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ORIGINAL ARTICLE

The relationship of neutrophil-to-lymphocyte ratio with gastrointestinal bleeding in Henoch–Schonlein purpura

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Abstract Henoch–Schönlein purpura (HSP) is the most common systemic vasculitis of childhood. Gastrointestinal (GI) bleeding is one of the major complications of HSP. The blood neutrophil-to-lymphocyte ratio (NLR) is identified as a potentially useful marker of clinical outcome in inflammatory diseases. NLR may be a useful biomarker of GI bleeding in children with HSP, which has a neutrophil-dominated inflammation. The aim of this study was to evaluate NLR in patients with HSP and to investigate the relationship with GI bleeding. The study consisted of 63 HSP patients and 38 age- and sex-matched healthy children. C-reactive protein, white blood cell count, platelet count, mean platelet volume (MPV), hemoglobin level, and NLR were evaluated. Logistic regression analysis and receiver operating characteristic (ROC) analysis were used to determine the variables associated with GI bleeding. NLR and MPV were the only two indicators associated with GI bleeding in HSP in logistic regression analysis. The area under the ROC curve analysis indicated that NLR could be a more efficient potential predictor of GI bleeding in HSP when compared to MPV. This study suggested that higher NLR might predict GI bleeding in HSP.

Keywords Henoch–Schönlein purpura · Neutrophil-to-lymphocyte ratio · Gastrointestinal bleeding

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Introduction

Henoch–Schönlein purpura (HSP) is the most common systemic vasculitis of childhood, which typically presents with palpable purpura of the skin often accompanied by joint and abdominal pain [1]. Besides, many HSP patients may have hematuria as an evidence of kidney involvement, which might rarely progress to permanent renal damage [1]. Forty–70 % of children with HSP suffer from gastrointestinal involvement [2–5]. Gastrointestinal (GI) bleeding—more frequently occult or less commonly overt bleeding—occurs in 18–52 % of these patients [2–6]. Although HSP is a self-limiting disease, severe acute complications, such as invagination and intestinal perforation might be seen [6]. Previously, few studies showed that thrombocytosis, leukocytosis and high C-reactive protein (CRP) levels were associated with more severe disease in HSP, particularly gastrointestinal bleeding [7, 8]. Also, we previously reported that low mean platelet volume (MPV) might be related to GI bleeding in HSP [9].

The blood neutrophil-to-lymphocyte ratio (NLR) is identified as a potentially useful marker of clinical outcome in disease states with an inflammatory component [10–15]. As inflammation in the HSP is neutrophil dominated, NLR may be a useful biomarker of clinical severity in children with HSP. To date, there are no reports about the NLR in patients with HSP. The objective of this study is to evaluate the relationship between blood NLR and gastrointestinal bleeding in children with HSP.

Patients and methods

All patients diagnosed as HSP between November 2006 and 2013 in Pediatric Rheumatology Department of Dokuz

Eylül University Hospital (Izmir, Turkey) were reviewed. The European League against Rheumatism/Paediatric Rheumatology European Society (EULAR/PRES) diagnostic criteria for HSP [16] were used to define the disease as palpable purpura (a mandatory criterion) in the presence of at least one of the following: (1) diffuse abdominal pain; (2) any biopsy showing predominant IgA deposition; (3) arthritis or arthralgia; and (4) renal involvement (hematuria and/or proteinuria). Age- and sex-matched healthy children who attended the well-child outpatient clinics of our hospital constituted the control group.

Demographic data, signs and symptoms of disease and following laboratory data at the time of diagnosis were recorded from the computerized patient database: erythrocyte sedimentation rate (ESR), CRP, hemoglobin level, white blood cell count (WBC), platelet count, MPV and NLR. Complete blood count parameters were recorded for healthy children from the same computerized database.

The complete blood count analyses were performed in the same Coulter analyzer, which is routinely checked every month in the central laboratory of our institution. Standard tubes with constant amount of ethylenediaminetetraacetic acid were used.

Gastrointestinal hemorrhage was defined as occult blood in stool, melena, or hematochezia. Glomerulonephritis was defined as the presence of hematuria (>5 red blood cells per high-power microscopic field in a centrifuged specimen), pyuria (>5 white blood cells per high-power microscopic field in a centrifuged specimen), or proteinuria (>300 mg/24 h). The study protocol was approved by the ethics committee of the Dokuz Eylul University, Faculty of Medicine, and conducted in accordance with the ethical principles described by the Declaration of Helsinki.

