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Anti-Nötrofil Sitoplazmik Antikor İlişkili Vaskülitlerde Hematolojik Parametrelerin Prognostik Değeri

Prognostic Value of Hematological Parameters in Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis

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Öz

Giriş ve Amaç: Nötrofil-Lenfosit oranı (NLO), Platelet-Lenfosit oranı (PLO) ve Monosit-Lenfosit oranı (MLO) dahil olmak üzere hematolojik parametreler, çeşitli hastalıklarda prognoz ve aktivitenin yeni belirleyicileri olarak gösterilmiştir. Bu çalışmada, anti-nötrofil sitoplazmik antikor (ANCA) ilişkili vaskülit (AİV) tanısı olan hastalarda NLO, PLO ve MLO' nun hastalık şiddeti ve prognozu ile ilişkisini araştırmayı amaçladık.

Gereç ve Yöntemler: 92 AİV hastasının tıbbi kayıtları geriye dönük olarak incelendi. Klinik ve laboratuvar verileri ve hastalık sonuçları kaydedildi. Beş faktör skoru (FFS) ≥ 2 olan hastalar ağır hastalık olarak sınıflandırıldı.

Bulgular: Ortanca yaşı 60 olan 92 hasta dahil edildi. NLO≥4.8 (RR 1.83), PLO≥151.8 (RR 2.02) ve MLO≥0.38 (RR 1.85) olan hastalarda ciddi hastalık riski daha yüksekti. Korelasyon analizinde, NLO, PLO ve MLO, C reaktif protein düzeyi ve eritrosit sedimantasyon hızı (ESH) ile pozitif korelasyon gösterdi. NLO, PLO ve MLO remisyon ile ilişkilendirildi. Sadece PLO'su yüksek olan hastalarda nüks oranı daha yüksekti. MLO ayrıca son dönem böbrek hastalığının (SDBY) gelişimi ile de korele idi. NLO, PLO ve MLO düzeyleri yüksek olan hastalarda böbrek tutulumu daha sıktı.

Sonuç: Tanı anında NLO, PLO ve MLO'nun AİV şiddeti ve prognozu ile ilişkili olduğunu gösterdik. Bu çalışma AİV'li hastalarda MLO'nun hastalık şiddeti ve SDBY ile ilişkisini gösteren ilk çalışmadır.

Anahtar Kelimeler: Antinötrofil sitoplazmik antikor ilişkili vaskülit, Monosit/lenfosit oranı, Nötrofil/lenfosit oranı, Trombosit/lenfosit oranı.

Abstract

Objective: Hematological parameters including neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR), and monocyte–lymphocyte ratio (MLR) have been demonstrated as new predictors of prognosis and activity in various diseases. In this study, we aimed to investigate the associations of NLR, PLR and MLR with disease severity and prognosis in patients with anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV).

Materials and Methods: Medical records of 92 AAV patients were investigated retrospectively. The clinical and laboratory data, and disease outcomes were recorded. The patients having five factor score (FFS) ≥ 2 were categorized as severe disease.

Results: 92 patients with a median age of 60 years were included. Patients with NLR≥4.8 (RR 1.83), PLR≥151.8 (RR 2.02) and MLR≥0.38 (RR 1.85) had higher risk of severe disease. In correlation analysis, NLR, PLR and MLR were positively correlated with C reactive protein and erythrocyte sedimentation rate (ESR). NLR, PLR and MLR were associated with remission.

Conclusion: Only the patients with high PLR had higher relapse rate. MLR was also correlated with development of end-stage renal disease (ESRD). Renal involvement was more frequent in patients with high levels of NLR, PLR and MLR.
Conclusions: We showed that NLR, PLR and MLR at diagnosis were associated with the severity and prognosis of AAV. This is the first study, showing the correlation of MLR with disease severity and ESRD in patients with AAV.

Keywords: Antineutrophil cytoplasmic antibody-associated vasculitis, Monocyte / lymphocyte ratio
Neutrophil / lymphocyte ratio, Platelet / lymphocyte ratio.

