 65$  yaş HZ hastalarında PLT, eozinofil sayısı ve PNO değerleri,  $< 65$  yaş hastalardan istatistiksel açıdan daha düşükken, MPV ve NLO değerleri daha yükseltti ( $p < 0,05$ ).

**Address for Correspondence/Yazışma Adresi:** Esma İnan Yüksel MD, Biruni University Faculty of Medicine, Department of Dermatology, İstanbul, Türkiye

**Phone:** +90 506 930 24 05 **E-mail:** esmainanyuksel@gmail.com **Received/Geliş Tarihi:** 18.10.2021 **Accepted/Kabul Tarihi:** 11.04.2023

**ORCID:** orcid.org/0000-0002-8318-7426

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**Sonuç:** İmmünokompetan HZ hastalarda trombositopeni ve lenfopeni ortaya çıkmaktadır. Bu hastalarda NLO ve PLO değerleri artmaktadır.  $\geq 65$  yaş HZ hastalarında, enflamasyon belirteçlerindeki artış ve trombosit sayısında azalma daha belirgindir.

**Anahtar Kelimeler:** Herpes zoster, enfiamasyon, kemik iliği, trombositopeni

## Introduction

Varicella-zoster virus (VZV) is a DNA virus that is a member of the Herpesviridae family<sup>1</sup>. Primary VZV infections lead to chickenpox (varicella). After the first infection, VZV settles in the sensory ganglia of the dorsal root or cranial nerves and stays latent. Then, with the effect of some facilitating factors, such as older age, chronic diseases [e.g., diabetes mellitus (DM)], physiological and psychological trauma, and immunosuppression, it reactivates, causing painful vesicular eruptions in the dermatome innervated by the relevant ganglion and resulting in the clinical manifestation of herpes zoster (HZ). Transient viremia caused by VZV reactivation is typically controlled by the immune system in HZ patients, and the disease is confined to the relevant dermatome. However, in patients with a weakened immune system and widespread HZ accompanied by internal organ involvement<sup>2</sup>, viremia may show a more severe course.

Some herpesviruses, such as cytomegalovirus (CMV) and Epstein-Barr, have a suppressive effect on the bone marrow<sup>3</sup>. However, there are conflicting studies on the effects of VZV on the bone marrow<sup>4,5</sup>. The most common hematological disorder in chickenpox infections is thrombocytopenia, which occurs roughly four times more frequently in adults than children<sup>6,7</sup>. While there have been a few studies in the literature that evaluate changes in hematological parameters in HZ patients presenting with hematological disorders, no study has investigated the effects of HZ infections on bone marrow functions or the severity of systemic inflammation in immunocompetent patients<sup>2,8</sup>. Recently, new markers of inflammation have been identified by comparing the ratios of some hemogram parameters, and they have been shown to indicate the severity of inflammation in many acute and chronic diseases and provide more valuable data for prognosis prediction than using each parameter alone. The neutrophil-to-lymphocyte ratio [(NLR): Neutrophil count/lymphocyte count] is one of these parameters used to demonstrate the balance of immune system functions and the inflammatory response<sup>9</sup>. Other useful prognostic parameters for evaluating the balance between inflammation and hemostasis include the platelet-to-lymphocyte ratio [(PLR): Platelet count/lymphocyte count], the systemic immune inflammation index [(SII): Neutrophil count  $\times$  platelet count/lymphocyte count], and the platelet-to-neutrophil ratio [(PNR): Platelet count/neutrophil count]<sup>10-13</sup>. Furthermore, recent studies have shown that changes in mean platelet volume (MPV) are useful in assessing the severity of inflammation and prognosis in infectious, ischemic, and neoplastic diseases, as well as some chronic diseases<sup>14</sup>.

In this study, we aimed to examine hemogram parameters and new inflammatory markers, such as NLR, PLR, PNR, SII, and MPV, in terms of their utility in evaluating bone marrow functions, particularly platelet function, and the severity of systemic inflammation in adult HZ patients who did not have any hematological disease or immunosuppression.

