The relationship between monocyte-to-lymphocyte ratio and the risk of gastrointestinal system involvement in children with IgA vasculitis: A preliminary report

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Abstract

Background. Immunoglobulin A (IgA) vasculitis is the most common systemic vasculitis of childhood. It can affect the gastrointestinal system (GS) and the renal system.

Objectives. To evaluate the monocyte-to-lymphocyte ratio (MLR) and other hematological markers in predicting GS and renal system complications of IgA vasculitis in children.

Materials and methods. One hundred and fifteen children with IgA vasculitis and 95 healthy children were included in this study. Demographic characteristics, organ involvement, and laboratory findings, including neutrophil, lymphocyte, monocyte and platelet (Plt) counts, red blood cell volume distribution width (RDW), platelet distribution width (PDW), mean platelet volumes (MPV), monocyte/platelet counts, neutrophil/lymphocyte ratio (NLR), and platelet/lymphocyte ratio (PLR), were evaluated.

Results. Among 115 children with IgA vasculitis, 34 (29.5%) cases had GS involvement, and renal involvement was observed in 12 children (10.4%). Neutrophil, monocyte and Plt count and MLR, NLR and PLR values were higher in the IgA vasculitis group than in control groups. Moreover, the neutrophil count and NLR and MLR levels were significantly higher in children with GS involvement than in those without GS involvement. Logistic regression analysis showed MLR was the sole risk factor for GS involvement among these parameters. Furthermore, a cut-off MLR value of 0.245 differentiated children with IgA vasculitis with GS involvement from those without GS involvement (area under the curve (AUC) 0.694, with a sensitivity of 52.9% and specificity of 77.8%).

Conclusions. An elevated MLR value could serve as a useful marker in predicting GS involvement in IgA vasculitis in children. Therefore, monitoring the blood MLR value may serve as an important novel indicator to pediatricians regarding the involvement of GS and disease severity of IgA vasculitis.

Key words: IgA vasculitis, neutrophil-to-lymphocyte ratio, gastrointestinal system involvement, monocyte-to-lymphocyte ratio, platelet-to-lymphocyte ratio

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Background

Immunoglobulin A (IgA) vasculitis is the most common systemic vasculitis of childhood.[1] The average annual incidence of this disease in children is about 20/100,000.[2] Although the disease is most often characterized by a mild, self-limiting course with a good prognosis, it may present a progressive course and high recurrence in some cases.[3] It not only affects the small vessels of the skin, but also the gastrointestinal and renal systems in some cases, including severe gastrointestinal bleeding and renal insufficiency.[4] Therefore, easily accessible and cost-effective laboratory parameters that can be used to predict the severity of the disease are needed.

Blood cell-derived parameters, including white blood cell (WBC) and its subtype cell counts (neutrophils, lymphocytes and monocytes), hemoglobin (Hb), red blood cell volume distribution width (RDW), platelet (Plt), platelet distribution width (PDW) and mean platelet volume (MPV), are commonly used clinical indicators,[5–7] which also have the advantage of simple retrieval from routine blood examination, with established detection methods and rapid results. Moreover, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are new inflammatory indicators easily obtained from blood count. Recently, studies have shown that NLR and PLR are increased in a variety of other conditions, including cardiovascular disease,[8] diabetes mellitus,[9] immune system diseases,[10] and cancer,[11] and they can be used as novel inflammation parameters to predict the severity of these diseases. Similarly, NLR and PLR were reported to be associated with gastrointestinal bleeding among children with recent IgA vasculitis.[12] Of note, monocyte-to-lymphocyte ratio (MLR) was also suggested as a new inflammatory marker, and its clinical value has been investigated in patients with cancer,[13] cirrhosis[14] and retinopathy.[15] However, few studies have investigated the relationship between MLR and severity of IgA vasculitis in children.

Objectives

We aimed to study the value of MLR and other blood cell-derived parameters, including neutrophil, lymphocyte, monocytes and Plt count, MPV, NLR and PLR in predicting the disease course, including gastrointestinal and renal involvement and recurrence in children with IgA vasculitis.