1. Introduction

Anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) are life-threatening diseases characterized by necrotizing vasculitis of small and medium-sized vessels. According to clinical manifestations and pathological features, AAV is classified as granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), eosinophilic GPA (EGPA), and renal limited vasculitis (RLV) [1]. They are associated with increased morbidity and mortality because of the involvement of vital organs which result in renal failure, alveolar and gastrointestinal hemorrhage and myocarditis.

AAV have a particular predilection for kidneys; rapidly progressive glomerulonephritis (RPGN) is frequently observed, and end-stage renal disease (ESRD) develop approximately in 25% of these patients [2]. The long-term survival of patients with AAV has improved over the past decades; a 5-year survival rate in many cases was reported as high as 80% [3]. The disease has transformed into a chronic pattern including remission and relapse periods with novel management regimens. One of the major challenges in the treatment is absence of reliable biomarkers for activity and prognosis. Due to the limited value of conventional inflammation markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), it is essential to establish new prognostic markers predicting renal and patient survival at diagnosis and early stages of AAV.

In recent years, several hematological parameters obtained from complete blood count (CBC) including neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR), and monocyte–lymphocyte ratio (MLR) have been demonstrated as new predictors of prognosis in inflammatory, neoplastic, and cardiovascular diseases. Higher levels of NLR and PLR were found to be associated with poor prognosis in coronary artery diseases and some gynecological and hepatobiliary malignancies [4-7]. It has been reported that NLR level is correlated with mortality in acute coronary syndrome [4]. A recent study [8] showed that PLR was more sensitive indicator of inflammation than NLR in hemodialysis patients. MLR has also proven to be a new prognostic factor in patients with coronary artery disease, malignancy and tuberculosis [9-11].

Although there have been few studies [12-15] showing the relation of NLR and PLR with disease activation and prognosis in vasculitis, MLR has not been researched before in AAV. Therefore, we designed a retrospective study to investigate the utility of NLR, PLR, and MLR to assess the disease severity and prognosis in patients with AAV.

2. Materials and methods

This study is a retrospective study approved by the Ethics Committee (date/number: 01.07.2020/20.478.486/429). We included 92 immunosuppressive drug-naïve patients with AAV, followed up in the Departments of Nephrology and Rheumatology in a single tertiary care center between 2004 and 2019. All patients met the classification criteria adopted at the 2012 Chapel Hill Consensus Conference for the diagnosis of GPA, MPA, EGPA, or RLV [1]. RLV was defined as biopsy-proven idiopathic pauci-immune glomerulonephritis without other symptoms of systemic disease. The patients with vasculitis secondary to other diseases such as Henoch-Schönlein purpura, systemic lupus erythematosus, cryoglobulinemia, malignancy and infection were excluded from the study.

Medical records of the patients were examined, and demographic, clinical, laboratory and biopsy findings, treatment and follow-up datas were obtained. We recorded laboratory parameters at admission including ESR, CRP, CBC, renal and liver function tests, and urine analysis. Anti-neutrophil cytoplasmic and perinuclear antibodies (c-ANCA and p-ANCA) were analyzed by immunofluorescence method.

Vasculitis specific findings at presentation including purpura and other skin findings, pulmonary involvement, arthritis, and gastrointestinal, cardiovascular, and neurological manifestations were recorded. Renal involvement was defined as biopsy proven pauci-immune glomerulonephritis, active urinary sediment, and/or increase in serum creatinine. We used 24-hour proteinuria in the analysis. Hematuria is defined as the count of urinary erythrocytes at high power field (Urinary erythrocytes /high power field in microscopy). The estimated glomerular filtration rate (eGFR) was calculated by the short Modification of Diet in Renal Disease Study equation (MDRD) formula [16].

Vasculitis activation and severity was evaluated with the five-factor score (FFS) system determined and suggested by the French Vasculitis Study Group [17]. FFS consists of five items: (1) age > 65, (2) Cardiac failure, (3) Gastrointestinal involvement, (4) Renal failure (plasma creatinine concentration > 1.7 mg/dL [150 micromole/L]), (5) Absence of ear, nose and throat (ENT) involvement (its presence is associated with a better prognosis). One point is given for the presence of each factor. The FFS score ranges from 0 to 2. In the absence of any of these items, a score of zero is given, 1 point for an item and 2 points for two or more items. This scoring system has been shown to

be associated with prognosis and severity of vasculitis [17]. We defined the group of severe AAV as having FFS ≥ 2.