## Materials and Methods

This study was approved by the Non-Interventional Research Ethics Committee of Firat University (approval number: 01.06.2021-2270). Patients diagnosed with HZ who presented to the dermatology outpatient clinic between June 2011 and 2021 were screened retrospectively from the hospital database using the International Classification of Diseases-10 diagnostic codes (B02-B02.9). Patients under the age of 18 yr, those with cancer, immunosuppression, or any hematological disease, those on systemic steroids or immunosuppressive drugs, and those with an active infection other than HZ were excluded from the study. The study's control group included healthy individuals of similar ages and gender distributions. The demographic data of the patients were obtained. White blood cell (WBC) count, leukocyte subtypes, hemoglobin (HGB) count, hematocrit (HCT) count, red blood cell (RBC) count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), MCH concentration, red cell distribution width (RDW), platelet count (PLT), platelet distribution width (PDW), platelet crit (PCT), and MPV values were recorded. The groups calculated and compared NLR, PLR, PNR, and SII values. Hemogram parameters and inflammatory markers were compared between patients aged  $< 65$  and  $\geq 65$  yr to indicate changes in inflammatory markers according to age groups among HZ patients.

### Statistical Analysis

Statistical Package for the Social Sciences (SPSS, version 25.0, IBM Corp., Armonk, New York) was used for statistical analyses. In the analysis of the data obtained from the study, mean  $\pm$  standard deviation values for data with a normal distribution were used; median (interquartile range) values for those without a normal distribution were used for numerical variables; and numbers and percentages were used for categorical variables. The Kolmogorov-Smirnov test was used to determine the normality of the variable distribution. The variance homogeneity was evaluated using Levene's test. In comparing the groups, the Student's t-test and the Mann-Whitney U test were used for numerical variables, and the chi-square and Fischer's exact tests were used for categorical variables. A p-value of  $< 0.05$  was considered statistically significant.

## Results

The patients' demographic and laboratory characteristics are shown in Table 1. The study included 461 HZ patients and 1,000 healthy controls. Of the patients with HZ, 251 (54%) were female, and 210 (46%) were male, with a mean age of  $56.3 \pm 17.99$  yr. Of the 1,000 healthy controls, 550 (55%) were female, and 450 (45%) were male, with a mean age of  $75 \pm 16.81$  yr. There was no statistically significant difference between the two groups in terms of age or gender.

In the HZ group, 6.1% of the patients had thrombocytopenia, 2.4% had thrombocytosis, 2.4% had leukopenia, 3.3% had leukocytosis,



0.7% had neutropenia, 3% had neutrophilia, 8% had lymphopenia, and 0.4% had lymphocytosis. The mean WBC, lymphocyte, neutrophil, eosinophil, PLT, and PCT counts were statistically significantly lower, and the mean monocyte count, PDW, RBC, HGB, and HCT values were statistically significantly higher in the HZ group than in the control group. NLR and PLR, new inflammatory markers, were significantly higher in HZ patients than in controls ( $p<0.05$ ). There was no statistically significant difference between the two groups in terms of PNR, SII, or MPV ( $p>0.05$ , Table 1).

Comparisons were performed to determine the distribution of inflammatory markers according to age groups among patients with HZ, PLT, PCT, and eosinophil count, and those aged  $\geq 65$  had lower levels ( $p<0.05$ ). While there was no difference between the two age groups in terms of lymphocyte or neutrophil count, monocyte count was significantly higher in patients aged  $\geq 65$  ( $p<0.05$ ). Lastly, MPV and NLR, which are inflammatory markers, were significantly higher in the  $\geq 65$  groups, but PNR was significantly lower ( $p<0.05$ , Table 2).

**Table 1. Comparison of demographic characteristics, hemogram parameters, and inflammatory markers between the patients with herpes zoster and controls**