Materials and methods

Study design and participants

This study was conducted in full accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Changshu No. 2 People's Hospital (approval No. 2020-KY-45).

This retrospective study included 115 children with IgA vasculitis who were admitted to the Department of Pediatrics, Changshu No. 2 People's Hospital from January 1, 2016 to January 1, 2020. The IgA vasculitis was diagnosed according to the EULAR/PRINTO/PRES 2013 criteria.[16,17] Ninety-five age and gender-matched healthy children were enrolled as the control group. Patients with other autoimmune diseases; severe heart, lung and endocrinal diseases; or those with fungal and tuberculosis infections were excluded.

Gastrointestinal system (GS) involvement was defined as the presence of abdominal pain, vomiting or gastrointestinal hemorrhage.[18] Renal involvement was defined as the presence of hematuria (>5 red blood cells per high-power microscopic field) and/or proteinuria (protein concentration in spot urine ≥30 mg/dL or spot urine protein/creatinine ratio >0.5 in children <2 years of age and >0.2 in children ≥2 years of age).[19] The recurrence of IgA vasculitis was defined as a new flare of cutaneous lesions or other manifestations of vasculitis in a patient at least 4 weeks after the initial IgA vasculitis diagnosis.[3]

Laboratory assessments

The venous blood sample was collected in the fasting state at the time of admission to the hospital (before the start of the treatment). Blood routine, urine routine and fecal occult blood tests were conducted by the Department of Clinical Laboratory of Changshu No. 2 People's Hospital. The leukocyte count (neutrophil, monocyte and lymphocyte count), Plt count, RDW, Hb, PDW, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were recorded, and the NLR, MLR, and PLR were calculated.

Statistical analyses

All data were analyzed using the SPSS v. 19.0 software package (IBM Corp., Armonk, USA). The Shapiro–Wilk test was used to test the distribution of analyzed variables. Mean ± standard deviation (SD) were used to describe continuous data. To compare differences between 2 groups, independent t-tests for continuous variables with normal distribution were used. The percentages were used to describe categorical data, which were analyzed with χ^2 tests. Logistic regression analysis was performed for multivariate analysis. The receiver operating characteristic (ROC) curve analysis was conducted to evaluate the cutoff value of blood count parameters. Results with $p < 0.05$ were considered statistically significant.

Results

Clinical characteristics and blood cell counts in the IgA vasculitis group and in healthy children

There were 56 (48.69%) boys and 59 (51.30%) girls with IgA vasculitis included in the study. Among the children with IgA vasculitis, 34 (29.56%) cases had GS involvement, and renal involvement was observed in 12 children (10.43%); only 3 cases (2.61%) had both GS and renal involvement. Additionally, 22 (19.13%) children had at least one recurrence of IgA vasculitis during follow-up.

The WBC, neutrophil, monocyte and Plt counts and MPV, NLR, MLR and PLR values were significantly higher in the IgA vasculitis group compared with control groups. However, there were no differences in lymphocyte count and Hb, RDW and PDW levels between the IgA vasculitis and control groups (Table 1).

Comparison of blood cell count parameters in children with IgA vasculitis with or without internal organ involvement

The neutrophil count and NLR and MLR levels were found to be significantly higher in children with GS involvement compared to those without GS involvement. However, there was no difference in WBC count, lymphocyte count, monocyte count or Hb, Plt, RDW, PDW, MPV, PLR, CRP and ESR values between the 2 groups (Table 2).

The blood cell parameters were similar between children with and without renal involvement (Table 3). Additionally, there were no differences in hematological parameters between children with IgA vasculitis with or without recurrence groups, except for the PDW value (Table 4).

Multivariate analysis for children with IgA vasculitis with GS involvement

Independent variables of multivariate analysis were selected as the statistically significant variables between children with IgA vasculitis, with and without GS involvement. The results showed that MLR was an independent risk factor for IgA vasculitis combined with GS ($p < 0.05$, Table 5).

Diagnosis value of MLR in the differential of IgA vasculitis combined with GS involvement

The ROC curve analysis showed that the area under the curve for MLR diagnosis of IgA vasculitis combined with GS was 0.694, with a sensitivity of 52.9% and a specificity of 77.8%, and the cutoff point was 0.245 (Fig. 1).