End-stage renal disease was defined as eGFR<15 ml/min per 1.73 m2 or requirement of RRT for >3 months. Relapse was defined as the reactivation of vasculitis in any system. Remission was the absence of vasculitic lesions or symptoms in any organ, with or without treatment.

2.1. Statistics

Statistical analysis were performed using SPSS version 21.0 (21st edition; IBM Corp., Armonk, NY, USA). Continuous variables were expressed as median (interquartile range, IQR), categorical variables as numbers and percentages. The significance of the difference between the two groups was analysed using the chi-square test and Fisher's Exact Test in terms of categorical variables and the Mann-Whitney U test in continuous variables. Spearman correlation analysis was done to find the relationship between NLR, PLR and MLR and other clinical and laboratory variables. In comparative analysis, the odds ratio (OR) of variables with p<0.05 was evaluated using univariate and multivariate binary logistic regression analysis. ROC (Receiver Operator Characteristics Curve) analysis was performed to determine the optimal cut-off values of NLR, PLR, and MLR. Relative risk (RR) was analysed using contingency tables and chi-square test. P<0.05 was considered statistically significant.

3. Results and Discussion

3.1. Demographic and diagnostic characteristics of the patients

92 patients with a median age of 60 years were included in the study. The median duration of the disease was 68 months. According to the clinical classification, we identified 23 patients (25%) with MPA, 46 (50%) with GPA, 19 (21%) with RLV, and 4 (4%) with EGPA. Twenty-seven patients with GPA and all patients in MPA and RLV group had renal involvement. 43 patients with AAV patients had lung involvement. The rates of neurological, joint, ENT, and skin manifestations were noted as 10%, 31%, 45%, and 25%, respectively. ANCA-positivity was detected in 74 patients (80%). Median CRP and ESR were 31 mg/L and 57 mm/h, respectively. The median values of NLR (4.74), PLR (182.46), and MLR (0.40) were calculated. The demographic characteristics and laboratory data at diagnosis were shown in Table 1.

3.2. Comparison of variables between patients with and without severe AAV

The disease severity and prognosis were evaluated with FFS. The patients were divided into two groups according to the FFS values at diagnosis; FFS < 2 was found in 36 patients and FFS ≥ 2 in 56 patients. There was no difference between the two groups in terms of gender and ANCA positivity. The patients with FFS ≥ 2 were older. Among laboratory findings, median creatinine and ESR were substantially higher in patients with FFS ≥ 2. A significant decrease was detected in lymphocyte count (1,97 x10³/μL vs 1.40 x10³/μL, p=0.001) in patients with FFS ≥ 2.We found higher levels of NLR, PLR and MLR in patients with FFS ≥ 2. Levels of hematuria, and proteinuria were significantly higher in patients with severe AAV. The comparison of the variables between the patients with and without severe AAV is given in Table 2.

Table 1. Baseline characteristics of patients with AAV (n=92)

Variables	Values
Demographic data	
Age (year)	60.00 (19.75)
Male gender (n,%)	48 (63.2)
Disease duration (month)	39.00 (74.00)
SBP (mmHg)	130.00 (30.00)
DBP (mmHg)	80.00 (20.00)
Clinical classification (n, %)	
MPA	23 (25.0)
GPA	46 (50.0)
RLV	19 (21.1)
EGPA	4 (3.9)
FFS (n, %)	
FFS<2	36 (39.0)
FFS≥2	56 (61.0)
Laboratory parameters at diagnosis	
Hemoglobin (g/dL)	10.05 (3.65)
White blood cell (x10³/μL)	9.82 (5.62)
Neutrophil (x10³/μL)	6.68 (5.32)
Lymphocyte (x10³/μL)	1.60 (0.98)
Monosit (x10³/μL)	0.61 (0.38)
Platelet (x10³/μL)	268.00 (133.75)
MPV (fl)	8.70 (1.28)
NLR	4.74 (5.79)
PLR	182.46 (140.97)
MLR	0.40 (0.41)
Creatinine (mg/dL)	3.17 (4.37)
Serum albumin (g/dL)	3.20 (1.20)
eGFR (ml/min/1.73 m^2)	23.30 (70.20)
CRP (mg/L)	31.00 (76.00)
ESR (mm/h)	57.00 (49.00)