	Herpes zoster, (n=461)	Control, (n=1,000)	p-value
<b>Gender (n, %)</b>			
Female	251 (54)	550 (55)	0.843
Male	210 (46)	450 (45)	-
Age, year (SD)	56.3 (17.99)	57 (16.81)	0.743
WBC count ( $10^3/\mu\text{L}$ ) (IQR)	6.68 (2.07)	7.16 (2.58)	<b>0.000</b>
Leukopenia (n, %)	13 (2.80)	12 (1.20)	<b>0.031</b>
Leukocytosis (n, %)	15 (3.30)	59 (5.90)	<b>0.039</b>
RBC count ( $10^6/\mu\text{L}$ ) (SD)	4.94 (0.51)	4.83 (0.49)	<b>0.000</b>
HGB (g/dL) (SD)	14.05 (1.54)	13.79 (1.62)	<b>0.016</b>
HCT (%) (SD)	42.68 (4.36)	41.68 (4.58)	<b>0.021</b>
MCV (fL) (SD)	86.60 (5.45)	86.86 (6.30)	0.463
MCH (pg) (SD)	28.53 (2.31)	28.59 (2.80)	0.724
MCHC (g/dL) (SD)	49.50 (69.46)	49.14 (68.54)	0.927
RDW (%) (SD)	14.11 (1.48)	14.31 (1.68)	0.169
PLT count ( $10^3/\mu\text{L}$ ) (SD)	251 (69.68)	266.1 (73.80)	<b>0.000</b>
Thrombocytopenia (n, %)	28 (6.10)	29 (2.90)	<b>0.005</b>
Thrombocytosis (n, %)	11 (2.40)	41 (4.10)	0.128
MPV (fL) (SD)	8.45 (1.06)	8.46 (1.05)	0.870
PDW (%) (IQR)	43.40 (13.60)	42.45 (14.72)	<b>0.003</b>
PCT (%) (SD)	0.21 (0.06)	0.22 (0.62)	<b>0.000</b>
Lymphocyte count ( $10^3/\mu\text{L}$ ) (SD)	1.87 (0.72)	2.16 (1.37)	<b>0.000</b>
Lymphopenia (n, %)	37 (8.00)	24 (2.40)	<b>0.000</b>
Lymphocytosis (n, %)	2 (0.40)	6 (0.60)	0.100
Neutrophil count ( $10^3/\mu\text{L}$ ) (IQR)	3.91 (1.66)	4.17 (2.09)	<b>0.001</b>
Neutropenia (n, %)	3 (0.70)	1 (0.10)	0.096
Neutrophilia (n, %)	14 (3.00)	39 (3.90)	0.455
Monocyte count ( $10^3/\mu\text{L}$ ) (IQR)	0.45 (0.20)	0.43 (0.21)	<b>0.040</b>
Eosinophil count ( $K/\mu\text{L}$ ) (IQR)	0.13 (0.12)	0.15 (0.14)	<b>0.000</b>
Basophil count ( $K/\mu\text{L}$ ) (SD)	0.56 (0.24)	0.48 (0.62)	0.355
NLR (IQR)	2.20 (1.34)	2.00 (1.10)	<b>0.001</b>
PLR (IQR)	138.25 (73.55)	125.43 (58.86)	<b>0.001</b>
PNR (SD)	65.58 (25.46)	65.87 (26.00)	0.920
SII (SD)	632.60 (460.42)	615.56 (389.97)	0.598

HCT: Hematocrit, HGB: Hemoglobin, IQR: Interquartile range, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, MCV: Mean corpuscular volume, MPV: Mean platelet volume, NLR: Neutrophil-to-lymphocyte ratio, PCT: Platelet crit, PLR: Platelet-to-lymphocyte ratio, PLT: Platelet count, PNR: Platelet-to-neutrophil ratio, RBC: Red blood cell, RDW: Red cell distribution width, SD: Standard deviation, SII: Systemic immune inflammation index, WBC: White blood cell



## Discussion

Although chickenpox infections typically have a benign course, they can, albeit rarely, cause pneumonia, skin infections, encephalitis, and some hematological disorders. There are conflicting reports in the literature on the effects of VZV on the bone marrow. Abro et al.<sup>7</sup> evaluated adult patients with chickenpox and observed thrombocytopenia in 41.8%, leukopenia in 2.7%, and leukocytosis in 24.5%. The rate of thrombocytopenia was found to be 30% in another study evaluating patients older than 15 yr with chickenpox<sup>15</sup>. In contrast, Zerboni et al.<sup>16</sup> revealed that VZV infection and VZV vaccine increased the levels of bone marrow-stimulating cytokines interleukin-2 (IL-2), IL-10, and interferon gamma in patients with bone marrow suppression. Only a few studies evaluate bone marrow functions in HZ patients with underlying hematological disorders. Kamber et al.<sup>5</sup> assessed bone marrow functions in 41 patients who underwent stem cell transplantation due to multiple myeloma and developed VZV reactivation, demonstrating that platelet recovery time was shortened, neutrophil recovery time was not prolonged, and life expectancy was improved in these patients. Anazi et al.<sup>3</sup> performed the long-term follow-up of hematological parameters after chickenpox and dermatomal HZ infections in 14 patients with bone marrow suppression and found an increase in leukocyte and PLT and hemoglobin concentration

