ORIGINAL REPORT

Decreased Neutrophil-to-lymphocyte Ratio in Patients with Vitiligo: National Data Analysis

Sarah WEISSMANN[1,2], Amit Shira BABYEV[2], Michal GORDON[2], Inbal GOLAN-TRIPTO[1,3] and Amir HOREV[1,4]
[1]Faculty of Health Sciences, Ben Gurion University of the Negev, Beer Sheva, [2]Clinical Research Unit, Soroka University Medical Center, Beer Sheva, [3]Pediatric Pulmonary Unit, Soroka University Medical Center, Beer Sheva, and [4]Pediatric Dermatology Service, Soroka University Medical Center, Beer Sheva, Israel

Vitiligo is characterized by depigmented skin lesions involving melanocyte defects and immune dysregulation. Haematological markers like neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been explored in various skin disorders. Given vitiligo's proposed pathogenesis, we hypothesized differences in NLR and PLR in vitiligo patients compared to controls. In a national retrospective cohort study (2005–2020) in Israel, blood count data from patients diagnosed with vitiligo (ICD-10 codes) were analysed, excluding patients with recent infections, surgeries, or malignancies. Controls matched for age and sex were selected. Sub-analyses examined age groups, treatment type, and matched controls. Children ($n = 3,796$) and adults ($n = 38,608$) with vitiligo showed significant differences in gender distribution, cell counts, and ratios. Vitiligo patients ($n = 38,358$) exhibited lower NLR, decreased neutrophils and platelets, and increased lymphocytes compared with controls. Non-systemically treated vitiligo patients ($n = 33,871$) displayed lower NLR and neutrophils compared with matched controls. Systemically treated vitiligo patients ($n = 4,487$) showed lower NLR, higher PLR, and reduced lymphocytes. Logistic regression identified associations between increased lymphocyte and platelet counts and being systemically treated. This study highlights significant haematological differences in vitiligo patients, emphasizing the potential utility of NLR as an accessible tool for vitiligo assessment. Further investigations are warranted to elucidate the roles of neutrophils and lymphocytes in vitiligo pathogenesis.

Key words: vitiligo; neutrophil-lymphocyte ratio; vitiligo; national data.

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Corr: Amir Horev, MD, Pediatric Dermatology Service, Soroka University Medical Center, Yitzhack I. Rager Blvd 151, POB 151, Beer Sheva, 84101, Israel. E-mail: horev8@gmail.com

SIGNIFICANCE

Blood count ratios in patients with vitiligo were investigated, focusing on markers of inflammation to better understand the disease's underlying mechanisms. These markers have not yet been widely studied in large populations. By comparing the medical records and blood counts of children and adults with vitiligo with those of a healthy population, it was found that the neutrophil-to-lymphocyte ratio was lower in vitiligo patients. This finding enhances our understanding of the cellular processes involved in vitiligo and highlights the significant roles played by specific immune cells.

Vitiligo is a skin disorder characterized by chronic, acquired dyschromia that leads to autoimmune targeting of melanocytes, causing hypochromic or achromic macules or patches on the skin. Systemic manifestations such as sensorineural deafness, uveitis, and thyroiditis often accompany vitiligo. Vitiligo has a complex pathogenesis that includes genetic components, metabolic changes due to oxidative stress, melanocyte adhesion, and innate and adaptive immune targeting of melanocytes. As currently understood, the pathogenesis of vitiligo begins with a triggering event (emotional stress, trauma, chemical exposure, or metabolite imbalance) that causes oxidative stress in melanocytes. Melanocytes are more susceptible to oxidative damage leading to an increased expression of proinflammatory proteins and decreased expression of epithelial adhesion molecules. This causes an autoimmune reaction and damage to melanocytes through the type 1-IFN pathway and T-cell sensitization (1, 2). Histologically, vitiligo lesions demonstrate decreased melanocytes and infiltration of large numbers of T lymphocytes with complete microscopic loss of melanin in the lesioned skin (3).