Statistical analysis

All data were analyzed using Statistical Package for Social Sciences 16.0 (SPSS, Inc., Chicago, Illinois, USA) for windows. Quantitative variables were expressed as mean ± SD for normally distributed data and as medians (25th and 75th percentiles) for non-normally distributed data. Quantitative data for dual groups were compared by using the Student's *t* test or Mann–Whitney *U* test when appropriate, whereas χ^2 test was performed for qualitative data. Intercorrelations between parameters were computed through the Pearson's correlation analysis. Backward stepwise logistic regression analysis was performed to determine the variables associated with GI bleeding in patients with HSP. Receiver operating characteristic (ROC) curves were operated to evaluate possible indicators of GI bleeding in HSP. p value ≤ 0.05 was considered as significant.

Table 1 Comparison of complete blood count parameters between patients and controls

Parameter	HSP patients ($n = 63$)	Healthy controls ($n = 38$)	p value**
Hb (g/dL)	12.3 ± 1	12.9 ± 0.9	0.004
PLT ($\times 10^3/\mu L$)	416.3 ± 138.2	296.1 ± 86.7	<0.001
MPV (fL)	7.5 ± 0.8	8.2 ± 0.6	<0.001
WBC ($\times 10^3/\mu L$)	12.4 ± 4.7	8.1 ± 2.3	<0.001
Neutrophil ($\times 10^3/\mu L$)	8.1 ± 4.6	4.3 ± 1.6	<0.001
Lymphocyte ($\times 10^3/\mu L$)	3.2 ± 1.5	2.8 ± 0.7	0.110
NLR (%)	3.2 ± 2.6	1.5 ± 0.5	<0.001

Data were presented as mean ± SD

** Student's *t* test, $p < 0.05$ is significant

Results

There were 72 patients diagnosed as HSP in the study period. The initial laboratory data were missing in the computerized database in nine patients; thus, a total of 63 HSP patients were enrolled in the study. There were 33 boys and 30 girls with HSP and 21 boys and 17 girls in the healthy control group ($p = 0.78$). Mean age of the HSP patients was 6.5 ± 2.6 years and controls were 7.1 ± 2.2 years ($p = 0.23$).

All the patients had palpable purpura. Fifty-two patients (82 %) had arthritis or arthralgia mostly in ankles, followed by knees. Thirty-two patients (51 %) complained of abdominal pain, and 22 of them (35 %) had GI bleeding. Among the nine patients who were not eligible for the study, three had GI bleeding. Only one patient presented with intussusception. Glomerulonephritis was found in seven patients (11 %). The first sign of HSP was purpura in all patients. The mean time to admission from the onset of purpura was 1.8 ± 0.9 days (min:1, max:5 days).

Platelet, WBC and neutrophil counts were significantly higher in patients with HSP than healthy controls (p values are 0.000) (Table 1). However, lymphocyte counts did not significantly differ between patients and controls ($p = 0.110$). HSP patients had significantly higher NLR than healthy controls (3.2 ± 2.6 vs. 1.5 ± 0.5, $p < 0.001$). HSP patients had significantly lower MPV levels than healthy controls (7.5 ± 0.8 vs. 8.2 ± 0.6, $p < 0.001$) (Table 1).

Platelet counts, WBC counts, and CRP levels were significantly higher in patients with GI bleeding when compared to patients without GI bleeding ($p = 0.008$, $p = 0.002$, and $p = 0.013$, respectively) (Table 2). While neutrophil count was significantly higher, lymphocyte count was significantly lower in patients with GI bleeding than the patients without ($p < 0.001$ and $p = 0.015$,

Table 2 Comparison of laboratory parameters between patients with and without GI bleeding

Parameter	Patients without GI bleeding ($n = 41$)	Patients with GI bleeding ($n = 22$)	p value**
Hb (g/dL)	12.4 (11.6–12.8)	12.2 (11.6–13.1)	0.801
ESH (mm/h)	29 (24–36)	31 (17–43)	0.716
CRP (mg/L)	8.3 (3.7–23.7)	37.7 (5.6–55)	0.013
PLT ($\times 10^3/\mu L$)	352 (310–430)	451 (357–571)	0.003
MPV (fL)	7.7 (7.0–8.0)	7.0 (6.5–7.9)	0.019
WBC ($\times 10^3/\mu L$)	10.2 (8.5–13.1)	14.5 (12.3–18.2)	0.002
Neutrophil ($\times 10^3/\mu L$)	4.6 (6.0–7.4)	7.5 (10.6–14.7)	0.000
Lymphocyte ($\times 10^3/\mu L$)	2.6 (3.1–3.8)	1.6 (2.6–3.3)	0.015
NLR (%)	1.7 (1.13–2.8)	3.5 (2.86–8.6)	<0.001

