Neutrophil-to-lymphocyte ratio: A biomarker for predicting systemic involvement in adult IgA vasculitis patients

Authors:

Géza Róbert Nagy[1], Lajos Kemény[1], Zsuzsanna Bata-Csörgő[1]

[1]Department of Dermatology and Allergology, University of Szeged, Szeged, Hungary

Running head: Neutrophil-to-lymphocyte ratio in adult IgA vasculitis

Abstract word count: 213

Manuscript word count: 2330

Table count: 3

Figure count: 2

Number of references: 25

Funding sources: None

Conflict of Interest Disclosure: None Declared.

Corresponding Author: Géza Róbert Nagy, MD.

E-mail: n.geza@outlook.com

Address: Koranyi fasor 6, 6720 Szeged, HUNGARY.

Abstract

Background: IgA vasculitis (IgAV) is a small-vessel leucocytoclastic cutaneous vasculitis, often associated with kidney and gastrointestinal (GI) manifestations. Although predictive factors for systemic involvement have been extensively studied in children, there is paucity in the literature regarding adult patients. Neutrophil-to-lymphocyte ratio (NLR) is an inflammatory marker, used to assess systemic inflammation in various diseases.

Objective: We sought to evaluate whether NLR can be used for predicting renal and GI involvement in adult IgA vasculitis patients.

Methods: This was a retrospective review of adult patients who were diagnosed with IgAV at our institution between 2004 and 2016.

Results: A total of 40 patients met our inclusion criteria. Half of the enrolled patients had clinical symptoms suggestive of systemic involvement, of which 6 (15%) had only renal, 3 (7.5%) had only GI and 11 (27.5%) had both renal and GI involvement. Pretreatment NLR was significantly associated with renal and/or GI manifestations of the disease ($p<0.001$). The optimal cut-off value of NLR, for predicting systemic involvement was 3.34, with a specificity of 95% and a sensitivity of 85%. In addition, pretreatment NLR was also found to be significantly correlated with the severity of the systemic manifestations of IgAV ($p=0.022$).

Conclusion: This study suggests that NLR is a potential indicator for prognosticating systemic involvement in adult IgAV.

Introduction

Immunoglobulin A vasculitis (IgAV), formerly known as Henoch-Schönlein purpura, is an immune complex-mediated small-vessel leucocytoclastic cutaneous vasculitis, characterized by palpable purpura, arthralgia or arthritis, gastrointestinal (GI) and renal involvement.[1] It is often regarded as a disease of childhood, but contrary to popular belief, it is not uncommon in adults.[2] Although it is considered to be the same entity, the clinical manifestations and disease course differ greatly in these two age groups. Previous studies have demonstrated that unlike in children, adult patients develop systemic involvement more frequently, with a high risk of severe GI bleeding and chronic kidney disease.[3,4] This highlights the importance and the need of prognostic markers that can help identify IgAV patients who are at risk of developing unfavorable extracutaneous manifestations. While predictive factors have been extensively studied in children, there is limited data on adults.[5–7]

Blood neutrophil-to-lymphocyte ratio (NLR) is an inexpensive and easily obtainable laboratory marker for quantifying systemic inflammation, which has been used to predict clinical outcomes in patients with various internal malignancies, cardiovascular disease and liver cirrhosis.[8–12] As this ratio integrates information on two immune pathways, it may provide a predictive ability that outweighs other inflammatory parameters. The aim of this study was to evaluate the utility of this ratio in predicting renal and GI involvement in adult IgAV patients.

Patients and methods

Patients

A retrospective review of adult patients diagnosed with IgAV between January 2004 and January 2016 was performed. In accordance with the study criteria used by Takeuchi et al.[13] and Poterucha et al.,[14] patients needed to have palpable purpura consistent with the disease, skin biopsy specimen showing leucocytoclastic vasculitis on light microscopy and IgA deposition on direct immunofluorescence.

Patients were excluded if they had an immunologic comorbidity, coexisting internal malignancy, hematological disorder, cryoglobulinemia or any chronic renal or GI diseases. Additionally, patients who experienced hematochezia, melena or hematemesis two days before or after blood sampling, were also excluded owing to the possibility of neutrophilia being the secondary effect of an acute hemorrhage.

The study was approved by the local ethics review committee.