Haematological markers of inflammation such as the neutrophil-to-lymphocyte (NLR) and platelet-to-lymphocyte (PLR) ratios may be used in the assessment of inflammatory skin diseases, such as atopic dermatitis, psoriasis vulgaris, lupus erythematosus, vitiligo, rosacea, erythema nodosum, urticaria, and dermatomyositis (4). Because of the proposed pathogenesis of vitiligo, we hypothesized that NLR and PLR would be different in patients with vitiligo compared to controls.

In this study, we sought to investigate the absolute neutrophil, lymphocyte, and platelet counts as well as neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in vitiligo patients. We performed sub-analyses investigating differences in cell counts and ratios between adults and children, patients treated with systemic medication versus non-systemic medication or no treatment, and patients compared to their age and gender-matched controls.

MATERIALS AND METHODS

Study design

In a national retrospective cohort study performed in Israel between 2005 and 2020, we included patients of all ages diagnosed with vitiligo and evaluated the associations between NLR, PLR, and vitiligo. We extracted data from patient medical records through a data-sharing platform, MDClone (https://mdclone.com/), and included only patients insured by the Clalit health maintenance organization (HMO). Clalit HMO is the largest public healthcare provider organization in Israel and serves more than half of Israel's population, covering around 4,600,000 people. The study was approved by the local Ethics Committee of SUMC (No. 0434-15-SOR).

Study population

We included all patients insured by Clalit HMO diagnosed with vitiligo according to ICD-10 codes. We excluded all patients with acute infection, surgery, or malignancy within 30 days of their blood test. Data were extracted using Clalit's data-sharing platform powered by MDClone software on 15 November 2023. MDClone is a big-data platform with data-synthesizing capabilities. The diagnoses of vitiligo were made by the patient's primary physician or by a dermatologist. Controls were matched for age and sex, and the nearest blood count to that of their matched patient was taken. We excluded controls who had an infection, malignancy, or history of surgery within 30 days of their blood test. We investigated the differences between patients treated with at least 1 systemic vitiligo-related medication (corticosteroids, mycophenolate mofetil, baricitinib, tacrolimus, cyclosporine, upadacitinib, or tofacitinib) versus patients treated with non-systemic medications or receiving no treatment.

Laboratory analysis

NLR and PLR were calculated by dividing the absolute neutrophil and platelet counts by the absolute lymphocyte count. Patients with no blood test within 30 days of diagnoses were excluded.

Statistical analysis

We compared continuous variables using Student's *t*-test or Mann–Whitney *U* test. We used 95% confidence intervals (95% CI), and a two-sided p-value <0.05 to indicate statistical significance. All statistical analyses were done using R software (version 4.0.2; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

In this study, we examined the clinical, demographic, and laboratory features of 42,404 patients diagnosed with vitiligo, stratified by age and medication use. Of the 42,404 patients with vitiligo, there were 10,610 males (25.0%) and 31,794 females (74.9%). The mean age was 50.73 years. 35,377 patients had been prescribed systemic steroids and 347 patients other drugs including ruxolitinib, Janus kinase inhibitors, baricitinib, tofacitinib, cyclosporine, tacrolimus, azathioprine, and mycophenolate mofetil.

Children vs adults

Significant differences were found between adults with vitiligo ($n=38,608$) and children with vitiligo ($n=3,796$) as seen in **Table I**. A notable gender distribution difference was observed, with 23.2% males among adults and 43.5% among children ($p<0.001$). Laboratory parameters demonstrated distinctions in NLR, PLR, neutrophil, platelet, and lymphocyte counts. Higher NLR was found in adults (2.07 ± 1.19 vs 1.34 ± 1.25, $p<0.001$), elevated PLR and absolute neutrophil count were also found in adults (129.33 ± 50.81 vs 109.35 ± 45.14, $p<0.001$) and (3.99 ± 1.60 vs 3.56 ± 1.95, $p<0.001$), respectively. However, lower platelet counts in adults (250.13 ± 69.15 vs 312.40 ± 88.08, $p<0.001$), and decreased lymphocyte count in adults (2.11 ± 0.71 vs 3.35 ± 1.72, $p<0.001$) were observed.

