Iran J Pediatr. 2016 October; 26(5):e8191. doi: 10.5812/ijp.8191.

Published online 2016 October 10. **Research Article**

The Relationship of Neutrophil-Lymphocyte Ratio and Platelet-Lymphocyte Ratio with Gastrointestinal Bleeding in Henoch-Schonlein Purpura

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Received 2016 August 09; **Revised** 2016 September 06; **Accepted** 2016 October 01.

Abstract

Objectives: Henoch-Schonlein Purpura (HSP) is the most widespread systemic vasculitis during childhood. Gastrointestinal tract retention and gastrointestinal bleeding are among its major complications. Neutrophil-Lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) are indicators related to inflammatory diseases. This study evaluated the relationship between NLR or PLR and gastrointestinal bleeding in HSP.

Methods: The study consisted of 119 patients and 40 healthy children in the same age group. White Blood Cell (WBC) count, hemoglobin level, platelet count, mean platelet volume (MPV), neutrophil count and lymphocyte count were recorded. The NLR and PLR were calculated based on the results of complete blood count tests performed during the first visit to the hospital.

Results: The average neutrophil count and NLR of the patients with HSP were found to be significantly increased compared to the control group (P = 0.0001). No significant difference was observed between the PLR average of HSP and control groups (P = 0.053). Platelet count average (P = 0.0001) and PLR (P = 0.001) of the patients with gastrointestinal system (GIS) bleeding were found to be statistically significantly increased compared to those who did not have gastrointestinal bleeding. No significant difference was found in the NLR of the patients with and without gastrointestinal bleeding (P = 0.060).

Conclusions: While the NLR was significantly increased in patients with HSP in this study, the PLR was found to be more significant in patients with gastrointestinal bleeding. Similar to NLR, PLR may also be used as an inflammatory indicator among children with HSP, who have gastrointestinal bleeding.

Keywords: Henoch-Schonlein Purpura, Neutrophil-Lymphocyte Ratio, Platelet-Lymphocyte Ratio, Gastrointestinal Bleeding

1. Background

Henoch-Schonlein Purpura (HSP) is the most common systemic vasculitis with Immunoglobulin A (IgA) deposition in children (1). Palpable purpura, arthritis or arthralgia, gastrointestinal involvement with abdominal pain and renal disease are classic manifestations of the disease (2). Henoch-Schonlein Purpura is often self-limited, but renal involvement occurs in 40% - 50% of patients within four to six weeks of the initial presentation (3). Gastrointestinal (GI) involvement occurs in 50 to 75% of patients, and abdominal pain, vomiting and gastrointestinal bleeding are the main findings. Although GI bleeding is generally occult, grossly bloody or melanotic stools are observed in 30% of patients, and intussusception has been reported in 1 to 5% of patients (4, 5). While GIS retention can limit itself in HSP, serious complications such as invagination and perforation may develop (6). Steroid treatment rapidly improves abdominal pain and decreases the risk of invagination and surgical intervention (7). A few studies have reported that thrombocytosis, leukocytosis, high C-reactive protein (CRP) levels, mean platelet volume (MPV) and blood Neutrophil-lymphocyte ratio (NLR) were associated with severe HSP (8-11). It is known that NLR is a beneficial marker in inflammatory diseases. It has also been reported to be a significant inflammatory marker in the early period in HSP-related gastrointestinal bleeding among children (10). To the best of our knowledge, there are no reports concerning Platelet-Lymphocyte ratios (PLRs) in children with or without gastrointestinal bleeding in HSP. Platelet-lymphocyte ratios is an inflammatory marker that can be easily, rapidly and inexpensively determined (12). The objective of this study was to evaluate the relationship between blood NLR or PLR and gastrointestinal bleeding in children with HSP.

