

# Neutrophil-to-Lymphocyte Ratio: A Biomarker for Predicting Systemic Involvement in IgA Vasculitis

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## Abstract

**Context:** "IgA vasculitis, is an immune complex mediated, self limited cutaneous small vessel vasculitis, characterized by palpable purpurae, arthralgia or arthritis, gastrointestinal and/or renal involvement." Systemic involvement is considered to be the presence of gastrointestinal (GI) and/or renal involvement in IgA vasculitis patients. Neutrophil-to-lymphocyte ratio (NLR) is a relatively cost-effective and easily obtainable laboratory parameter integrating information on two immune pathways to provide a superior predictive ability over other inflammatory parameters regarding systemic involvement.

**Aims:** The aim of the study was to assess the predictive value of NLR with regard to the systemic involvement in IgA vasculitis.

**Subjects and Methods:** This was a hospital-based cross-sectional study of patients diagnosed with IgA vasculitis, irrespective of age, between 2017 and 2019.

**Results:** The study consisted of 33 patients with a mean age of  $33.52 \pm 19.78$  years. Joint involvement was observed in 52% (17), whereas systemic manifestations in the form of renal involvement were present in 7 (21%), GI in 19 (57.6%), and renal and/or GI in 22 (66.7%) patients. NLR was found to be significantly associated with GI manifestations ( $P < 0.001$ ). Optimal cutoff value of NLR for predicting systemic involvement was 3.25, with a specificity of 100% and sensitivity of 59%.

**Conclusions:** NLR can be considered as a biomarker for predicting systemic involvement in IgA vasculitis, presenting with only cutaneous with/without joint manifestations.

**Key Words:** Arthralgia, gastrointestinal involvement, Henoch–Schonlein purpura, renal involvement

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## Introduction

Vasculitides represent a group of disorders presenting in a myriad of ways characterized primarily by inflammation of the blood vessel wall with any organ system involvement.<sup>[1]</sup> Cutaneous vasculitides are a heterogeneous group of inflammatory disorders affecting cutaneous blood vessels, which may either be idiopathic or triggered by infections, drugs, underlying malignancies, or connective tissue disorders, of which skin involvement may occur as a heralding sign.<sup>[2]</sup>

The worldwide annual incidence of cutaneous vasculitis varies from 15.4–29.4 per million, affecting all ages, with slight female preponderance, and children over adults.<sup>[3]</sup> Children are the common sufferers of Henoch–Schonlein

purpura (HSP)/IgA vasculitis, with an estimated annual incidence of 3.0–26.7 cases/million children. There is a sparsity of epidemiological data on the relative frequency of various types of vasculitis in India, although HSP is known to be one of the commoner forms of vasculitis in India. Since the management of a patient with suspected vasculitis requires vigorous search for any treatable underlying cause, its epidemiological and etiological associations need to be thoroughly deciphered.

The histopathological evidence of vascular inflammation is confirmatory of vasculitis,<sup>[3]</sup> whereas the direct immunofluorescence (DIF) study helps in further categorization of the condition. The very fact that essential histological information coupled with DIF and etiological association enables a precise diagnosis of vasculitis

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syndromes,<sup>[3]</sup> paving the way to the most efficacious therapeutic approach, envisages the need for a similar correlating study.

"IgA vasculitis, is an immune complex mediated, self limited cutaneous small vessel vasculitis, characterized by palpable purpura, arthralgia or arthritis, gastrointestinal and renal involvement.<sup>[4]</sup>" HSP, despite being found in all age groups, has an increased propensity for children,<sup>[5]</sup> whereas the disease severity, chances of systemic involvement and risk of complications are more for adults.<sup>[5,6]</sup> The incidence of gastrointestinal (GI) involvement is between 50% and 75%, renal involvement is 40%–50%, and arthritis or arthralgia is 15%–25% of cases,<sup>[5]</sup> with the complications being severe GI bleeding due to intussusception or perforation and chronic kidney disease leading to end-stage renal failure. This calls attention to the need for predictive markers for systemic involvement in adult HSP patients, taking also into consideration the dearth in hitherto data among adults.<sup>[6]</sup>

Blood neutrophil-to-lymphocyte ratio (NLR) is a noninvasive, relatively cost-effective, and easily obtainable laboratory parameter integrating information on two immune pathways to provide a superior predictive ability over other inflammatory parameters.<sup>[6]</sup> A rise in NLR can be seen in inflammatory conditions, following an increase in neutrophil counts and fall in lymphocyte counts, according to the severity of the underlying pathology, and hence can be used as an efficient marker of prognosis, as far as systemic involvement is concerned, in adult IgA vasculitis. Hence the need arises for a study on the role of NLR in predicting and prognosticating systemic involvement in adult HSP patients.