Discussion

The IgA vasculitis is an immune complex-mediated small vessel vasculitis with variable skin, gastrointestinal and renal involvement. In order to predict the risk of GS and kidney involvement in IgA vasculitis, several

Table 1. Comparison of clinical characteristics and blood cell-derived parameters between children with immunoglobulin A (IgA) vasculitis and healthy children

Variable	IgA vasculitis (n = 115)	Control (n = 95)	Test statistic	p-value
Age [years]	8.29 ±2.59	8.57 ±1.58	–0.90†	0.3674
Gender (M/F)	56/59	50/45	0.32‡	0.5702
WBC [10^9/L]	9.49 ±3.62	5.91 ±1.24	9.07†	<0.0001
N [10^9/L]	6.08 ±3.25	2.93 ±0.97	8.97†	<0.0001
M [10^9/L]	0.56 ±0.35	0.3 ±0.11	7.46†	<0.0001
L [10^9/L]	2.73 ±1.32	2.52 ±0.54	1.57†	0.1189
Hb [g/L]	126.28 ±11.26	128.60 ±7.21	–1.71†	0.0879
Plt [10^9/L]	328.06 ±95.94	264.66 ±55.89	5.94†	<0.0001
RDW	12.79 ±0.9	12.74 ±0.58	0.44†	0.6606
PDW	13.04 ±2.67	12.69 ±2.05	1.02†	0.3108
MPV	10.12 ±1.32	10.5 ±0.87	–2.37†	0.0186
NLR	2.83 ±2.41	1.21 ±0.47	7.05†	<0.0001
MLR	0.22 ±0.14	0.12 ±0.05	7.31†	<0.0001
PLR	147.09 ±84.18	110.47 ±34.49	4.34†	<0.0001

Data are presented as mean ± standard deviation (SD). P-values were calculated using χ^2 test for categorical variables and the independent t-test for continuous variables. † t-value; ‡ χ^2-value; WBC – white blood cell count; N – neutrophil count; M – monocyte count; L – lymphocyte count; Hb – hemoglobin; Plt – platelet count; RDW – red blood cell volume distribution width; PDW – platelet distribution width; MPV – mean platelet volumes; NLR – neutrophil-to-lymphocyte ratio; PLR – platelet-to-lymphocyte ratio; MLR – monocyte-to-lymphocyte ratio.

Table 2. Comparison of clinical characteristics and blood cell-derived parameters between immunoglobulin A (IgA) vasculitis children with gastrointestinal system (GS) involvement and without GS involvement

Variable	GS involvement (+) (n = 34)	GS involvement (–) (n = 81)	Test statistic	p-value
Age [years]	8.38 ±2.81	8.25 ±2.52	0.25†	0.7997
Gender (M/F)	15/19	41/40	0.41‡	0.5245
WBC [10^9/L]	10.37 ±4.55	9.12 ±3.1	1.70†	0.0914
N [10^9/L]	7.23 ±4.02	5.59 ±2.76	2.17†	0.0351
M [10^9/L]	0.66 ±0.47	0.51 ±0.28	1.77†	0.0837
L [10^9/L]	2.37 ±1.05	2.88 ±1.39	–1.94†	0.0554
Hb [g/L]	128.79 ±11.19	125.22 ±11.18	1.56†	0.1209
Plt [10^9/L]	318.38 ±103.35	332.12 ±93.02	–0.70†	0.4858
RDW	12.86 ±0.94	12.76 ±0.89	0.55†	0.5858
PDW	13.24 ±2.71	12.95 ±2.66	0.52†	0.6067
MPV	10.26 ±1.37	10.07 ±1.31	0.69†	0.4923
NLR	3.81 ±3.25	2.42 ±1.83	2.33†	0.0245
MLR	0.30 ±0.18	0.19 ±0.11	3.14†	0.0030
PLR	154.18 ±72.32	144.11 ±88.93	0.58†	0.5607
CRP	6.42 ±4.35	5.01 ±3.83	1.71†	0.0929
ESR	8.68 ±5.13	9.09 ±4.71	–0.42†	0.6791