40 days after the infection in these patients. This increase continued until the 1,050<sup>th</sup> day, and platelet activation was more prominent than in other hematological parameters<sup>3</sup>. Although the authors detected pain and dermatomal involvement in all HZ patients, neither study evaluated clinical severity or the relationship between clinical findings and hematological parameters<sup>3,5</sup>. In another study, Bollea-Garlatti et al.<sup>2</sup> found thrombocytopenia and leukopenia in 56.10% and 31.71% of patients with disseminated HZ, respectively; however, they did not compare these results between immunocompromised and immunocompetent patients. Hayran et al.<sup>17</sup> recently evaluated the demographic, clinical, and laboratory data of 100 hospitalized patients followed up with HZ to assess hematological parameters and found that the mean values of leukocytes, neutrophils, lymphocytes, monocytes, platelets, MCV, MCH, PDW, and RDW were within normal limits. Although 14 patients had disseminated HZ, their hematological changes were not evaluated separately. PDW values were higher in patients with ophthalmic involvement, indicating platelet suppression. Due to a lack of data for patients followed up in the outpatient clinic, hematological parameters or clinical features were not evaluated<sup>17</sup>. In the present study, we evaluated hematological parameters in 461 immunocompetent patients with HZ who presented to the outpatient clinic to detect changes in bone marrow function. Of these patients,

**Table 2. Comparison of hemogram parameters and inflammatory markers between the age groups among patients with herpes zoster**

	≥65 yr (n=177)	<65 yr (n=284)	p-value
WBC count ( $10^3/\mu\text{L}$ ) (SD)	6.99 (1.98)	6.89 (2.15)	0.458
RBC count ( $10^6/\mu\text{L}$ ) (SD)	4.84 (0.53)	4.99 (0.49)	0.940
HGB count (g/dL) (IQR)	13.92 (2.00)	14.13 (2.10)	0.095
HCT (%) (SD)	42.36 (4.60)	42.90 (4.19)	0.140
MCV (fL) (SD)	87.46 (5.66)	86.07 (5.26)	<b>0.001</b>
MCH (pg) (SD)	28.80 (2.27)	28.37 (2.32)	0.200
MCHC (g/dL) (SD)	49.27 (68.66)	49.64 (70.07)	0.294
RDW (%) (SD)	14.39 (1.49)	14.00 (1.46)	<b>0.001</b>
PLT ( $10^3/\mu\text{L}$ ) (SD)	239.92 (72.68)	254.99 (68.46)	<b>0.001</b>
MPV (fL) (SD)	8.54 (1.11)	8.39 (1.03)	<b>0.007</b>
PDW (%) (SD)	43.77 (12.20)	44.10 (10.72)	0.753
PCT (%) (SD)	0.20 (0.06)	0.21 (0.06)	<b>0.001</b>
Lymphocyte count ( $10^3/\mu\text{L}$ ) (IQR)	1.89 (0.95)	1.88 (0.79)	0.719
Neutrophil count ( $10^3/\mu\text{L}$ ) (SD)	4.17 (1.47)	4.17 (1.80)	0.607
Monocyte count ( $10^3/\mu\text{L}$ ) (IQR)	0.51 (0.21)	0.48 (0.20)	<b>0.001</b>
Eosinophil count (K/ $\mu\text{L}$ ) (SD)	0.15 (0.13)	0.16 (0.13)	<b>0.001</b>
Basophil count (K/ $\mu\text{L}$ ) (IQR)	0.74 (0.04)	0.43 (0.03)	0.146
NLR (SD)	2.58 (1.38)	2.49 (1.50)	<b>0.002</b>
PLR (SD)	146.18 (67.61)	154.57 (115.11)	0.411
PNR (SD)	62.91 (24.89)	67.85 (25.95)	<b>0.001</b>
SII (SD)	611.40 (377.23)	633.63 (494.15)	0.542