Values are expressed as a median (interquartile range, IQR) and number (n) (%)

AAV: ANCA-Associated Vasculitis, ANCA: Antineutrophil Cytoplasmic Antibody, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, MPA: Microscopic Polyangiitis, GPA: Granulomatosis with Polyangiitis, EGPA: Eosinophilic Granulomatosis with Polyangiitis, FFS: Five Factor Score, MPV: Mean Platelet Volume, NLR: Neutrophil/Lymphocyte Ratio, PLR: Platelet /Lymphocyte Ratio, MLR: Monocyte/Lymphocyte Ratio, e-GFR: Estimated Glomerular Filtration Rate, CRP: C-Reactive Protein, ESR: Erythrocyte Sedimentation Rate

Table 2. Comparison of variables between patients with and without severe AAV

Variables	FFS<2 (n:36)	FFS≥2 (n:56)	p
Demographic data			
Age at diagnosis (years)	53 (18.75)	65 (14.25)	<0.001
Male gender (n,%)	19(39.58)	29 (60.42)	0.980
ANCA positivity (n,%)	23 (37.70)	38 (62.30)	0.959
Acute reactants at diagnosis			
ESR (mm/h)	35 (42)	67 (48)	<0.001
CRP (mg/L)	20.50 (75.53)	33 (77.00)	0.283
Laboratory results at diagnosis			
WBC (x10³/µL)	9.65 (6.39)	9.95 (5.33)	0.899
Hemoglobin (g/dL)	12.25 (4.25)	9.50 (2.33)	0.001
Platelet (x10³/µL)	252.00 (203.25)	282.50 (133.75)	0.778
Neutrophil (x10³/µL)	6.32 (4.25)	7.35 (5.37)	0.364
Lymphocyte (x10³/µL)	1.97 (1.23)	1.40 (6.77)	0.001
Monocyte (x10³/µL)	0.60 (0.30)	0.69 (0.52)	0.826
NLR	3.57 (3.23)	5.65 (5.64)	0.011
PLR	136.35 (174.64)	194.33 (115.99)	0.043
MLR	0.34 (0.26)	0.49 (0.41)	0.017
Creatinine (mg/dl)	0.79 (0.86)	3.85 (2.85)	<0.001
Serum albumin (g/dL)	3.80 (1.37)	3.00 (0.84)	0.001
AST (U/L)	22.0 (8.0)	19.5 (17.0)	0.260
ALT (U/L)	20.50 (16.50)	17.50 (16.25)	0.118
eGFR (ml/min/1.73 m^2)	95.59 (42.24)	15.30 (14.05)	<0.001
Hematuria (mg)	0.00 (51.00)	76.00 (205.75)	<0.001
Proteinuria (g/L)	0.00 (1400.00)	2450.00 (3382.50)	<0.001

Values are expressed as a median (interquartile range, IQR) and number (n) (%)
AAV: ANCA-Associated Vasculitis, ANCA: Antineutrophil Cytoplasmic Antibody, FFS: Five Factor Score, ESR: Erythrocyte Sedimentation Rate, CRP: C-Reactive Protein, WBC: White Blood Cell, NLR: Neutrophil/Lymphocyte Ratio, PLR: Platelet/Lymphocyte Ratio, MLR: Monocyte/Lymphocyte Ratio, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, eGFR: Estimated Glomerular Filtration Rate

3.3. Association of NLR, PLR and MLR with clinical and laboratory findings

In correlation analysis, NLR, PLR and MLR were positively correlated with CRP (r=0.378, p=0.002; r=0.531, p<0.001; r=0.402, p=0.001, respectively) and ESR (r=0.403, p=0.001; r=0.386, p=0.001; r=0.397, p=0.001, respectively). NLR, PLR and MLR were inversely correlated with serum albumin (r=-0.413, p<0.001; r=-0.312, p=0.006; r=-0.387, p<0.001, respectively). NLR and MLR were negatively related with eGFR (r=-0.359, p=0.001; r=-0.387, p=0.002, respectively). All correlation analysis summarized in Table 3.