Data are presented as mean ± standard deviation (SD). P-values were calculated using χ^2 test for categorical variables and the independent t-test for continuous variables. † t-value; ‡ χ^2-value; WBC – white blood cell count; N – neutrophil count; M – monocyte count; L – lymphocyte count; Hb – hemoglobin; Plt – platelet count; RDW – red blood cell volume distribution width; PDW – platelet distribution width; MPV – mean platelet volumes; NLR – neutrophil-to-lymphocyte ratio; PLR – platelet-to-lymphocyte ratio; MLR – monocyte-to-lymphocyte ratio; CRP – C-reactive protein; ESR – erythrocyte sedimentation rate.

Table 3. Comparison of clinical characteristics and blood cell-derived parameters between immunoglobulin A (IgA) vasculitis children with renal involvement and without renal involvement

Variable	Renal involvement (+) (n = 12)	Renal involvement (–) (n = 103)	Test statistic	p-value
Age [years]	9.42 ±2.88	8.16 ±2.54	1.60†	0.1114
Gender (M/F)	5/7	51/52	0.27‡	0.6067
WBC [10^9/L]	8.82 ±3.26	9.57 ±3.66	–0.68†	0.4980
N [10^9/L]	5.68 ±2.73	6.12 ±3.31	–0.44†	0.6602
M [10^9/L]	0.43 ±0.23	0.57 ±0.36	–1.38†	0.1691
L [10^9/L]	2.65 ±1.33	2.74 ±1.32	–0.22†	0.8241
Hb [g/L]	128.75 ±12.86	125.99 ±11.09	0.80†	0.4240
Plt [10^9/L]	323 ±87.14	328.65 ±97.28	–0.19†	0.8479
RDW	13.03 ±1.09	12.76 ±0.88	0.96†	0.3349
PDW	14.07 ±2.19	12.92 ±2.7	1.42†	0.1583
MPV	10.33 ±1.4	10.1 ±1.32	0.55†	0.5812
NLR	2.62 ±1.95	2.85 ±2.47	–0.31†	0.7550
MLR	0.2 ±0.14	0.23 ±0.14	–0.71†	0.4803
PLR	143.98 ±61.63	147.45 ±86.65	–0.13†	0.8929
CRP	4.63 ±3.86	5.51 ±4.09	–0.67†	0.4991
ESR	8.58 ±4.12	9.01 ±4.91	–0.29†	0.7732

Data are presented as mean ± standard deviation (SD). P-values were calculated using χ^2 test for categorical variables and the independent t-test for continuous variables. † t-value; ‡ χ^2-value; WBC – white blood cell count; N – neutrophil count; M – monocyte count; L – lymphocyte count; Hb – hemoglobin; Plt – platelet count; RDW – red blood cell volume distribution width; PDW – platelet distribution width; MPV – mean platelet volumes; NLR – neutrophil-to-lymphocyte ratio; PLR – platelet-to-lymphocyte ratio; MLR – monocyte-to-lymphocyte ratio; CRP – C-reactive protein; ESR – erythrocyte sedimentation rate.

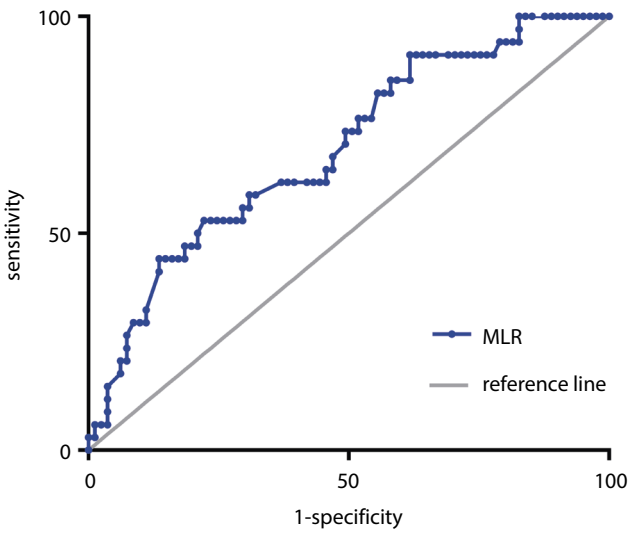

Fig. 1. Receiver operating characteristic curves of the monocyte-to-lymphocyte ratio (MLR) for children with immunoglobulin A (IgA) vasculitis with gastrointestinal system involvement