Limited use of DIF study in tertiary care hospitals has resulted in meagre studies on its diagnostic yield in vasculitis. This study has been undertaken to comprehend the relevance of NLR as a biomarker in predicting risk of systemic involvement in patients with IgA vasculitis, in a tertiary care center in North Karnataka.

## Subjects and Methods

The current study was a hospital based cross-sectional study including 33 patients diagnosed with IgA vasculitis, irrespective of age, sex, or duration of disease, conducted between November 2017 and August 2019. Patients with coexisting internal malignancy and a history of hematological disorders (which may alter the total and differential counts or cause bleeding manifestations), chronic renal or GI diseases, and on anti-coagulant medications (aspirin, warfarin, and heparin)/nonsteroidal anti-inflammatory drugs and who experienced hematochezia, melena, or hematemesis 2 days before blood sampling were excluded from the study. Informed consent was obtained from all participating patients.

Biodata (name, age, sex, and address) of patient, relevant history, and clinical examination findings were recorded.

Relevant drug exposure was considered if exposure was within 4 weeks of appearance of the lesion. NLR is calculated based on the initial complete hemogram, by dividing the neutrophil count with the lymphocyte count.<sup>[7]</sup> GI involvement is defined as hematochezia, melena, or hematemesis or positive fecal hemoglobin (Hb). Renal involvement is determined through hematuria (>5 red blood cells per high-power microscopic field in a centrifuged specimen) or proteinuria (>150 mg/24 h)<sup>[6]</sup>/ (urine protein  $\geq 1+$  on microscopic urinalysis).<sup>[8]</sup>

The following baseline investigations were carried out for all the patients.

- Complete hemogram,
- C-reactive protein (CRP)
- Serum urea and creatinine levels
- Urine analysis
- Stool analysis
- Stool guaiac test.

Other specific tests were done whenever indicated. Two skin biopsies were taken and sent for histopathology examination and DIF. NLR and disease severity in patients with renal and/or GI involvement were correlated by a simple 7-point scoring system based on the clinical manifestations and course of the disease, observed among enrolled cases, wherein the severity of systemic involvement is directly proportional to the obtained score.<sup>[6]</sup> Patients received one point for each of the following features: hematuria, proteinuria, renal impairment, fecal Hb positivity, macroscopic bleeding from the GI tract, the necessity of intensive care/surgery/dialysis or blood transfusion, and death, the maximum score being 7.<sup>[6]</sup>

Statistical analysis was performed using the IBM Statistical Package for the Social Sciences (IBM SPSS version 23) and INSTAT softwares. The results were presented as graphs, mean  $\pm$  standard deviation, counts, and percentages. Sensitivity and specificity analyses were performed using receiver operating characteristics (ROC) curves. Optimal cutoff values of platelet-to-lymphocyte ratio (PLR), mean platelet volume (MPV), CRP, and NLR were defined by the Youden's index. Categorical variables were compared using Chi-square test, and quantitative variables were compared using independent *t*-test and Mann-Whitney U-test. For all tests, significance was achieved at  $P < 0.05$ . All statistical tests performed were two tailed.

Shri B M Patil Medical College Hospital and Research Centre Institutional Ethical Committee clearance (reference number: 142/17) was undertaken for the study.

## Results

In the study population comprising 33 patients, males outnumbered females in a ratio of 1.5:1, and the mean age was  $33.5 \pm 19.8$  years. All the patients had palpable purpurae, among whom majority had lesions confined to

lower extremities. Seventeen (52%) patients had arthritis or arthralgia. Systemic involvement in the form of renal and/or GI manifestations was present in 22 (67%) patients, among which 19 (58%) had GI involvement and 7 (21%) had renal involvement. The major GI manifestation observed was abdominal pain in 12 (36%) patients, followed by GI bleeding in the remaining 10 patients. The presence of occult blood in stool was observed in 14 (42%) patients. Proteinuria was the major renal manifestation (5 patients), followed by hematuria in 2 patients.