The optimal cut-off of NLR, PLR and MLR for severe AAV (FFS ≥ 2) was extrapolated by calculating the area under the receiver operator characteristic curve (AUROC) and selecting the maximised sum of sensitivity and specificity. The cut off values of NLR, PLR, MLR for severe disease were found to be 4.8 (sensitivity 61%, specificity 70%), 151.8 (sensitivity 74%, specificity 64%) and 0.38 (sensitivity 68%, specificity 67%), respectively (Figure 1).

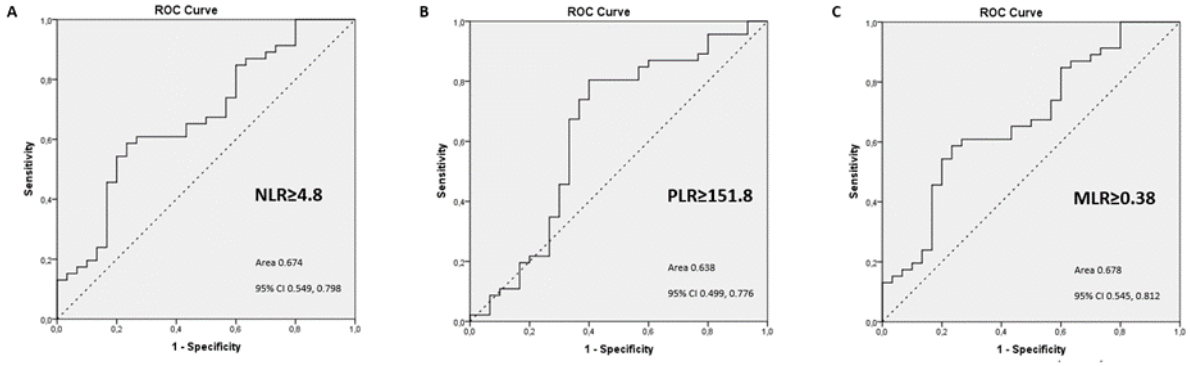
We assessed the associations between the high levels of NLR (NLR ≥ 4.8), PLR (PLR ≥ 151.8) and MLR (MLR ≥ 0.38) and clinical findings with the chi-square test. The Patients with renal involvement (57% vs. 28%, p = 0.031), neurological involvement (86% vs. 46%, p = 0.047), and dialysis requirement at diagnosis (71% vs. 35%, p = 0.002) exhibited the larger proportion of high NLR than without.

The patients with high PLR had greater proportion of renal involvement (67% vs. 33%, p = 0.011), dialysis requirement at diagnosis (84% vs 42%, p < 0.001), pulmonary involvement (70% vs. 47%, p = 0.04), and neurological involvement (100% vs. 55%, p = 0.021). MLR was higher in patients with renal involvement (64% vs. 33%, p = 0.030) and required dialysis at diagnosis (88% vs 32%, p0.001). Whereas the patients with skin manifestations exhibited the less proportion of high MLR that those without (22% vs. 60%, P = 0.033).