inexpensive and practical biomarkers were investigated. The current study demonstrated that children with IgA vasculitis with GS involvement showed higher neutrophil counts and MLR and NLR values. Moreover, elevated MLR was found to be a risk factor for GS involvement in children with IgA vasculitis, and ROC analysis indicated that MLR could be a predictive parameter of GS involvement in IgA vasculitis. To the best of our knowledge, this study is the first to comprehensively assess new blood cell-derived inflammatory biomarkers, especially MLR, in relation to GS involvement and disease course in IgA vasculitis in children.

In the current study, we found that the incidence of GS involvement in the current cohort is 29.56% (n = 34), and 10.43% (n = 12) for renal involvement. According to a cross-section study conducted in Turkey, clinical manifestations with gastrointestinal symptoms and renal involvement among children with IgA vasculitis appeared in, respectively, 56% and 29.8% of cases.[20] Similarly,

Table 4. Comparison of clinical characteristics and blood cell-derived parameters between immunoglobulin A (IgA) vasculitis children with recurrence and without recurrence

Variable	Recurrence (+) (n = 22)	Recurrence (–) (n = 93)	Test statistic	p-value
Age [years]	8.05 ±2.64	8.34 ±2.59	–0.48†	0.6295
Gender (M/F)	12/10	47/46	0.11‡	0.7352
WBC [10^9/L]	8.77 ±3.09	9.66 ±3.72	–1.04†	0.2995
N [10^9/L]	5.47 ±2.32	6.22 ±3.43	–0.97†	0.3351
M [10^9/L]	0.56 ±0.43	0.56 ±0.33	0.04†	0.9685
L [10^9/L]	2.6 ±1.12	2.76 ±1.36	–0.53†	0.5976
Hb [g/L]	126.55 ±15.35	126.22 ±10.16	0.12†	0.9021
Plt [10^9/L]	316.55 ±106.3	330.78 ±93.73	–0.62†	0.5336
RDW	12.7 ±0.71	12.81 ±0.94	–0.48†	0.6314
PDW	14.25 ±2.63	12.75 ±2.61	2.42†	0.0170
MPV	10.1 ±1.53	10.13 ±1.28	–0.08†	0.9382
NLR	2.54 ±1.72	2.9 ±2.55	–0.63†	0.5309
MLR	0.22 ±0.10	0.23 ±0.15	–0.29†	0.7749
PLR	141.38 ±69.41	148.44 ±87.58	–0.35†	0.7250
CRP	4.48 ±3.57	5.64 ±4.15	–1.18†	0.2397
ESR	9.55 ±5.53	8.83 ±4.66	0.63†	0.5324

Data are presented as mean ± standard deviation (SD). P-values were calculated using χ^2 test for categorical variables and the independent t-test for continuous variables. † t-value; ‡ χ^2-value; WBC – white blood cell count; N – neutrophil count; M – monocyte count; L – lymphocyte count; Hb – hemoglobin; Plt – platelet count; RDW – red blood cell volume distribution width; PDW – platelet distribution width; MPV – mean platelet volumes; NLR – neutrophil-to-lymphocyte ratio; PLR – platelet-to-lymphocyte ratio; MLR – monocyte-to-lymphocyte ratio; CRP – C-reactive protein; ESR – erythrocyte sedimentation rate.