The duration of clinical manifestations of IgA vasculitis in a good majority of 23 (70%) patients in this study was below a week, with a mean duration of  $7.12 \pm 4.80$  days. Recurrent episodes were present only in 8 (24%) patients.

Laboratory parameters were compared in the patients with and without GI involvement. There was no statistically significant difference observed between the averages of Hb, total count, platelet count, erythrocyte sedimentation rate, CRP, MPV, and PLR among the two groups, as shown in Table 1. NLR was significantly higher in patients with features of gastrointestinal tract (GIT) involvement in comparison to those without the same ( $P = 0.0155$ ). Highly significant statistical association was observed between the presence of occult blood in stool and GI involvement, with a positive predictive value of 68% and negative predictive value of 93%.

NLR, PLR, MPV, and CRP were considered for statistical analysis as indicators of GI involvement in IgA vasculitis, using Chi-square test, and optimal cutoff values were derived. In the ROC curve for GIT involvement, the area under ROC curve (AUROC) of NLR was 74.8% and the optimal cutoff value was 3.25, as shown in Figure 1. Using this cutoff value, the sensitivity and specificity were 63.2% and 92.9%, respectively. The AUROC curve of MPV

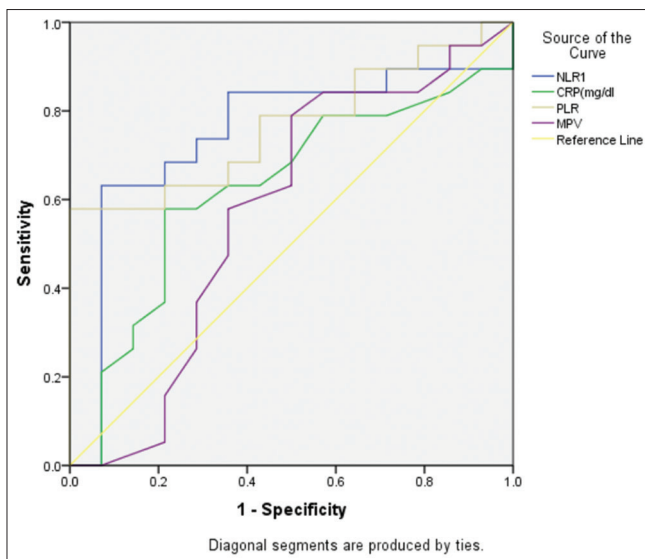
was 57.3% and the optimal cutoff value was 9.35, with a sensitivity of 78.95% and specificity of 50%. In the ROC curve for GIT involvement, the AUROC of CRP was 62.6% and the ideal cutoff value was 10.5. Using this cutoff value, the sensitivity and specificity were 57.8% and 78.6%, respectively. The AUROC of PLR was 76.7% and the optimal cutoff value was 148.55, using which the sensitivity was 58% and specificity was 100%.

The AUROC analysis indicates that PLR and NLR can be reliable predictors of GIT involvement in IgA vasculitis. There was no statistically significant association between NLR, PLR, or MPV with renal involvement in IgA vasculitis. No statistically significant association was observed between NLR, PLR, and MPV, with joint manifestations of arthritis or arthralgia. Chi-square analysis using NLR, PLR, and MPV as prognostic indicators for systemic involvement in IgA vasculitis revealed statistically significant association between NLR and PLR with systemic manifestations in IgA vasculitis, whereas MPV was not significantly associated with the same.

**Table 1: Comparison of demographic and laboratory parameters in patients with and without gastrointestinal involvement**

Variables	Without GIT	With GIT	P
<i>n</i>	14	19	
Demographic, mean (median)±SD			
Age (years)	36.57 (37.5)±20.85	31.26 (30.0)±19.2	0.4616 (NS)
Gender, <i>n</i> (%)			
Male	6 (30)	14 (70)	0.07
Female	8 (61.5)	5 (38.5)	(NS)
Laboratory findings			
Hb	13.18 (13.65)±3.11	13.38 (13.3)±1.74	0.8318 (NS)
TC	10622 (10230)±3609.3	1035.32 (10010)±344.7	0.8323 (NS)
PC	3.17 (2.96)±1.74	3.49 (3.07)±1.313	0.3392 (NS)
ESR	31.8 (17)±34.14	37.84 (30)±31.72	0.3717 (NS)
CRP	12.0 (5.56)±22.93	13.65 (11.1)±13.42	0.292 (NS)
MPV	9.61 (9.45)±0.92	9.68 (9.7)±0.623	0.7885 (NS)
NLR	2.89 (2.18)±3.05	3.86 (3.7)±2.17	0.0155* (HS)
PLR	101.73 (101.72)±31.204	172.05 (158.68)±95.28	0.3266 (NS)