Table 3. Correlation of NLR, PLR, and MLR with demographic and laboratory findings in AAV

	NLR		PLR		MLR	
	r	**p**	**r**	**p**	**r**	**p**
Age (year)	0.319	0.005	0.106	0.364	0.113	0.182
CRP (mg/L)	0.378	0.002	0.531	<0.001	0.402	0.001
ESR (mm/h)	0.403	0.001	0.386	0.001	0.397	0.001
Albumin (mg/dL)	-0.413	<0.001	-0.312	0.006	-0.442	<0.001
eGFR (ml/min/1.73 m2)	-0.359	0.001	-0.215	0.062	-0.387	0.002
Proteinuria (g/24 h)	0.032	0.788	0.073	0.540	0.077	0.559
Hematuria (HPF)	0.178	0.132	0.107	0.368	0.257	0.042

NLR: Neutrophil/Lymphocyte Ratio, PLR: Platelet /Lymphocyte Ratio, MLR: Monocyte/Lymphocyte Ratio, CRP: C-Reactive Protein, ESR: erythrocyte sedimentation rate, e-GFR: Estimated Glomerular Filtration Rate, HPF: high power field



ESR was increased in patients with high NLR (p = 0.002), PLR (p < 0.001), and MLR (p = 0.003). The group with FFS ≥2 at diagnosis exhibited the higher levels of NLR, PLR and MLR than those without as mentioned above.

3.4. Relative risk of severe AAV based on FFS

When we analysed relative risk, the patients having NLR ≥ 4.8 (RR 1.83, 95% Cl 1.05-3.18, p = 0.019), PLR ≥ 151.8 (RR 2.02, 95% Cl 1.22-3.32, p = 0.001), and MLR ≥ 0.38 (RR 1.85, 95% Cl 1.07- 3.17, p = 0.013) had a significantly higher risk of severe AAV than those not having (Figure 2).

3.5. Association of NLR, PLR and MLR with renal and patient outcomes

12 patients died during the study period. We found no association between mortality and NLR, MLR, and PLR. Twenty-four patients with renal involvement reached ESRD during follow up. ESRD was associated with only higher MLR (73% vs 45%, p = 0.036).

Out of 92 patients, 60 (65%) achieved disease remission with induction therapy. Relapse occurred at 30 patients (33%) in our patients. In the groups with high levels of NLR, PLR and MLR, the remission rates were found to be decreased than those without (40% vs. 63%, p=0.048; 49% vs. 73%, p=0.035; 42% vs. 74%, p = 0.016, respectively). Only high PLR was associated with relapse rate (81% vs. 51%, p = 0.017).

3.6. Univariable and multivariable binary logistic regression analysis

Since age, creatinine, ESR, NLR, PLR, and MLR exhibited significant differences between patients with and without severe AAV, these categorical variables based on the cut-off of each one were included in the univariable binary logistic regression analysis. Creatinine ≥ 2.1 mg/dl (OR 41.000), ESR ≥ 52 mm/h (OR 6.300), age ≥ 58 years (OR 5.333), NLR ≥ 4.8 (OR 3.111), PLR ≥ 151.8 (OR 4.894), and MLR ≥ 0.38 (OR 3.709) were associated with severe AAV. When we performed the multivariable binary logistic regression analysis, only age at the time of diagnosis, creatinine, and ESR were the independent predictors of severe AAV at diagnosis (Table 4).

