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Platelet/lymphocyte ratio and mean platelet volume in patients with granulomatosis with polyangiitis

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Abstract

Background: Granulomatosis with polyangiitis (GPA) is a granulomatous necrotizing vasculitis with high morbidity and mortality. Anti-neutrophil cytoplasmic antibody is a valuable diagnostic marker, however its titer lacks predictive value for the severity of organ involvement. Platelet to lymphocyte ratio (PLR) and mean platelet volume (MPV) has been regarded as a potential marker in assessing systemic inflammation. We aimed to explore the value of PLR and MPV in the assessment of disease activity and manifestations of disease in GPA.

Methods: 56 newly diagnosed GPA patients and 53 age-sex matched healthy controls were included in this retrospective and cross-sectional study with comparative group. Complete blood count was performed with Backman Coulter automatic analyzer, erythrocyte sedimentation rate (ESR) with Westergen method and C-reactive protein (CRP) levels with nephelometry. The PLR was calculated as the ratio of platelet and lymphocyte counts.

Result: Compared to control group, ESR, CRP and PLR were significantly higher and MPV significantly lower in GPA patients. In patients group, PLR was positively correlated with ESR and CRP ($r = 0.39$, $p = 0.005$ and $r = 0.51$, $p < 0.001$, respectively). MPV was negatively correlated with ESR and CRP ($r = -0.31$, $p = 0.028$ and $r = -0.34$ $p = 0.014$, respectively). Patients with renal involvement had significantly higher PLR than patients without renal involvement (median:265.98, IQR:208.79 vs median:180.34 IQR:129.37, $p = 0.02$). PLR was negatively correlated with glomerular filtration rate ($r = -0.27$, $p = 0.009$). A cut-off level of 204 for PLR had 65.6% sensitivity and 62.5 specificity to predict renal involvement.

Conclusion: PLR exhibit favorable diagnostic performance in predicting renal involvement in patients with GPA.

Keywords: Granulomatosis with polyangiitis, Platelet to lymphocyte ratio, Mean platelet volume, Biomarker, Activity

Background

Granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis (WG) is an autoimmune vasculitis characterized by granulomatous inflammation with necrotizing vasculitis affecting small to medium sized vessels [1]. The main autoantibody associated with the disease is the cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA), usually directed against the enzyme proteinase-3 (PR-3) [2]. Due to involvement of vital organs, GPA has significant morbidity and mortality. Renal involvement observed as rapidly progressive glomerulonephritis may lead to end-stage renal failure. Other potentially fatal common manifestations are alveolar and gastrointestinal hemorrhage and myocarditis. With the advanced treatment regimens, the disease has become more of a chronic relapsing–remitting pattern. Relapses occur in 50% or more of patients during the long-term follow-up [3]. One of the major challenges in the management of GPA is lack of reliable markers for activity and predicting relapse to guide therapy. Moreover, association between initial presentation features and subsequent relapses are controversial [4]. Because of ANCA titres and conventional inflammation markers such as C-reactive protein (CRP) and erythrocyte

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sedimentation rate (ESR) have limited value, new biomarkers are needed for the assessment of disease activity, and to predict relapse [5–7].

Platelet to lymphocyte ratio (PLR) is absolute count of platelets divided by the absolute count of lymphocytes derived from routine complete blood count (CBC). PLR was emerged as a marker of inflammation and used in combination with other inflammatory markers to determine severity of inflammation in many diseases. In recent years, utility of PLR was evaluated in numerous studies including cancers, cardiovascular diseases, rheumatic disease [8–11]. As novel markers of inflammation, we aim to investigate utility of PLR and mean platelet volume (MPV) in the assessment of disease activity and manifestations of disease in patients with GPA.

Methods

This study was planned as the retrospective and cross-sectional study with comparative group. 56 patients with GPA who were diagnosed between 2012 and 2017 were included. All patients met the Chapel Hill Consensus Conference Nomenclature/Criteria for Vasculitis and/or the American College of Rheumatology (ACR) criteria for GPA [12, 13]. 53 age and sex-matched healthy subjects were served as control group. Subjects in either group with one of the following concomitant diseases/situations were excluded: 1) acute or chronic infections; 2) concomitant inflammatory diseases 3) metabolic diseases including diabetes mellitus, thyroid dysfunction, liver disease and 4) any kind of malignancy.