Hb: Hemoglobin, TC: Total count, PC: Platelet Count, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, MPV: Mean platelet volume, NLR: Neutrophil-to-lymphocyte ratio, SD: Standard deviation, PLR: Platelet-to-lymphocyte ratio, NS: Not significant, HS: Highly significant, GIT: Gastrointestinal tract



**Figure 1: Receiver operating characteristic curve of prognostic variables for IgA vasculitis**

In the ROC curve for systemic involvement (both renal and GI), the AUROC of NLR was 79.3% and the optimal cutoff value was 3.25. Using this cutoff value, the sensitivity and specificity were 59% and 100%, respectively, making NLR a better prognostic indicator compared to PLR for systemic involvement in IgA vasculitis. The Youden's index values of variables analyzed are given in Table 2.

The 7-point scoring system to assess the severity of systemic involvement in IgA vasculitis patients with renal or GIT manifestations was not found to be significantly associated with NLR in the present study, as a vast majority of the study population of 63.6% had only a score of, zero as shown in Figure 2.

**Table 2: Youden index**

PLR with GIT involvement	PLR with systemic involvement	NLR with Systemic involvement	NLR with GIT involvement
0	0	0	0
7.14	9.09	-4.54	-5.26
1.58	4.54	-9.09	-10.52
8.73	0	0	-3.38
15.87	-4.54	18.18	10.90
10.31	-9.09	27.27	18.04
17.46	0	22.72	12.78
24.60	9.09	18.18	19.92
19.04	4.54	27.27	27.06
13.49	0	36.36	34.21
20.63	9.09	45.45	41.35
27.77	18.18	54.54	48.49
34.92	13.63	50	43.23
29.36	9.09	45.45	37.96
23.80	4.54	40.90	45.11
30.95	13.63	36.36	39.84
38.09	9.09	45.45	46.99
45.23	18.18	40.90	41.72
39.68	27.27	50	48.87
46.82	22.72	59.09	56.01
53.96	31.81	54.54	50.75
61.11	40.90	50	45.48
55.55	50	45.45	40.22
50	45.45	40.90	34.96
44.44	40.90	36.36	29.69
38.88	36.36	31.81	24.43
33.33	31.81	27.27	19.17
27.77	27.27	22.72	13.90
22.22	22.72	18.18	8.64
16.66	18.18	13.63	3.38
11.11	13.63	9.09	-1.87
5.55	9.09	4.54	-7.14
0	4.54	0	0
20			
10			

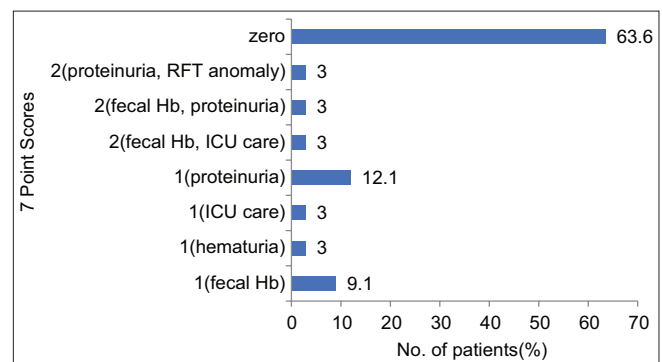
T: Gastrointestinal tract, PLR: Platelet-to-lymphocyte ratio, NLR: Neutrophil-to-lymphocyte ratio

## Discussion

IgA vasculitis is an IgA-mediated immune response, characterized by excessive production of pro-inflammatory cytokines, like interleukin (IL)-1, IL-6 and tumor necrosis factor- $\alpha$ , with small vessel inflammation and endothelial cell injury.<sup>[9,10]</sup> NLR is an inexpensive indicator that can be easily and quickly detected in inflammatory reactions.<sup>[11]</sup>