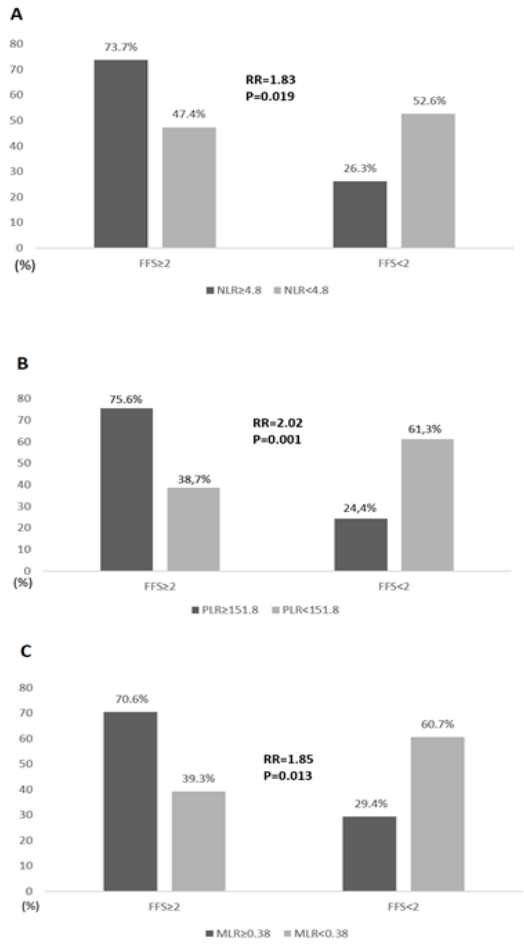


Figure 2. A The patients having NLR ≥ 4.8 had a significantly higher risk of severe AAV than those not having (RR 1.83, 95% Cl 1.05-3.18, p = 0.019). B The patients having PLR ≥ 151.8 had a significantly higher risk of severe AAV than those not having (RR 2.02, 95% Cl 1.22-3.32, p = 0.001). C The patients having MLR ≥0.38 had a significantly higher risk of severe AAV than those not having (RR 1.85, 95% Cl 1.07-3.17, p = 0.013). NLR neutrophil–lymphocyte ratio, PLR platelet–lymphocyte ratio, MLR monocyte–lymphocyte ratio, RR relative risk, CI confidence interval.

3.7. Discussion

In this study, we evaluated the association of NLR, PLR, and MLR with the disease activity, and prognosis of AAV at diagnosis in 92 immunosuppressive drug-naive patients in a single center. In present study, NLR ≥ 4.8 (RR 1.83), PLR ≥ 151.8 (RR 2.02), and MLR ≥ 0.38 (RR 1.85) could predict the disease severity. In terms of disease outcomes in AAV, there was a significant relationship between NLR, PLR, and MLR at diagnosis and remission, but not with mortality. Only the patients with high PLR had higher relapse rate. All these hematological parameters were associated with renal involvement and dialysis requirement at diagnosis but solely MLR was correlated with development of ESRD.

In recent years, NLR, PLR, and MLR have been reported as potential new markers of systemic inflammation. The neutrophils, lymphocytes, monocytes, and platelets play an active role in inflammation. The neutrophil count generally increases in proportion to the severity of the inflammatory event. Active neutrophils are closely related to AAV pathogenesis and play a critical role as both target and effector cells.

Table 4. Univariable and multivariable binary logistic regression analyses for severe AAV.

Covariates	**Univariable analysis**			**Multivariable analysis**		
	OR	**95% confidence interval**	**p**	**OR**	**95% confidence interval**	**p**
Creatinine ≥ 2.1 (mg/dl)	41.000	10.783, 155.900	<0.001	128.267	8.907, 18047.128	<0.001
ESR ≥ 52 (mm/h)	6.300	2.170, 18.292	0.001	9.987	1.367, 72.976	0.023
Age ≥ 58 (years)	5.333	1.958, 14.528	0.001	9.122	1.309, 63.576	0.026
NLR ≥ 4.8	3.111	1.188, 8.147	0.021	0.687	0.051, 9.240	0.777
PLR ≥ 151.8	4.894	1.814, 13.200	0.002	1.982	0.189, 20.796	0.569
MLR ≥ 0.38	3.709	1.288, 10.685	0.015	0.205	0.012, 3.578	0.277

In contrast to neutrophils, the lymphocyte count decreases in most of autoimmune inflammatory diseases. The number of CD4 + T cells were found to be low in GPA [18]. Platelets also play a significant role in inflammation, thrombosis, and cardiovascular pathophysiology. In general, number of platelets increases in the active phase of AAV. Platelets and some soluble molecules lead to vascular damage by mediating the inflammatory response [19]. Monocyte, another critical cell in inflammation, is one of the cell types that express ANCA antigens and mediate most of the systemic inflammatory effects in AAV [20]. Therefore, it was thought that in patients with systemic vasculitis, NLR, PLR and MLR could reflect the inflammatory burden and the ratio of 2 cells was more reliable than a single hematological parameter.