Data were presented as median (25th and 75th percentile)

** Mann–Whitney U test, $p < 0.05$ is significant

Table 3 Logistic regression analysis for possible risk factors of GI bleeding in HSP

	B	SE	Wald	p value	Exp (B)	95 % CI	
						Lower	Upper
CRP	0.017	0.017	1.046	0.306	1.017	0.985	1.051
WBC	0.000	0.000	2.203	0.138	1.000	1.000	1.000
PLT	0.000	0.000	0.134	0.715	1.000	1.000	1.000
MPV	−1.2	0.500	6.241	0.019	0.287	0.108	0.764
NLR	0.78	0.245	10.1	0.000	2.182	1.349	3.529

respectively) (Table 2). MPV was significantly lower in patients with GI bleeding than patients without bleeding ($p = 0.019$) (Table 2). NLR was significantly higher in patients with GI bleeding than patients without ($p < 0.001$) (Table 2). The mean time to admission was similar in patients with and without GI bleeding [1.5 (1–3) vs. 2.0 (1.0–2.0), $p = 0.61$].

Platelet counts, WBC counts, CRP levels, MPV, and NLR were included in logistic regression analysis as potential indicators of GI bleeding in HSP. Only two indicators, NLR and MPV, were associated with gastrointestinal bleeding in HSP (p values are 0.001 and 0.012, respectively) (Table 3).

The area under the ROC curve (AUC_{ROC}) analysis indicated that NLR could be a more efficient potential predictor of GI bleeding in HSP when compared to MPV. NLR ($AUC_{ROC} = 0.842$, 95 % CI 0.74–0.94, $p < 0.001$) was higher than MPV's ($AUC_{ROC} = 0.68$, 95 % CI 0.53–0.82, $p = 0.019$). The cutoff NLR level with optimal sensitivity and specificity was found as 2.82 (sensitivity 81.0 %, specificity 76 %). When the cutoff value of NLR was selected as 3.0, the sensitivity decreased to 68 % and specificity increased to 83 % (Fig. 1).

There was not a significant correlation between NLR and age of the patient ($r = 0.003$, $p = 0.982$). Also, there was not a significant correlation between NLR and time to admission ($r = -0.117$, $p = 0.359$).

We subgrouped the 32 HSP patients with abdominal pain into two groups according to the existence of GI bleeding. There were 22 patients with GI bleeding and 10 patients without GI bleeding. There were no significant differences regarding platelet counts, WBC counts, CRP

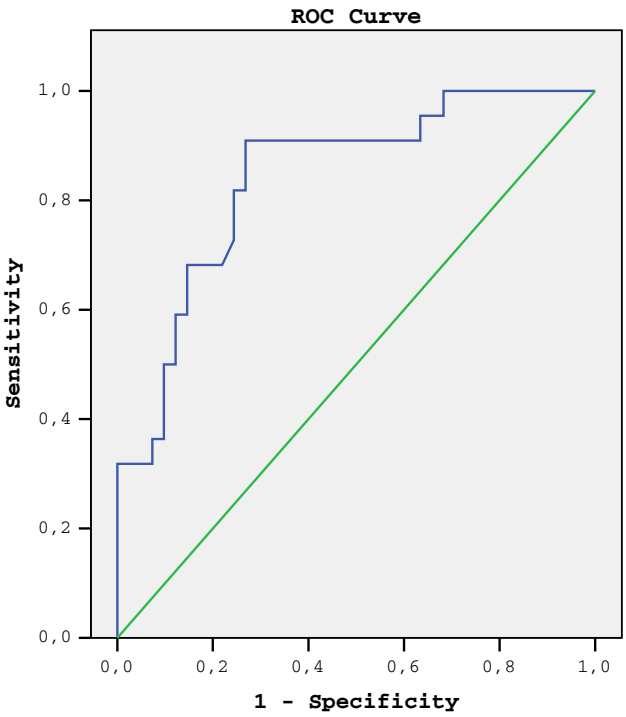

Fig. 1 ROC curve of admission NLR for predicting GI bleeding in HSP

levels, and MPV between these two groups ($p = 0.589$, $p = 0.190$, $p = 0.203$ and $p = 0.204$, respectively). However, NLR was significantly higher in those with GI bleeding than those without GI bleeding [3.6 (2.8–8.6) vs. 2.0 (1.5–3.2), $p = 0.007$].