In this cross-sectional study of 33 patients with IgA vasculitis, adolescents and adults >50 years constituted the majority, much in tune with studies conducted by Khetan *et al.*<sup>[7]</sup> The observation of systemic involvement in the form of renal or GI manifestations in 67% of the patients was consistent with those in a study by Nagy *et al.*,<sup>[6]</sup> which was but retrospective in nature, whereas few other similar studies revealed lesser frequency of extracutaneous manifestations in IgA vasculitis. A history of recurrent lesions was seen in 24% of the patients which was in accordance with the studies done by Gupta *et al.*<sup>[12]</sup> (18%) and Ekenstam and Callen<sup>[13]</sup> (16%), which could be due to the relapsing nature of IgA vasculitis.

NLR, PLR, and MPV being known inflammatory markers in different disease conditions, according to various studies conducted previously, the current study opted to assess the association of each of these parameters with the presence or severity of systemic involvement in IgA vasculitis patients who were DIF proven. Statistically significant association with high NLR values was present in patients with either GI alone or concurrent GIT and renal involvement, whereas no significant association could be derived in those with pure renal involvement. This observation was partly consistent with those of Nagy *et al.*,<sup>[6]</sup> as their study turned up with a positive association between NLR and GIT as well as renal involvement both individually and in conjunction. In view of significant statistical association between positivity for stool for occult blood and the presence of GI involvement in IgA vasculitis patients, stool for occult blood (guaiac test) can probably be considered as a screening test for GI involvement in IgA vasculitis patients even in the absence of overt GIT manifestations at presentation, as per the current study, to guide the line of management accordingly. The present



**Figure 2: 7-point score in the study population. Score with observed component abnormalities in brackets, shown (Y-axis). Percentage of study population corresponding with each of the scores represented along X-axis**



**Table 3: Studies on Sensitivity and specificity association with neutrophil-to-lymphocyte ratio**

Study	Sensitivity (%)	Specificity (%)	Optimal NLR
Current study	59	100	3.25
Nagy <i>et al.</i> <sup>[6]</sup>	85	95	3.34
Park <i>et al.</i> <sup>[14]</sup>	74.1	75	3.18
Makay <i>et al.</i> <sup>[15]</sup>	81	76	2.82

NLR: Neutrophil-to-lymphocyte ratio

study deduced statistically significant association of high PLR in addition to NLR with systemic involvement in the form of concurrent renal and GIT involvement in IgA vasculitis. Further analysis of the two parameters through Chi-square test revealed NLR to be a better indicator of systemic involvement, with “*P*” = 0.001 for NLR as opposed to 0.004 for PLR.

The inference from the current study with reference to Table 3 indicates the utility of NLR as a better marker of systemic involvement in IgA vasculitis.

The 7-point scoring system used by Nagy *et al.*<sup>[6]</sup> significantly associated with NLR and disease severity in their retrospective study, which could not derive a significant association between the two parameters in the current study, which could most probably be attributed to the cross-sectional nature of our study.

Of all the considered laboratory data, NLR proved to be of the strongest predictive value to indicate systemic involvement in IgA vasculitis as elicited from the highest AUROC curve value on statistical analysis in the present study, which is consistent with the observation by Nagy *et al.*<sup>[6]</sup> in their retrospective analysis. The current study is the only cross-sectional study undertaken till date to assess the role of NLR in predicting systemic involvement in IgA vasculitis.

The current study is significant as it can be considered as an avenue to extrapolate the utility of NLR in guiding the management of IgA vasculitis lacking GIT/renal manifestations on presentation through prophylactic initiation of systemic corticosteroid administration so as to prevent progression to systemic involvement and complications, which is otherwise not recommended, thereby paving the way to a better prognosis and disease outcome, the association of NLR with systemic involvement hereby being statistically proven. This study can be a harbinger for long-term follow-up studies in future to help establish it as a powerful prognostic tool.

## Conclusion

High NLR is significantly associated with pure GI as well as concurrent renal and GI involvement in IgA vasculitis patients. NLR was observed to have better predictive association with systemic involvement in IgA vasculitis, in comparison with PLR. NLR is a simple, reliable, cost-effective, and efficient inflammatory marker to predict systemic involvement in IgA vasculitis. Future long-term follow-up studies can better substantiate this study.

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## Conflicts of interest

There are no conflicts of interest.

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