Demographic, clinical and laboratory data were retrieved from medical records. Disease activity was assessed with Birmingham Vasculitis Activity Score for WG vasculitis (BVAS/WG) [14]. Blood collection and calculation of BVAS/WG were held at the same time. All blood samples were collected from newly diagnosed patients. Complete blood count (CBC) was performed with Backman Coulter automatic analyzer within 2 h of blood collection. ESR and CRP levels were determined with Westergen method and nephelometry respectively. The PLR was calculated as the ratio of platelet and lymphocyte counts of the same CBC. Renal involvement was diagnosed if patient had at least one of the following findings: a. active, biopsy proven, pauci-immune glomerulonephritis, b. active urinary sediment, c. rise in serum creatinine > 30% or > 25% decline in creatinine clearance which was attributed to active AAV in the kidney. The study protocol was approved by the Local Research Ethics Committee. A written informed consent form was signed by the all participants. Study was conducted in accordance with the ethical principles as described by the declaration of Helsinki.

Statistical analysis

Statistical Package for Social Science (SPSS) version of 16.0 was used for the analyzes (SPSS Inc., Chicago, IL). The variables were analyzed using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov) for the distribution of normality. All demographic and quantitative data were presented as means ± SD or percentages (%). Comparison of categorical data was performed by chi-square tests. Mann-Whitney U-test was used to compare independent samples which did not have a normal distribution. A p-value < 0.05 were considered statistically significant. Spearman test was used for the assessment of correlations between variables. Sensitivity, specificity and cut off values are determined by using ROC curve and diagram. Comparison of ROC curves were used for comparing predictive performances of RDW, ESR and CRP variables to detect renal involvement.

Results

Fifty-six patients with GPA and 53 healthy controls were included. Clinical characteristics and laboratory findings of the study groups are shown in Table 1. The patients were predominantly male (58.9%) with a mean age of 48.14 ± 14.09 years. C-ANCA was positive in 51 (91.07%) of patients and p-ANCA was positive in 8 (16.07%) of patients. Mean BVAS/WG was 13.54 ± 4.94 at diagnosis. Clinical manifestations at diagnosis was as follow, general manifestation 51 (91.07%), ear nose throat involvement 33 (58.93%), pulmonary involvement 37 (66.1%), renal involvement 32 (57.1%), cutaneous involvement 25 (44.64%), ocular 17 (30.36%), gastrointestinal tract 5 (8.93%).

ESR, CRP and PLR were significantly higher in patients with GPA than controls. MPV was significantly lower in patients with GPA compared to healthy controls. In patients group, PLR positively correlated with ESR and CRP ($r = 0.39$, $p = 0.005$ and $r = 0.51$, $p < 0.001$, respectively). In contrast, MPV negatively correlated with ESR and CRP ($r = -0.31$, $p = 0.03$ and $r = -0.34$, $p = 0.014$, respectively). There were no significant correlations between PLR, MPV and BVAS/WG.

Patients with renal involvement had remarkably higher PLR than patients without renal involvement (median: 265.98, IQR: 208.79 vs median: 180.34 IQR:129.37, $p = 0.02$). Moreover, PLR negatively correlated with glomerular filtration rate ($r = -0.27$, $p = 0.009$). Patients with renal involvement tended to have lower MPV, but this difference did not reach statistical significance (median: 7.60, IQR:1.17 vs median 7.75, IQR:1.46, $p = 0.786$). Receiver operating characteristic curve of PLR, ESR and CRP for differentiating renal involvement is presented in Fig. 1. Area Under Curves (AUCs) for PLR, CRP and ESR were 0.703 (95% confidence interval [CI], 0.558–0.849, $p = 0.016$), 0.577 (95% CI: 0.416–0.738, $p = 0.362$), 0.508 (95% CI: 0.337–0.678, $p = 0.929$), respectively. A cut-off level of 204 for PLR had 65.6% sensitivity and 62.5 specificity (positive predictive value 70%, negative