Data collection

We analyzed the medical records and registered the following: gender, age, duration of symptoms before blood sampling, clinical symptoms, results of laboratory testing and initial treatment. The laboratory test results included C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cell count (WBC), neutrophil and lymphocyte counts, hematological parameters, urine and stool examinations. NLR was calculated based on the initial complete blood count test, by dividing the neutrophil count with the lymphocyte count. By reviewing the ambulatory records, we also registered any subsequent renal or GI symptoms following initial remission. Patients were followed from baseline visit until loss of follow-up or death.

Assessment of gastrointestinal and renal involvement

We defined GI involvement as clinical signs of hematochezia, melena or hematemesis; or a positive test result for fecal hemoglobin. Renal involvement was determined through hematuria (>5 red blood cells per high-power microscopic field in a centrifuged specimen; in the absence of concurrent urinary tract infections, urolithiasis and anticoagulant therapy) or proteinuria (>150 mg/24h), or presence of predominant mesangial IgA deposition on the renal biopsy specimen.

Statistical analysis

The normality of distribution was analyzed using the Shapiro-Wilk test and parametric or non-parametric statistical tests were used accordingly. Quantitative variables are displayed as mean ± standard deviation (SD) or with median and interquartile range (IQR). Continuous variables were compared using one-way analysis of variance or Kruskal-Wallis test for multiple groups and independent sample t-test or Mann-Whitney U test for dual groups. Categorical features are summarized with frequency count, percentage and were compared using Fisher's exact test. The intercorrelations between parameters were examined using Spearman's rank correlation coefficient test. A receiver operating characteristic (ROC) curve was performed to examine the prognostic utility of NLR and to identify the optimal cut-off value. Statistical analyses were performed using the Statistical Package for Social Science version 22 (SPSS Inc., Chicago, IL, USA) for Windows. All tests were two-tailed and P-values of less than 0.05 were considered statistically significant.

Results

Basic characteristics of the study sample

Forty adult patients with IgAV who met the inclusion criteria were identified. The median age was 61 years (range 19-82 years). The cohort included 23 (57.5%) females and 17 (42.5%) males. Half of the patients had clinical symptoms suggestive of GI and/or renal involvement, of which 6 (15%) had only renal, 3 (7.5%) had only GI and 11 (27.5%) had both renal and GI involvement. Because the presence or absence of arthritis and arthralgia was only recorded in 23 (57.5%) patients out of the enrolled 40 cases, we have not included this data in the statistical analysis. The median time between the appearance of cutaneous symptoms and initial blood analysis was 9.5 days (IQR 5-14 days). Patients received initial treatment after blood sampling and in all cases either corticosteroid monotherapy or a combination of corticosteroid and antibiotics were employed. Based on the severity of the subsequently developed renal and GI symptoms, therapies were altered accordingly at the discretion of the clinician.

Clinical features

As NLR represents an inflammatory response, we also included other routinely used inflammatory markers for comparison. Spearman correlation analysis indicated a significant correlation of NLR with CRP (ρ=0.482; p=0.002), ESR (ρ=0.37; p=0.019) and WBC (ρ=0.469; p=0.002), however no significant correlation was observed with the duration of symptoms before blood sampling (ρ=-0.269; p=0.094) or patient age (ρ=0.282; p=0.078). To further exclude the possibility of an acute hemorrhage having an effect on NLR, we compared the hematological laboratory values of the enrolled patients based on their organ involvements, which did not indicate a significant difference between the groups (Table 1).

When stratifying patients based on their renal and GI manifestations and comparing the inflammatory laboratory parameters, there were no statistically significant differences, irrespective of which organ involvement the patients had (Table 2). Intriguingly, CRP was quite low in those with only GI involvement, which may be due to the small number of patients in this group and their mild clinical manifestations of IgAV. These three patients did not have extensive cutaneous symptoms and only displayed fecal hemoglobin positivity without any macroscopic bleeding of the GI tract.

Because there were no statistically significant differences in the hematological and the inflammatory values following patient stratification with regards to their organ involvements, the enrolled cases were divided into two groups.

While group 1 included patients who only had cutaneous symptoms, group 2 consisted of patients who developed GI and/or renal manifestations of IgAV, in addition to the cutaneous symptoms. The demographic and clinical characteristics of these two groups are detailed in Table 3. Of the registered inflammatory markers, CRP ($p=0.002$) and NLR ($p<0.001$) were significantly higher in group 2, whereas the other laboratory parameters, age, gender and the duration of symptoms were not statistically associated with systemic involvement.