Table I. Clinical, demographic, and laboratory characteristics of patients with vitiligo stratified by age group

Factor	Adults $n=38,608$	Children $n=3,796$	p-value
Gender – male, *n* (%)	8,960 (23.2)	1,650 (43.5)	<0.001
Age, mean (SD)	51.97 (18.04)	9.12 (5.70)	<0.001
NLR, mean (SD)	2.07 (1.19)	1.34 (1.25)	<0.001
PLR, mean (SD)	129.33 (50.81)	109.35 (45.14)	<0.001
Neutrophils, mean (SD)	3.99 (1.60)	3.56 (1.95)	<0.001
Platelets, mean (SD)	250.13 (69.15)	312.40 (88.08)	<0.001
Lymphocytes, mean (SD)	2.11 (0.71)	3.35 (1.72)	<0.001

SD: standard deviation; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio.

Vitiligo patients vs controls

We performed an analysis including 38,358 vitiligo patients compared with an equal number of controls, age and sex-matched, as demonstrated in **Table II**. Significant differences were observed in various laboratory parameters, with vitiligo patients exhibiting lower NLR (2.05 ± 1.19 vs 2.18 ± 1.59, $p<0.001$), higher PLR (129.06 ± 50.71 vs 128.12 ± 54.71, $p=0.014$), decreased neutrophil count (3.98 ± 1.60 vs 4.25 ± 1.80, $p<0.001$), lower platelet count (251.72 ± 69.91 vs 254.25 ± 69.87, $p<0.001$), and decreased lymphocyte count (2.13 ± 0.73 vs 2.19 ± 1.29, $p<0.001$).

Table III focuses on vitiligo patients not treated with systemic medication ($n=33,871$) compared with controls. A similar pattern emerged with significantly lower NLR (2.05 ± 1.20 vs 2.19 ± 1.62, $p<0.001$) and decreased neutrophil counts (3.98 ± 1.62 vs 4.25 ± 1.81, $p<0.001$). Although PLR and platelet count were not significantly different, lymphocyte count was lower in mild vitiligo patients (2.13 ± 0.73 vs 2.19 ± 1.29, $p<0.001$).

Table II. Clinical, demographic, and laboratory characteristics of all patients with vitiligo compared with healthy controls

Factor	Control $n=38,358$	All vitiligo patients $n=38,358$	p-value
Gender – male, *n* (%)	8,756 (22. 8)	8,756 (22. 8)	1
Age, mean (SD)	50. 73 (19. 01)	50.73 019.01)	0. 972
NLR, mean (SD)	2.18 (1.59)	2.05 (1.19)	<0.001
PLR, mean (SD)	128. 12 (54. 71)	129. 06 (50. 71)	0.014
Neutrophils, mean (SD	4. 25 (1. 80)	3.98 (1. 60)	<0.001
Platelets, mean (SD)	254.25 (69.87)	251.72 (69. 91)	<0.001
Lymphocytes, mean (SD)	2. 19 (1. 29)	2.13 (0. 73)	<0.001

SD: standard deviation; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio

Table III. Clinical, demographic, and laboratory characteristics of mild vitiligo patients and severe vitiligo patients compared with healthy controls

Factor	Controls	Patients	*p*-value
Mild vitiligo patients, *n*	33,871	33,871	
NLR, mean (SD)	2.19 (1.62)	2.05 (1.20)	< 0.001
PLR, mean (SD)	128.25 (55.03)	128.78 (50.49)	0.192
Neutrophils, mean (SD)	4. 25 (1. 81)	3.98 (1.62)	< 0.001
Platelets, mean (SD)	254.39 (70.12)	251.50 (69. 85)	< 0.001
Lymphocytes, mean (SD)	2. 19 (1. 29)	2.13 (0. 73)	< 0.001
Severe vitiligo patients, *n*	4,487	4,487	
NLR, mean (SD)	2.16 (1.38)	2.07 (1.14)	0.001
PLR, mean (SD)	127.17 (52.20)	131.16 (52.32)	< 0.001
Neutrophils, mean (SD)	4.25 (1.74)	3.96 (1.49)	< 0.001
Platelets, mean (SD)	253.18 (67.93)	253.36 (70.39)	0.916
Lymphocytes, mean (SD)	2.20 (1.29)	2.11 (0.74)	0.001

SD: standard deviation; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio.