Table 5. Multivariate analysis for immunoglobulin A (IgA) vasculitis children combined with gastrointestinal system involvement

Parameter	Coefficient	SE	Wald χ^2 value	df	p-value	OR	95% CI	
							lower	upper
N	0.03	0.09	0.11	1.00	0.73	1.03	0.86	1.23
MLR	4.49	1.96	5.22	1.00	0.02	89.06	1.89	4190.12
NLR	0.09	0.13	0.48	1.00	0.49	1.09	0.85	1.40

N – neutrophil count; NLR – neutrophil-to-lymphocyte ratio; MLR – monocyte-to-lymphocyte ratio; SE – standard error; OR – odds ratio; 95% CI – 95% confidence interval; df – degrees of freedom.

gastrointestinal symptoms and renal kidney involvement among the children with IgA vasculitis in Poland were found in, respectively, 64.8% and 22.5% of cases.[25] In addition, GS involvement was found to be 46.1% in Korea.[12] However, according to a retrospective analysis conducted in China, the incidence of GS symptoms and kidney involvement was 28.78% and 13.33%, respectively, among children with IgA vasculitis, which is similar to our study and much lower than in other studies. We postulate the divergence of GS and kidney involvement may relate to racial and regional differences.

Blood cell count-derived inflammatory parameters, including NLR and PLR, are now recognized as novel biomarkers of chronic subclinical inflammation in diabetes mellitus,[21] coronary artery disease[8] and cancers.[22] In this study, we demonstrated that the NLR but not PLR value was significantly increased in children with IgA vasculitis with GS involvement compared to those without GS involvement, which is consistent with the study by Karadağ et al.[19] Furthermore, it was reported that elevated NLR and PLR may be relevant markers for predicting GS bleeding[23] and renal organ involvement[24,25] in children with IgA vasculitis. However, there was no relationship between NLR and PLR values and renal or GS involvement in the current study. This inconsistency may be due to different degrees of GS and kidney complication among the included participants, which suggests the predictive value of NLR and PLR in children with IgA vasculitis may depend on the severity of the disease, and further extensive multicenter studies are needed to clarify this issue.

The MLR has been demonstrated as a novel hematological parameter in several medical fields. Recently, Suszek et al. demonstrated that MLR is an effective marker of systemic lupus erythematosus activity,[26] and its value could also be used to identify disease activity of Takayasu arteritis[27] and rheumatoid arthritis.[28] Similarly, in the current study, MLR values were higher in children with IgA vasculitis with GS involvement than in those without GS involvement. Interestingly, MLR is the sole risk factor that predicted GS involvement in children with IgA vasculitis children. To our knowledge, this is the first study to reveal the predictive value of MLR in children with IgA vasculitis.

The elevated MLR level may result from increased monocyte counts or decreased lymphocyte counts. Monocytes are an essential source of pro-inflammatory mediators during various kinds of vasculitis.[29–31] It was reported that monocytes were the predominant cell type infiltrating glomeruli in IgA nephritis,[31] which indicates the monocyte count may reflect the development of IgA vasculitis. On the other hand, lymphocytes have been shown to play a broader role in modulating the inflammatory response at each phase of the vasculitis, and low lymphocyte count has been associated with IgA vasculitis progression in rat and rabbit models.[32] Local activation of the immune system or inflammation can increase lymphocyte apoptosis,[33] resulting in lower lymphocyte counts. Therefore, higher monocyte counts and/or lower lymphocyte counts may reflect an active role due to their immunomodulatory, pro-inflammatory effects on vasculitis. Thus, the MLR integrated with monocytes and lymphocytes provided a more reliable index to evaluate IgA vasculitis inflammation than either variable alone.

Limitations

This study has some limitations. Firstly, the sample size of this study is not large, and it is a single-center study. Secondly, the predictive value of MLR is probably more reliable than the commonly used laboratory inflammatory indicators CRP and ESR in evaluating GS involvement of IgA vasculitis in the current study; however, the predictive value of blood cell-derived inflammatory parameters cannot be compared with other inflammatory markers, including interleukin (IL)-6 and tumor necrosis factor alpha (TNF-α),[34–36] due to the retrospective design and lack of related data. Another limitation was the lack of dynamic changes in hematological parameters at IgA vasculitis diagnosis and after long-term follow-up, which could provide more information about the relationships between these hematological parameter values and disease course.

Conclusions

This study showed that neutrophil count and NLR and MLR levels were found to be significantly higher in the children with IgA vasculitis with GS involvement, and elevated MLR was an independent risk factor in predicting GS involvement in children with IgA vasculitis. Therefore, monitoring blood MLR values could provide an early indicator to clinicians regarding GS involvement and disease severity in children with IgA vasculitis.

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