Six (30%) patients in group 2 displayed GI involvement with the presence of macroscopic bleeding, whereas eight (40%) only had fecal hemoglobin positivity without a clinically apparent hemorrhage. In cases where gross blood was observed, an endoscopic examination was performed, which showed IgAV compatible macroscopic image in all of these patients.

With regards to renal symptoms, proteinuria was a frequent finding among those with a systemic involvement (n=15; 75%), however none of the patients developed nephrotic syndrome. In two

patients, renal involvement progressed into end stage renal disease, 11 and 14 days following initial blood analysis. A kidney biopsy was performed in both cases, which confirmed the association with IgAV. Additionally, these two individuals also developed severe GI bleeding, the former with intussusception and the latter with perforation as a secondary complication, both requiring surgical intervention.

Receiver operating characteristic curves of NLR versus other inflammatory markers

ROC curves of NLR and other inflammatory markers in relation to the systemic involvement are depicted in Figure 1. The area under the curve (AUC) for NLR, CRP, ESR and WBC was 0.892 (95% CI: 0.785-1; $p<0.001$), 0.779 (95% CI: 0.635-0.922; $p=0.003$), 0.669 (95% CI: 0.498-0.839; $p=0.068$) and 0.637 (95% CI 0.462-0.813; $p=0.089$), respectively. Of the considered laboratory data, NLR provided the strongest diagnostic value, as indicated by the highest AUC value. The optimal cut-off value of NLR for predicting systemic involvement was 3.34, with a specificity of 95% and a sensitivity of 85%.

NLR and disease severity

We further looked at the correlation of NLR and disease severity in patients with renal and/or GI involvement. For this, we have constructed a simple 7-point scoring system based on the clinical manifestations and course of the disease, observed among our enrolled cases. Patients received 1 point for each of the following features: hematuria, proteinuria, renal impairment, fecal hemoglobin positivity, macroscopic bleeding from the GI tract, the necessity of intensive care / surgery / dialysis or blood transfusion and death. NLR was found to be significantly correlated with the disease severity score ($\rho=0.51$; $p=0.022$) (Figure 2).

Discussion

Although IgAV is often a self-limiting and benign disease in children, severe complications may occur in adults, including renal impairment and serious GI bleeding requiring intensive care or surgery.[3,15] A number of studies have been conducted with the aim to correlate various clinical features with systemic involvement in adults, such as direct immunofluorescence findings of skin biopsy specimens and skin lesion distribution, though the results are dissenting.[13,14,16] Additionally, endoscopic features of GI lesions and histopathological findings of renal biopsies have also been studied, however these modalities can cause serious complications and may be contraindicated in certain cases.[17,18] Therefore, in order to gain more prognostic information, we examined the utility of a noninvasive and easily obtainable cost-effective laboratory parameter. To our knowledge this is the first biopsy-proven case-control study to investigate the predictive value of NLR for systemic involvement in adult IgAV patients.

Half of the patients included in our study developed renal and/or GI involvement, of which the majority concurrently had both organs affected. In accordance with this finding, other studies have also noted high incidence of simultaneous renal and GI manifestations in adult IgAV.[18,19] It should be mentioned however, that some researchers could not confirm this finding, which may be related to the varying criteria employed for defining systemic involvement.[13,20] Male gender has also been previously described as a poor prognostic indicator for systemic involvement, however our results did not reach statistical significance.[3,19]

When stratifying patients based on their renal and GI involvement and comparing the registered laboratory results, there were no significant differences in the hematological and the inflammatory laboratory values, which implies that NLR and the other inflammatory markers are not organ specific prognostic indicators and their elevated values were not the secondary effect of

a severe bleeding. Consequently, the high NLR observed in our study, is therefore likely to be the result of an inflammatory response.

Our results demonstrated that out of all the considered inflammatory parameters, NLR had the strongest diagnostic value. The optimal cut-off point for predicting systemic involvement was 3.34 with a specificity of 95% and a sensitivity of 85%. Additionally, we also found that pretreatment NLR values significantly correlated with the severity of the disease in patients who developed systemic involvement. It is important to note however, that when constructing the scoring system used to evaluate this correlation in our study, we only considered the presence or absence of certain clinical manifestations, rather than assessing the extent of renal or GI symptoms on a spectrum.