2. Methods

We retrospectively reviewed all patients diagnosed with HSP at the department of pediatrics at Bagcilar training and research hospital in Istanbul, Turkey, between January 2013 and May 2016. One hundred nineteen HSP patients and 40 healthy children were included in the study. Henoch-Schonlein Purpura was diagnosed in patients with non-thrombocytopenic palpable purpura on the extensor aspects of the legs or on the buttocks (mandatory criterion) in the presence of at least one of the following four features: diffuse abdominal pain, biopsy showing a predominant IgA deposition, arthritis or arthralgia, and renal involvement (hematuria and/or proteinuria) (12). Children, who were diagnosed with sepsis, obesity, hyperlipidemia, diabetes mellitus, hypertension, chronic renal disease, nephrotic syndrome, inflammatory bowel disease and chronic inflammatory disease or those who had received systemic steroid treatment before the blood count analysis, were excluded from the study. Patients with immunologic disorders were also excluded. The control group was made up of healthy volunteers from the same age group. All anthropometric data and physical examination findings related to the control group were normal. All anthropometric data, physical examination findings, blood biochemistry and coagulation test results were recorded. We collected demographic data, signs and symptoms of the disease and initial laboratory data from patient medical records. White blood cell (WBC) count, hemoglobin level, platelet count, MPV, neutrophil count and lymphocyte count were recorded. The NLR and PLR were calculated based on the results of complete blood count tests performed during the first hospital visit. The patients were selected from study participants, who presented a rash and who did not yet have stomachache or gastrointestinal bleeding. Renal involvement was indicated by abnormal urinalysis results in patients with HSP and was categorized into three types: normal levels of proteinuria (< 0.5 g/L) and hematuria (≥ 5 red blood cells per high-power microscopic field); low-grade proteinuria (< 1 g/L) and/or hematuria (≥ 5 red blood cells per high-power microscopic field); or heavy proteinuria (≥ 1 g/L) and/or hematuria (≥ 5 red blood cells per high-power microscopic field) (13, 14).

Gastrointestinal involvement was defined as occult blood in stool, melena, or hematochezia. The protocol was approved by the research ethics committee of Bagcilar training and research hospital (approval number 2016 - 486), in accordance with the declaration of Helsinki. Informed consent was obtained from all study participants and/or their parents.

3. Results

The mean age was 7.82 ± 3.01 years in the patient group and 8.45 ± 3.24 years in the control group, while the male/female ratio was 75/44 in the patient group and 19/21 in the control group. There were no significant differences in terms of age and gender between the patient and control group. No statistically significant difference was observed between the age average and gender distribution of the HSP and control group ($P > 0.05$). White Blood Count averages and platelet count averages of the patient group that was followed up due to HSP, were found to be significantly increased compared to the control group ($P = 0.0001$). The hemoglobin averages of the HSP group were found to be significantly decreased compared to that of the control group ($P = 0.046$). Platelet count averages of the HSP group were found to be statistically significantly increased compared to the control group ($P = 0.0001$).

Neutrophil averages of the HSP group were found to be significantly increased compared to the control group ($P = 0.0001$). No significant difference was observed between the lymphocyte average of the HSP and control group ($P = 0.388$).

The NLR averages of the HSP group were found to be significantly increased compared to that of the control group ($P = 0.0001$). No significant difference was observed between the PLR averages of the HSP and control groups ($P = 0.053$) (Table 1).

The logistic regression analysis was performed with WBC, hemoglobin, platelet, neutrophil, NLR and MPV variables, and determination of the factors affecting the presence of HSP, and WBC ($P = 0.001$), NRL ($P = 0.029$) and MPV ($P = 0.002$) were determined as effective factors (Table 2).

Gastrointestinal bleeding was identified in 41 patients with HSP. The mean age was 7.9 ± 3.1 years in patients with gastrointestinal bleeding and 7.77 ± 2.97 years in patients without gastrointestinal bleeding. No statistically significant difference was observed between the average age of the patients with gastrointestinal bleeding and those without gastrointestinal bleeding ($P = 0.819$). No statistically significant difference was observed between WBC, HB, Neutrophil, Lymphocyte and NLR averages of the patients with gastrointestinal bleeding ($P > 0.005$). Platelet count averages of the patients with gastrointestinal bleeding were found to be significantly increased compared to those without gastrointestinal bleeding ($P = 0.0001$). The PLR averages of the patients with gastrointestinal bleeding were found to be significantly increased compared to those without gastrointestinal bleeding ($P = 0.001$) (Table 3).