HCT: Hematocrit, HGB: Hemoglobin, IQR: Interquartile range, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, MCV: Mean corpuscular volume, MPV: Mean platelet volume, NLR: Neutrophil-to-lymphocyte ratio, PCT: Platelet crit, PLR: Platelet-to-lymphocyte ratio, PLT: Platelet count, PNR: Platelet-to-neutrophil ratio, RBC: Red blood cell, RDW: Red cell distribution width, SD: Standard deviation, SII: Systemic immune inflammation index, WBC: White blood cell



6.1% had thrombocytopenia, 2.8% had leukopenia, and 8% had lymphopenia. Although the mean platelet, leukocyte, lymphocyte, neutrophil, and eosinophil counts in HZ patients were within normal limits, we found lower values in these patients compared with the healthy controls. These hematological findings suggest that low-level viremia in HZ patients can suppress bone marrow functions if limited to dermatomal spread.

We found an increase in PDW values and a decrease in PLT in HZ patients. PDW is a measurement that reflects changes in platelet diameter and is more specific than MPV in showing platelet activity<sup>18</sup>. The increase in PDW and decrease in PLT in HZ patients support new platelet formation and activation.

Although varicella-associated thrombocytopenia is a well-known clinical picture, its pathogenesis remains unknown. According to various publications, this clinical manifestation is caused by platelet aggregation, platelet production being stopped by infected megakaryocytes due to the direct viral cytopathic effect, the destruction of infected platelets, or immune thrombocytopenia induced by anti-glycoprotein antibodies<sup>19,20</sup>. Autoantibodies against VZV surface glycoproteins cross-react with GPIIb/IIIa or GPIbIX-V surface integrins on the platelet surface, resulting in immune thrombocytopenia<sup>19,21</sup>. While thrombocytopenia caused by platelet destruction develops before the rash appears in the early phase of the disease and improves in a short time, immune thrombocytopenia often occurs later and has a longer course<sup>7</sup>. It is unclear whether the thrombocytopenia found in VZV infections is part of the viral or host-derived defense system. However, it is known that, in addition to their role in hemostasis, platelets secrete adhesion molecules and many inflammatory cytokines and play a role in the modulation of the inflammatory response by interacting directly with leukocytes and endothelial cells<sup>21</sup>. Platelets have been shown to have antiviral properties in viral infections, such as human immunodeficiency virus (HIV), vaccinia virus, and CMV<sup>21</sup>. Platelets can also interact with pathogenic viruses directly by expressing surface receptors, such as toll-like receptors and lectin<sup>21</sup>. VZV infects megakaryocytes and platelets in varicella infections<sup>19</sup>. Platelets infected with viruses, such as HIV and HCV, play a role in their transmission<sup>21</sup>. However, the role of platelets in the spread of disease in VZV infections is unknown.

In this study, the eosinophil count in HZ patients was lower than in controls. Eosinopenia occurs in many fungal, bacterial, and viral infections<sup>22</sup>. Eosinopenia has been demonstrated to be effective in indicating disease severity in patients with coronavirus disease 2019, but whether low eosinophils in VZV infections are important for clinical prognosis is unclear<sup>23</sup>. Monocytosis is a compensatory condition that causes phagocytosis when the neutrophil count is low<sup>24</sup>. Therefore, an increase in the number of monocytes in HZ patients is predicted, and monocytosis can be found in the early period of chickenpox, disseminated HZ, and localized HZ<sup>25</sup>.

This study found that HZ patients had increased HGB and RBC values. RBCs are blood cells with the longest half-life; therefore, effects on RBC series are reflected in late laboratory data. A case of pure red cell aplasia syndrome was reported in the literature, in which RBC increased 6 weeks after HZ infection, and the disease went into remission<sup>26</sup>.

Because we evaluated hemogram parameters in the early period of HZ, we cannot explain the increase in HGB and RBC in our patients. Longer-term studies will help reveal the effects of VZV infections on the RBC series.