Progression to end stage renal disease was observed in two individuals. Compared to children, adult IgAV patients are more likely to present with a delayed renal involvement, often requiring close monitoring and diligent testing for even up to 6 months following the onset of IgAV, despite favorable initial laboratory results.[21] While delayed renal involvement was not observed in any of our cases, it should be noted that 20 patients (10 individuals from group 1 and 10 individuals from group 2) did not have a follow-up time period of at least 6 months. Although one of the patients with a lower NLR than the cut-off value identified in our study developed renal manifestations of IgAV (microscopic hematuria and proteinuria) during his admission, he remained asymptomatic throughout the follow-up time period (9 years).

More than a third of our patients had GI involvement, which is in accordance with previous reports.[3,4] In most cases, the symptoms consisted of colicky abdominal pain with fecal hemoglobin positivity, however some patients developed macroscopic bleeding. Severe complications, such as intussusception and perforation were also observed in two cases, the latter

resulting in a fatal outcome. None of the patients in our cohort with a lower NLR value than 3.34 displayed any clinical signs suggestive of GI involvement, during their admission and follow-up, which further highlights the prognostic value of NLR. Although a recent study demonstrated the applicability of this ratio with regards to GI bleeding in adult patients with cutaneous vasculitis, the employed criteria for the diagnosis of IgAV did not include skin histopathology examination.[22] In consideration of the probable clinical overlap between hypersensitivity vasculitis and IgAV, differentiating between these two entities is imperative when assessing and predicting renal or GI involvement.[23] Consequently, the clinical significance of the presence or absence of IgA deposition found by direct immunofluorescence of the cutaneous biopsy specimen should not be overlooked, as it enhances the diagnostic specificity.[1,24,25]

The significance of our findings is limited by the retrospective nature of this study and its single-center sample size. Nevertheless, as our selection was based on both clinical and histopathological findings, with the exclusion of patients with other background diseases, we believe our data represent accurate observations. Larger prospective multi-center studies are required to validate our findings and to establish a generally acceptable cut-off value of this ratio.

In conclusion, our results suggest that NLR is a potential prognostic marker for systemic involvement in adult IgAV and can be used to identify patients at risk of developing extracutaneous manifestations. In addition, we also found that increased pretreatment NLR correlated with the severity of the systemic involvement. Whether this ratio may permit the design of prospective therapeutic studies, remains to be determined.

Table 1. Hematological laboratory values of enrolled patients based on their organ involvements.

Variable	Renal involvement (n=6)	GI involvement (n=3)	Renal and GI involvement (n=11)	No renal or GI involvement (n=20)	P-value[a]
Hemoglobin (g/dl), mean ± SD	128.5±26.8	144.7 ± 19.6	127.6 ± 20.3	133 ± 19	0.483
Hematocrit (L/L), mean ± SD	0.38 ± 0.1	0.42 ± 0.1	0.38 ± 0.1	0.39 ± 0.1	0.628
Erythrocyte count ($x10^{12}$/l), mean ± SD	4.39 ± 0.9	4.74 ± 0.49	4.26 ± 0.49	4.45 ± 0.53	0.591
Platelet count ($x10^{9}$/l), mean ± SD	278.5 ± 61.9	240.7 ± 20.9	306.7 ± 132.8	282.1 ± 71.9	0.558

[a]Continuous variables were compared using the Kruskal-Wallis test.

Table 2. Inflammatory laboratory values of patients with systemic manifestations based on their organ involvements.

Variable	**Renal involvement (n=6)**	**GI involvement (n=3)**	**Renal and GI involvement (n=11)**	**P-value[a]**
CRP (mg/l), mean ± SD	85.3 ± 48.2	13 ± 12.3	105 ± 93.3	0.051
ESR (mm/h), mean ± SD	59.2 ± 44.7	24.3 ± 20.8	50 ± 28.8	0.334
WBC ($x10^9$/l), mean ± SD	9.3 ± 2.5	11 ± 2.9	12.1 ± 5.4	0.635
NLR, mean ± SD	4.2 ± 1.7	5.4 ± 1.5	7.4 ± 3.4	0.057

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GI, gastrointestinal; NLR neutrophil to lymphocyte rate; WBC, white blood cell count;
[a]Continuous variables were compared using the Kruskal-Wallis test.