Also, in Table III, vitiligo patients treated with systemic medication ($n=4,487$) displayed distinct characteristics compared with controls, including a lower NLR (2.07 ± 1.14 vs 2.16 ± 1.38, $p=0.001$), higher PLR (131.16 ± 52.32 vs 127.17 ± 52.20, $p<0.001$), and reduced lymphocyte count (2.11 ± 0.74 vs 2.20 ± 1.29, $p=0.001$).

Non-systemically treated vitiligo patients vs systemically treated vitiligo patients

Stratification by treatment (patients treated with systemic medication versus non-systemic medication or no treatment) within the vitiligo patient cohort ($n=37,396$ non-systemically treated, 5,008 systemically treated) revealed significant differences, shown in **Table IV**. Systemically treated vitiligo patients were older (51.26 ± 21.80 vs 47.72 ± 21.07 years, $p<0.001$) and exhibited a lower proportion of males (23.0% vs 25.3%, $p=0.001$). Additionally, significant yet very minor differences were observed in platelet count (257.71 ± 74.78 vs 254.54 ± 72.41, $p=0.034$) and PLR (128.88 ± 52.46 vs 127.36 ± 50.40, $p=0.046$).

The logistic regression analysis for systemically treated patients with vitiligo ($n=5,008$) demonstrated associations between certain laboratory parameters and use of systemic medications (**Table V**). Specifically, a higher absolute lymphocyte count was associated with increased odds of being treated with a systemic medication (OR = 1.09, 95% CI = 1.04–1.15, $p<0.001$), and a higher platelet count (OR = 1.12, 95% CI = 1.06–1.18, $p=0.002$) was also associated with higher odds of being treated with a systemic medication. NLR, PLR, and neutrophils did not show significant associations with treatment choice.

Table IV. Clinical, demographic, and laboratory characteristics of patients with vitiligo, stratified by severity group

Factor	Mild $n=37,396$	Severe $n=5,008$	*p*-value
Gender – male, *n* (%)	9,456 (25.3)	1,154 (23.0)	0.001
Age, mean (SD)	47.72 (21.07)	51.26 (21.80)	< 0.001
NLR, mean (SD)	2.00 (1.22)	2.01 (1.15)	0.857
PLR, mean (SD)	127.36 (50.40)	128.88 (52.46)	0.046
Neutrophils, mean (SD)	3.96 (1.64)	3.93 (1.53)	0.303
Platelets, mean (SD)	254.54 (72.41)	257.71 (74.78)	0.034
Lymphocytes, mean (SD)	2.20 (0.87)	2.23 (1.04)	0.164

SD: standard deviation; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio

Table V. Regression for severe vitiligo

Characteristic	OR	95% CI	*p*-value
Neutrophil-to-lymphocyte ratio	0.98	0.95, 1.00	0.093
Platelet-to-lymphocyte ratio	1.03	0.98, 1.09	0.3
Lymphocytes	1.09	1.04, 1.15	< 0.001
Neutrophils	0.98	0.96, 1.01	0.2
Platelets	1.12	1.06, 1.18	0.001

OR: odds ratio; CI: confidence interval.

DISCUSSION

Our study found significant differences in NLR, PLR, and underlying cell counts between children and adults with vitiligo, patients and matched controls, and systemically vs non systemically treated vitiligo patients.