Table 1. Features of the Patients with Henoch-Schonlein Purpura and the Control Group

	Control Group (n = 40)	HSP Group (n = 119)	P
Age	8.45 ± 3.24	7.82 ± 3.01	0.259
Gender, No. (%)			0.084
Male	19 (47.50)	75 (63.00)	
Female	21 (52.50)	44 (37.00)	
WBC count	8.56 ± 2.16	12.34 ± 4.64	0.0001
Hemoglobin	13.11 ± 0.89	12.71 ± 1.15	0.046
Platelet count	282.15 ± 73.95	367.62 ± 136.25	0.0001
Neutrophil count	4.39 ± 1.68	7.62 ± 4.1	0.0001
Lymphocyte count	3.26 ± 1.03	3.75 ± 2.28	0.388*
NLR	1.45 ± 0.63	2.41 ± 1.54	0.0001
PLR	92.12 ± 30.83	117.92 ± 63.3	0.053*
MPV	7.69 ± 1.94	6.78 ± 1.14	0.0001

Table 2. Results of the Logistic Regression Analysis Performed to Determine the Parameters that are Most Affected by Henoch-Schonlein Purpura

	B	P	OR	95,0% CI for OR	
				Lower	Upper
WBC count	0.35	0.001	1.42	0.92	2.20
Hemoglobin	-0.15	0.525	0.86	0.55	1.36
Platelet count	0.00	0.869	1.00	1.00	1.01
Neutrophil count	-0.08	0.812	0.92	0.46	1.84
NLR	0.66	0.029	1.93	1.07	3.49
MPV	-0.46	0.002	0.63	0.47	0.84

Table 3. Comparison of the Patients With and Without Gastrointestinal Bleeding

	GI Bleeding (-) (n = 78)	GI Bleeding (+) (n = 41)	P
WBC count	12.05 ± 4.52	12.89 ± 4.87	0.347
Hemoglobin	12,65 ± 1,17	12,81 ± 1,13	0,477
Platelet count	335.82 ± 107.37	428.11 ± 163.86	0.0001
Neutrophil count	7.11 ± 3.74	8.57 ± 4.61	0.065
Lymphocyte count	3.78 ± 2.16	3.7 ± 2.5	0.868
NLR	2.17 ± 1.27	2.86 ± 1.89	0.060*
PLR	104.73 ± 48.5	143.01 ± 79.42	0.001

3.1. Statistical Evaluation

Statistical analyses in this system were performed using the number cruncher statistical system (NCSS) 2007 statistical software (Utah, USA) package program. In addition to descriptive statistical analysis (mean and standard deviation), the independent t-test was used for comparison of the binary groups and showed a normal distribution, the Mann-Whitney U test was used for comparison of the binary groups and did not show a normal distribution, and the chi-square test was used for comparison of the qualitative data. Logistic regression analysis was performed to determine factors that are affected by HSP. The results were evaluated at a significance level of $P < 0.05$.

4. Discussion

Neutrophil-lymphocyte and platelet-lymphocyte ratios are inexpensive indicators that can easily and quickly be detected in inflammatory reactions (15). The importance of these inflammatory indicators in GIS retention was assessed in this study together with HSP. Although a limited number of studies show that NLR can be a significant indicator in HSP (10, 16), there is no study assessing the relationship between PLR and HSP. This study showed that the number of platelets and neutrophils increases, NLR averages are high and MPV averages are low in patients with HSP. Henoch-Schonlein purpura is a leukocytoclastic vasculitis caused by the accumulation of IgA. Proinflammatory cytokines such as interleukins IL-1 and IL-6, and Tumor Necrosis Factor (TNF)-α are secreted as a result of inflammation and endothelial cell damage in small cells (17, 18). Increases in thrombocytosis, leukocytosis, CRP, and especially gastrointestinal system retention have been previously reported in HSP (8, 9). Other studies state that NLR can be a beneficial indicator, as an acute phase reactant, similar to CRP and sedimentation, in inflammatory diseases such as psoriasis and rheumatoid arthritis (19-21). Makay et al. (10) found NLR to be significantly higher in pediatric HSP patients with gastrointestinal bleeding than in those without gastrointestinal bleeding. They reported that MPV and NLR were two important factors in gastrointestinal bleeding in the logistic regression analysis (10). In the studies carried out by Park et al. (16), it was reported that NLR was higher in adults with gastrointestinal bleeding in HSP than in those without gastrointestinal bleeding, and the acute-off value was calculated. The NLR is obtained by dividing the number of neutrophils by number of lymphocytes. While an increase in neutrophils and decrease in lymphocytes are generally observed in cases of infection, they are also observed in cases of inflammation. The decrease in the number of lymphocytes occurs as a result of lymphocyte apoptosis in the cases of inflammation (22). Our study found that the number of lymphocytes did not change, although the number of neutrophils and NLR increased in children with HSP. In this respect, our study is consistent with the study carried out by Makay et al. (10). Henoch-Schonlein Purpura is an inflammatory incident, and NLR was increased significantly compared to the NLR in the control group, as indicated in other studies. However, in the study of Makay et al. the number of lymphocytes did not change in those with gastrointestinal bleeding compared to those without gastrointestinal bleeding, while the number of neutrophils and, consequently, NLR increased. In this study, the optimal cut-off NLR for predicting gastrointestinal bleeding was 2.82, with 81.0% sensitivity and 76% specificity. Unlike the study of Makay et al., in our study there was no clear increase in the number of neutrophils in patients with gastrointestinal bleeding, and the NLR did not increase significantly. Park et al. (16) observed that NLR increased in male patients with HSP and gastrointestinal bleeding, and reported the optimal cut-off value as 3.90, sensitivity as 81.0% and specificity as 88.6%. The results of our study are not consistent with these two studies.