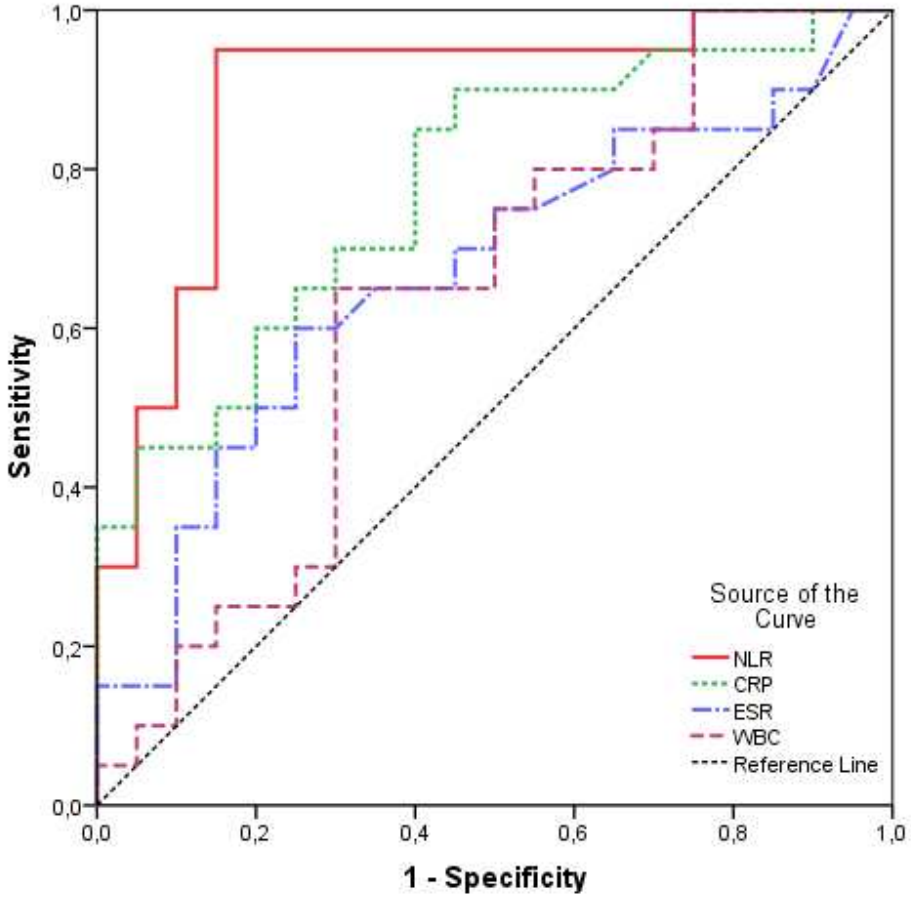
Table 3. Demographics and clinical findings of patients with respect to their systemic involvement.

Variable	**Group 1 (n=20)**	**Group 2 (n=20)**	**P-value[a]**
Age; years, mean ± SD	56 ± 20	60 ± 16.3	0.493
Gender, n (%)			0.056
Female	13 (65)	6 (30)	
Male	7 (35)	14 (70)	
Duration of symptoms; days, median (IQR)	11 (7-15.3)	7.5 (4-12.5)	0.081
CRP (mg/l), median (IQR)	13.1 (7.3-48.9)	68.2 (25.7-124.3)	**0.002**
ESR (mm/h), median (IQR)	22 (10-34.3)	43.5 (21.5-79.3)	0.068
WBC ($x10^9$/l), median (IQR)	8.2 (6.6-12)	10.9 (8.1-12.3)	0.142
NLR, median (IQR)	2.6 (1.6-3)	5.9 (4.3-7.1)	**<0.001**
Follow-up; months, median (IQR)	6.8 (3.5-24.9)	5.3 (2.1-19.1)	
End stage renal disease, n (%)	0 (0)	2 (10)	
Death, n (%)	0 (0)	1 (5)	

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IQR, interquartile range; NLR, neutrophil-to-lymphocyte rate; WBC, white blood cell count;