In previous studies, the correlation of NLR and PLR with disease activity and prognosis was shown in systemic rheumatological diseases such as Takayasu's arteritis [21], Behcet's disease [22], Kawasaki disease [23], Henoch Schönlein purpura [24], and systemic lupus erythematosus [25]. Kılıç E et al. [26] reported that NLR and PLR could be useful parameters in clinical practice to assess the disease activity in patients with rheumatoid arthritis. There are only a few studies demonstrating the clinical role of these ratios in patients with AAV [14, 15]. NLR was found to be significantly higher in patients with GPA than control group [12, 14]. Ahn et al. [13] showed that the patients having NLR ≥ 5.9 exhibited severe AAV and higher relapse rates than the patients having NLR < 5.9 at diagnosis. NLR and PLR were related with histopathological findings and mortality in a study of 54 patients with RPGN most of whom were diagnosed as AAV [27]. Similarly, Huang et al.[28] showed that high NLR could predict increased mortality in 188 patients with AAV . In our study, NLR was increased in patients with renal involvement and dialysis requirement at diagnosis. Therefore, patients with AAV, who have high NLR at admission, should be closely monitored for renal functions and renal outcomes.

The association between the platelet parameters and disease activity has been reported in autoimmune diseases such as AAV, inflammatory bowel disease, ankylosing spondylitis (AS), Behcet's disease, and RA [29]. During acute inflammation, the number and volume of platelets increase and they trigger the alternative complement pathway in patients with AAV. In recent years PLR was defined as a marker of inflammation to determine severity and prognosis of AAV. Park et al. [15], reported that the AAV patients with PLR ≥ 272 had higher risk of severe disease. In this study, the disease was more severe in patients with PLR ≥ 151.8, and renal, pulmonary, and neurological involvements were increased in these patients. In a recent study, it was revealed that increased PLR at diagnosis was associated with renal involvement but not with other organ involvement in patients with GPA [30]. Although no significant association between PLR and relapse was reported previously, we found that the patients with high PLR at admission had higher relapse rates at follow-up. Thus, it can be speculated that the patients with high PLR at diagnosis should be followed up more frequently and attentively due to the relapse risk.

Recently, few studies have demonstrated that MLR may also predict the activity and prognosis in rheumatological diseases. For example, MLR was reported to increase in AS and associated with CRP and ESR [31]. In patients with gout, increased MLR was observed in correlation with the degree of inflammation during the attacks [32]. Our study revealed that renal involvement, dialysis requirement at admission and ESRD at follow up were more common in patients with high MLR than in those without. This is the first study in the literature showing the relation of MLR with disease severity and ESRD in AAV patients.

Higher NLR, PLR and MLR were associated with decreased remission rate in our patients that wasn't mentioned in previous studies. This suggests that these parameters at diagnosis can be useful in planning the treatment regimen. We speculate that a higher NLR, PLR and MLR may indicate active vasculitis, and may support the possibility of a good response to immunosuppressive therapy.

In clinical practice, ESR and CRP are the most commonly used inflammatory parameters to assess the current activity of AAV. However, they have limited ability to distinguish inflammatory and infectious events and to predict renal and patient outcomes. The quantitative and qualitative changes of CBC parameters in rheumatologic disorders are not only related with the disease activity but also with clinical findings and prognosis. We also found that NLR, PLR, and MLR were associated with higher ESR and CRP. ESR was also one of the independent predictors of severe AAV at diagnosis in our population.

The retrospective design is the main limitation of our study. The absence of a standarised follow-up protocol may have complicated the interpretation of data. The number of patients and a long follow-up of time are the strengths of our study.

4. Conclusion

In conclusion, CBC is a cost-effective and simple laboratory test and may assess the degree of inflammation. New parameters such as NLR, PLR, and MLR may indicate systemic inflammation. Although there are studies in the literature showing the association of NLR and PLR with disease activity, and prognosis in patients with AAV, our study also showed this relation with MLR. Moreover, MLR was the only parameter related to ESRD in our patients. The association of NLR, PLR, and MLR with renal prognosis, remission, and relapse suggests that they may be used to decide the follow-up and treatment strategies in AAV. As a result, our study suggests that NLR, PLR, and MLR at diagnosis can be used to predict the severity and prognosis of AAV.

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