Our study showed that the PLR is significantly increased in children with GIS bleeding. There is no previous study on PLR in GIS retention in HSP. Platelets, similar to neutrophils, produce important cytokines that play a role in the activity of inflammatory diseases (23). Similar to NLR, PLR can also be used as an inflammatory indicator in certain diseases. In previous studies, it was observed that increased PLR is inversely correlated with clinical and pathological properties in certain malignancies and chronic diseases (24-26). It was reported that PLR increases in peripheral artery diseases and ischemia. It was reported that ischemic damage is increased in patients with a PLR over 150, compared to patients with a PLR below 150 (27). It was reported that PLR and autoimmune diseases are associated. Uslu et al. (21) reported that there is a correlation between the severity of the disease and the PLR in patients with rheumatoid arthritis. Wu et al. (28) reported that there is a correlation between the PLR and the severity of systemic lupus erythematosus.

Inflammation is a major indicator of the severity of autoimmune diseases. Neutrophil-Lymphocyte Ratio and PLR are both easily accessible and inexpensive parameters that show the severity of inflammatory diseases. Gastrointestinal system bleeding and stomachache are the most prevalent complications that require hospitalization among children with HSP. Steroid treatment has been applied to children with HSP for years. It is reported that starting steroid treatment early, shortens the duration of stomachache and reduces the need for intussusception and surgical intervention (29-31). In a study carried out by Ronkainnen et al. (29), it was reported that starting steroid treatment early reduced the severity of stomachache. In another multicenter study, it was noted that starting steroid treatment early reduced the risk of abdominal pain, endoscopy and surgical intervention (31). The plasma levels of certain cytokines that affect the number and volume of the platelets increase during the inflammatory process in HSP. Interleukin 6 is an important proinflammatory cytokine that causes thrombocytosis and affects platelet volume (32, 33). In our study, we believe that increased MPV and thrombocytosis among children with HSP were correlated with an increased level of IL-6. Lin et al. (34) reported that the level of IL-6 in children with HSP was significantly increased compared to the healthy control group. Additionally, it was reported that the level of

IL-6 is significantly lower in those with GIS and renal retention, related to their HSP, when compared to those, who did not have organ retention. This is explained by an increased IL-6 consumption at the later stages of inflammation, and this breakdown is protective against organ retention.

The limitations of our study were that it was carried out in a single center and was retrospective. Neutrophil-Lymphocyte Ratio and PLR increase in the active period of many inflammatory diseases such as rheumatoid arthritis and SLE. Gastrointestinal bleeding and stomachache are serious complications in HSP. Neutrophil-Lymphocyte ratio and PLR are easily accessible and inexpensive indicators; if these indicators are significantly increased in the early period of the disease, steroid treatment could be started early. Prospective studies are needed to confirm these findings.

4.1. Conclusion

In our study, the NLR in children with HSP was found to be significantly higher than in the control group; this level was not found to be statistically significant in children with gastrointestinal bleeding. However, the PLR in children with GIS bleeding is significantly higher than in those without gastrointestinal bleeding. In previous studies, it was reported that the NLR is a significant indicator for gastrointestinal bleeding. Our study also supports the use of PLR as an indicator of GIS retention in HSP.

Footnotes

Authors' Contribution: Conception and design of the study, Ozlem Bostan Gayret, Meltem Erol and Hikmet Tekin Nacaroglu; analysis and interpretation of the data, Ozlem Bostan Gayret, Meltem Erol and Hikmet Tekin Nacaroglu; writing and critical revision of the article, Ozlem Bostan Gayret and Meltem Erol.

Financial Disclosure: We declare that no financial or personal interests exist that might potentially influence the work presented.

Funding/Support: This study was supported by educational planning coordination committee and approved by the review board of bagcilar training and research hospital.

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