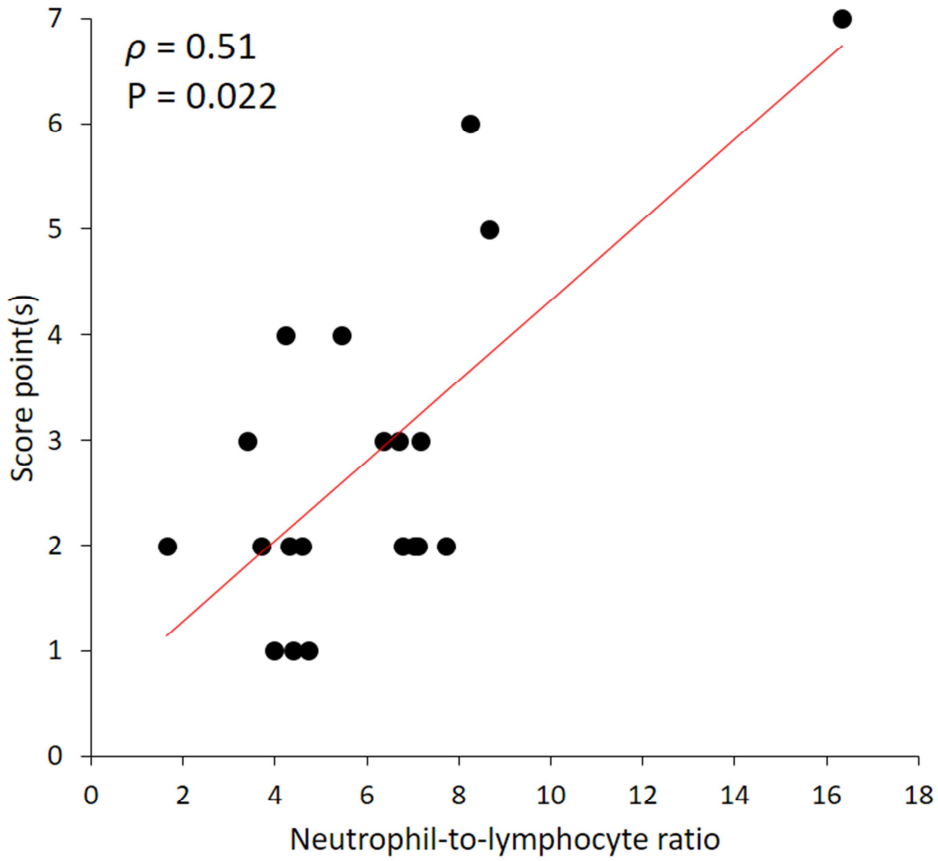
[a]Fisher's exact test was used to compare categorical variables. Student's t-test was used to compare age and Mann-Whitney U test was used to compare the duration of symptoms and laboratory values.

Figure 1. Receiver operating characteristic curves for predicting the development of renal and/or gastrointestinal involvement.



CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; NLR neutrophil-to-lymphocyte rate; WBC, white blood cell;

Figure 2. Correlation between pretreatment neutrophil-to-lymphocyte ratio and disease severity score.



The Spearman correlation test was used, giving the coefficient ρ, with P-value < 0.05 being significant.

References

1 Jennette JC, Falk RJ, Bacon PA, *et al.* 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum* 2013; **65**:1–11.

2 Hočevar A, Rotar Z, Ostrovršnik J, *et al.* Incidence of IgA vasculitis in the adult Slovenian population. *Br J Dermatol* 2014; **171**:524–7.

3 Hočevar A, Rotar Ž, Jurčić V, *et al.* Patient age, gender and extent of purpura may suggest short-term outcomes in adults with IgA vasculitis. *Rheumatology (Oxford)* 2015; **54**:1330–2.

4 Pillebout E, Thervet E, Hill G, *et al.* Henoch-Schönlein Purpura in adults: outcome and prognostic factors. *J Am Soc Nephrol* 2002; **13**:1271–8.

5 Makay B, Gücenmez ÖA, Duman M, Ünsal E. The relationship of neutrophil-to-lymphocyte ratio with gastrointestinal bleeding in Henoch-Schonlein purpura. *Rheumatol Int* 2014; **34**:1323–7.

6 Johnson EF, Lehman JS, Wetter DA, *et al.* Henoch-Schonlein purpura and systemic disease in children: retrospective study of clinical findings, histopathology and direct immunofluorescence in 34 paediatric patients. *Br J Dermatol* 2015; **172**:1358–63.

7 Nagamori T, Oka H, Koyano S, *et al.* Construction of a scoring system for predicting the risk of severe gastrointestinal involvement in Henoch-Schönlein Purpura. *Springerplus* 2014; **3**:171.