We demonstrated decreased NLR, PLR, and neutrophils in children compared with adults with vitiligo, and increased platelets and lymphocytes. It is most likely that these differences reflect physiologic discrepancies between adults and children in how they respond to vitiligo. Previous studies have suggested NLR is less correlated with inflammatory states such as metabolic syndrome in children compared with adults (5). PLR has not been shown to be significantly predictive of disease states in children, specifically brucellosis (6). Platelets and lymphocytes are known to be increased in children in response to infection and inflammatory conditions.

Interestingly, our study found a decrease in NLR in vitiligo patients compared with controls. Decreased NLR in vitiligo patients compared with controls is a unique finding that contrasts with previous studies such as Karagun and Solak et al. (7, 8). Karagun and Solak et al. found a higher NLR in patients with generalized vitiligo compared with controls and patients with focal vitiligo. Though NLR is typically increased in inflammatory states, chronic neutropenia has been associated with autoimmune conditions. Antibodies against neutrophils have been found in systemic lupus erythematosus as well as rheumatoid arthritis (9). Indeed, we found decreased absolute neutrophil counts in vitiligo patients compared with controls. It is also possible that vitiligo behaves differently from other inflammatory skin conditions due to a predominantly CD8+ T cell-mediated destruction of melanocytes (3). It is likely that the discrepancy between the findings of Karagun and Solak et al. and our findings is a result of a smaller sample size with a higher proportion of patients with underlying systemic inflammation compared with our population.

The normal range for NLR in an adult, non-geriatric population in good health is between 0.78 and 3.53 according to a study by Forget et al. (10) It is important to

note that our findings of 2.05±1.19 in vitiligo patients and 2.18±1.59 in healthy controls fall between the normal range of NLR according to the study by Forget et al. (10).

Notably, lymphocytes were decreased in vitiligo patients compared with controls. Previous studies have demonstrated that there is an imbalance of cytotoxic/suppressor and helper/inducer T-cells in peripheral blood in vitiligo patients (11). It has been suggested that this could lead to a predominance of T-cell subtypes in intracutaneous vitiligo sites, leaving relative lymphopenia in peripheral blood (11).

While we found statistically significant differences in PLR between patients and controls, the differences are minor and not clinically significant. This is reflective of similar statistically significant yet clinically insignificant changes in platelets between patients and controls.

Our comparisons of non-systemically treated vitiligo patients and their controls and systemically treated vitiligo patients and their matched controls reflect the general trends we found between all vitiligo patients and controls. However, there was no decrease in neutrophils in systemically treated vitiligo patients compared with their controls. The effect of systemic therapies on cell counts may underscore the differences between treatment with topical corticosteroids, topical calcineurin inhibitors, and newer topical treatments such as ruxolitinib compared with systemic therapies (12). Use of systemic therapy is indicated in severe vitiligo, which is typically assessed by area using the Vitiligo Area Scoring Index or Vitiligo European Task Force. It is likely that our systemically treated cohort is associated with severity as well.

Although there have been previous publications investigating NLR in vitiligo patients, this is the first study to investigate NLR and PLR on a national scale. However, our study has a few limitations: first, it is possible that our cohort included patients with other conditions such as autoimmune disorders that may affect NLR and PLR; however, we attempted to minimize this by excluding patients with acute inflammatory states such as infection, malignancy, or history of surgery within 30 days of their blood test. Second, we took data from 30 days before and after diagnosis; however, it is uncertain whether the disease was present at that time or had not yet begun.

As demonstrated in our study, decreased NLR is associated with the presence of vitiligo and treatment type. NLR can be used as an easy and useful tool in the assessment of vitiligo. The underlying mechanism behind the role of neutrophils and lymphocytes in vitiligo should be investigated in future studies.

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Study approval statement: This study protocol was reviewed and approved by the local Ethics Committee of SUMC, approval number [0434-15-SOR].

Consent to participate statement: this study has been granted an exemption from requiring informed written consent according to the Ethics Committee of SUMC (approval number 0434-15-SOR).

Data availability statement: Data are available only on request due to privacy or other restrictions. For requests, please contact the corresponding author, Sarah Weissmann.

The authors have no conflicts of interest to declare.

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