A balanced interaction between blood cells plays a critical role in inflammation, immune response, and hemostasis. In recent years, new inflammatory markers, including NLR, PLR, PNR, SII, and MPV, have been increasingly used to demonstrate this balance. NLR and PLR reflect the balance between acute and chronic inflammation. They are useful inflammatory markers in evaluating the clinical course of cardiac diseases, cerebral infarction, diabetic nephropathy, certain cancers, and some infectious diseases<sup>9,27,28</sup>. A high NLR indicates severe inflammation and is associated with circulating myeloid-derived suppressor cells, indicating decreased T- and B-lymphocyte proliferation<sup>9,29</sup>. SII is a useful prognostic parameter for evaluating inflammation in sepsis and cancer patients<sup>13</sup>. PNR is another useful prognostic marker for acute cerebral and myocardial infarction<sup>11,12</sup>. Lastly, changes in MPV have been associated with prognosis in cardiac and respiratory diseases, some autoimmune diseases, such as rheumatoid arthritis and systemic lupus erythematosus, DM, renal failure, and some neoplastic diseases<sup>14</sup>.

Our study observed that the NLR and PLR values increased in the presence of HZ infections in immunocompetent patients. Similarly, Soh et al.<sup>8</sup> showed increased NLR values in 102 patients with Ramsay Hunt syndrome, reporting an association between an increased NLR and a poor prognosis. These findings suggest that systemic inflammation increases in HZ patients, even if it is limited to the dermatome. While VZV increases inflammatory markers in HZ patients, conditions that cause an imbalance in the immune system and an increase in inflammation for any reason may lead to secondary VZV reactivation, leading to the development of HZ. Some chronic diseases associated with chronic inflammation, such as DM and chronic kidney failure, are known to predispose patients to VZV reactivation. This idea is further supported by the study of Sim et al.<sup>30</sup>, which showed that a preoperative increase in NLR was associated with the development of HZ and posttherapeutic neuralgia in liver transplant patients. Studies that reveal the relationship between increased inflammatory markers and some complications, such as severe skin involvement in HZ, development of disseminated shingles, vascular complications, and posttherapeutic neuralgia, can help clinicians in the follow-up and treatment of HZ patients.

We found that the MPV and NLR values were higher and the PNR value and platelet and eosinophil counts were lower in patients with HZ aged  $\geq 65$  yr. These findings indicate that elderly HZ patients had higher levels of inflammation and more severe thrombocytopenia. In elderly patients, HZ can cause more severe clinical manifestations, including large hemorrhagic bullae and skin necrosis<sup>31</sup>. Complications, such as ophthalmic shingles, acute retinal necrosis, and cerebral arteritis, are also more common in elderly patients. However, whether these vascular complications are caused by VZV directly, immunological reactions or postinfectious inflammation is unknown<sup>31</sup>. NLR, PNR, and MPV have been shown to have prognostic significance in ischemic events, such as cerebral infarction and myocardial infarction<sup>11,12,32,33</sup>. Hayran et al.<sup>17</sup> showed that PDW values were higher in elderly patients



with HZ ophthalmicus, resulting in platelet suppression. There is a need for further clinical studies to evaluate whether the increased NLR and MPV values and the lower PLT and PNR values observed in our elderly HZ group are associated with increased vascular complications in these patients.

### Study Limitations

Because our study aimed to evaluate bone marrow functions and inflammation severity in immunocompetent HZ patients, we included patients who presented to the outpatient clinic in the sample and conducted the study retrospectively to increase the sample size. However, because of the limited clinical data of the patients who were followed up and treated in the outpatient clinic, clinical characteristics could not be evaluated in detail; therefore, the clinical features of HZ could not be compared based on laboratory results. This is the most important limitation of our study. Another important limitation is that the severity of HZ was not compared using laboratory results.

## Conclusion

HZ infections can cause thrombocytopenia, leukopenia, and lymphopenia in immunocompetent patients. There is an increase in NLR and PLR, which are new inflammatory markers, in these patients. The increase in PLR and MPV and the decrease in PNR and PLT are more pronounced in HZ patients aged  $\geq 65$  yr than in younger patients.

### Ethics

**Ethics Committee Approval:** This study was approved by the Non-Interventional Research Ethics Committee of Fırat University (approval number: 01.06.2021-2270).

**Informed Consent:** Retrospective study.

**Peer-review:** Externally and internally peer-reviewed.

### Authorship Contributions

Concept: E.İ.Y., D.Ç., Design: E.İ.Y., D.Ç., B.D., Data Collection or Processing: E.İ.Y., D.Ç., B.D., O.E., Analysis or Interpretation: E.İ.Y., O.E., Literature Search: E.İ.Y., B.D., Writing: E.İ.Y., O.E.

**Conflict of Interest:** The authors declared that they have no conflict of interest.

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