8 Zhang L, Wang R, Chen W, *et al.* Prognostic significance of neutrophil to lymphocyte ratio in patients with gallbladder carcinoma. *HPB (Oxford)* 2016; **18**:600–7.

9 Stotz M, Gerger a, Eisner F, *et al.* Increased neutrophil-lymphocyte ratio is a poor prognostic factor in patients with primary operable and inoperable pancreatic cancer. *Br J Cancer* 2013; **109**:416–21.

10 Tanoglu A, Karagoz E. Predictive role of the neutrophil-to-lymphocyte ratio in patients with advanced hepatocellular carcinoma receiving sorafenib. *Asian Pac J Cancer Prev* 2014; **15**:1063.

11 Tamhane UU, Aneja S, Montgomery D, *et al.* Association between admission neutrophil to lymphocyte ratio and outcomes in patients with acute coronary syndrome. *Am J Cardiol* 2008; **102**:653–7.

12 Kwon JH, Jang JW, Kim YW, *et al.* The usefulness of C-reactive protein and neutrophil-to-lymphocyte ratio for predicting the outcome in hospitalized patients with liver cirrhosis. *BMC Gastroenterol* 2015; **15**:146.

13 Takeuchi S, Soma Y, Kawakami T. IgM in lesional skin of adults with Henoch-Schönlein purpura is an indication of renal involvement. *J Am Acad Dermatol* 2010; **63**:1026–9.

14 Poterucha TJ, Wetter DA, Gibson LE, *et al.* Correlates of systemic disease in adult Henoch-Schönlein purpura: a retrospective study of direct immunofluorescence and skin lesion distribution in 87 patients at Mayo Clinic. *J Am Acad Dermatol* 2012; **67**:612–6.

15 Blanco R, Martínez-Taboada VM, Rodríguez-Valverde V, *et al.* Henoch-Schönlein purpura in adulthood and childhood: two different expressions of the same syndrome. *Arthritis Rheum* 1997; **40**:859–64.

16 Tancrede-Bohin E, Ochonisky S, Vignon-Pennamen MD, *et al.* Schönlein-Henoch purpura in adult patients. Predictive factors for IgA glomerulonephritis in a retrospective study of 57 cases. *Arch Dermatol* 1997; **133**:438–42.

17 Nam EJ, Kim GW, Kang JW, *et al.* Gastrointestinal bleeding in adult patients with Henoch-Schonlein purpura. *Endoscopy* 2014; **46**:981–6.

18 Pillebout E, Thervet E, Hill G, *et al.* Henoch-Schönlein Purpura in adults: outcome and prognostic factors. *J Am Soc Nephrol* 2002; **13**:1271–8.

19 Hung SP, Yang YH, Lin YT, *et al.* Clinical Manifestations and Outcomes of Henoch-Schönlein Purpura: Comparison between Adults and Children. *Pediatr Neonatol* 2009; **50**:162–8.

20 Zhang Y, Huang X. Gastrointestinal involvement in Henoch-Schönlein purpura. *Scand J Gastroenterol* 2008; **43**:1038–43.

21 Ilan Y, Naparstek Y. Schonlein-Henoch syndrome in adults and children. *Semin Arthritis Rheum* 1991; **21**:103–9.

22 Park CH, Han DS, Jeong JY, *et al.* The Optimal Cut-Off Value of Neutrophil-to-Lymphocyte Ratio for Predicting Prognosis in Adult Patients with Henoch-Schönlein Purpura. *PLoS One* 2016; **11**:e0153238.

23 Calvo-Río V, Loricera J, Ortiz-Sanjuán F, *et al.* Revisiting clinical differences between hypersensitivity vasculitis and Henoch-Schönlein purpura in adults from a defined population. *Clin Exp Rheumatol* 2014; **32**:S34-40.

24 Alalwani M, Billings SD, Gota CE. Clinical significance of immunoglobulin deposition in leukocytoclastic vasculitis: a 5-year retrospective study of 88 patients at cleveland clinic. *Am J Dermatopathol* 2014; **36**:723–9.

25 Hočevar A, Rotar Z, Jurčić V, *et al.* IgA vasculitis in adults: the performance of the EULAR/PRINTO/PRES classification criteria in adults. *Arthritis Res Ther* 2015; **18**:58.