Discussion

Henoch–Schönlein purpura is a leukocytoclastic vasculitis associated with a principally IgA-mediated immune response, particularly characterized by excessive production of pro-inflammatory cytokines, such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α, with consequent small vessel inflammation and endothelial cell injury [17, 18]. Previous studies suggested that thrombocytosis, leukocytosis, and high CRP levels were associated with GI bleeding in HSP [7, 8]. Similar results were observed in this study, though logistic regression analysis revealed that only two indicators, NLR and MPV, were associated with GI bleeding. We previously reported that low MPV might be related to GI bleeding in HSP [9]. This study further revealed that NLR was significantly increased in HSP patients with GI bleeding when compared to patients without GI bleeding. To the best of our knowledge, this is the first study evaluating the NLR in patients with HSP.

Although we believe the fact that NLR cannot completely capture the complexity of inflammation and immune responses in HSP, this disease is shown to be neutrophil dominated, and it may be rationale to think that high NLR might be related to more severe immune response in HSP, in part. NLR is measured by dividing neutrophil count to lymphocyte count. A rise in neutrophil count accompanied by a fall in lymphocyte count is commonly seen in various infectious and noninfectious causes of systemic inflammation and stress [19, 20]. Besides, lymphopenia may occur in some inflammatory conditions, such as sepsis, due to increased lymphocyte apoptosis [21]. As expected, we found significantly higher neutrophil counts in HSP patients compared to their healthy peers. Although lymphocyte counts did not significantly differed between HSP patients and controls in this study, patients with GI bleeding had significantly lower lymphocyte counts than those without GI bleeding.

Neutrophil-to-lymphocyte ratio (NLR) is shown as a potentially useful indicator of clinical outcome in disease states with an inflammatory component [10–15]. For example, it is associated with poor outcome in patients with cardiovascular diseases, malignities, cystic fibrosis, and familial Mediterranean fever [10–15]. However, this is the first study to evaluate the association of high NLR levels in severe HSP as GI involvement. Although we replicated our previous observation that lower MPV levels were associated with GI bleeding in HSP [9], this study added that NLR could be a more efficient potential predictor of GI bleeding in HSP than MPV as indicated by the area under the ROC curve analysis.

It has been an issue of debate for many years when to use corticosteroids in HSP patients. The suggested benefits of early corticosteroid treatment included shortened duration of abdominal pain, decreased risk of intussusception, and decreased risk of surgical intervention [22–25]. In a prospective study including 171 patients, Ronkainen et al. [22] demonstrated that prednisone was effective in reducing the intensity of abdominal pain. In a multicenter retrospective study, Weiss et al. [23] showed that early corticosteroid administration was associated with significantly reduced risks for abdominal surgery, endoscopy, and abdominal imaging in patients with HSP in the hospital setting. Thus, early steroid treatment is effective in terms of relieving gastrointestinal symptoms and preventing complications. The results of this study revealed that HSP patients with GI bleeding had significantly higher NLR than those with abdominal pain in the absence of GI bleeding. In this study, the optimal cutoff NLR for predicting GI bleeding was 2.82 with 81.0 % sensitivity and 76 % specificity. We suggest that this cutoff NLR may be used to choose the patients who will receive corticosteroids among those who suffer from abdominal pain.

The major limitations of this study are its retrospective design, small number of patients, and inclusion of children who all attended the same rheumatology clinic. So, multicenter prospective studies including larger number of patients are needed to confirm and generalize our results.

In conclusion, blood NLR was found as significantly increased in HSP patients with GI bleeding. Neutrophil-to-lymphocyte ratio, which is calculated from the complete blood count, is an easily accessible biomarker; it does not require specialized equipment or assays. We suggest that blood NLR may be considered as a useful marker for predicting GI bleeding in HSP.

Conflict of interest None of the authors have conflict of interest.

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