Table 1 Clinical characteristics and laboratory findings of the study population

	GPA patients	Controls	p
Age mean ± SD (years)	48.14 ± 14.09	46.77 ± 14.14	0.614
Males (n)	33 (58.9%)	26 (49.1%)	0.301
WBC (× 10^3/mL)	11.600 (3.240; 35.490; 6.907)	7.040 (4.100; 11.870; 2.413)	< 0.001
Neutrophils (× 10^3/mL)	8.230 (1.300; 33.420; 6.830)	4000 (2.300; 11.870; 1.525)	< 0.001
Lymphocytes (× 10^3/mL)	1.665 (0.300; 5.550; 0.951)	2.320 (1.270; 4.090; 0.690)	< 0.001
Platelets (× 10^3/mL)	308.000 (82.600; 1126.000; 191.500)	224.600 (136.000; 373.900; 73.600)	< 0.001
ESR (mm/H)	47.5 (3; 131; 60)	8 (1; 34; 7.50)	< 0.001
CRP (mg/L)	34 (1.27; 300; 99.14)	3.1 (1.16; 7.40; 2.07)	< 0.001
MPV	7.54 (6.08; 10.38; 1.29)	8.62 (6.88; 13.10; 1.41)	< 0.001
PLR	212.65 (29.86; 1638.33; 159.62)	101.43 (58.37; 210.63; 35.44)	< 0.001
Creatinine (mg/dL)	0.912 (0.45; 19.90; 1)	0.79 (0.53; 1.12; 0.24)	0.002
GFR	83.50 (2.70; 141.0; 75.25)	99.70 (65.30; 130.70; 21.30)	0.003

Values are presented as median (min; max; interquartile range). *GPA* Granulomatosis with polyangiitis, *WBC* white blood cell, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *MPV* mean platelet volume, *PLR* platelet/lymphocyte ratio, *GFR* glomerular filtration ratio

predictive value 57.7%) for renal involvement (Fig. 2). Patients with alveolar hemorrhage tended to have higher PLR and lower MPV but this difference did not reach statistical significance (277.34 ± 181.95 vs 240.61 ± 252.43 $p = 0.382$ for PLR, 7.69 ± 0.66 vs 7.83 ± 1.08, $p = 0.809$ for MPV, respectively).

Discussion

Significant progress has been made in the understanding of pathogenesis and treatment of GPA, but there is still unmet need for biomarkers for predicting specific organ involvement, disease activity, relapse and long term prognosis. Identification of such markers may guide the

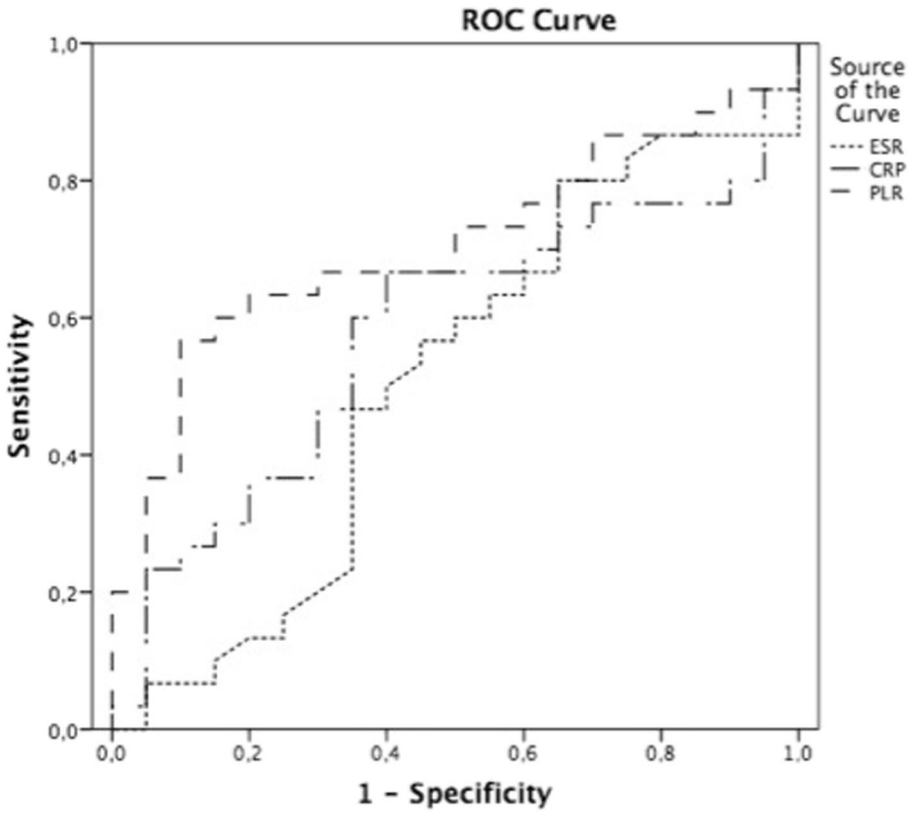

Fig. 1 Receiver operating characteristic curve of PLR, ESR and CRP for differentiating renal involvement

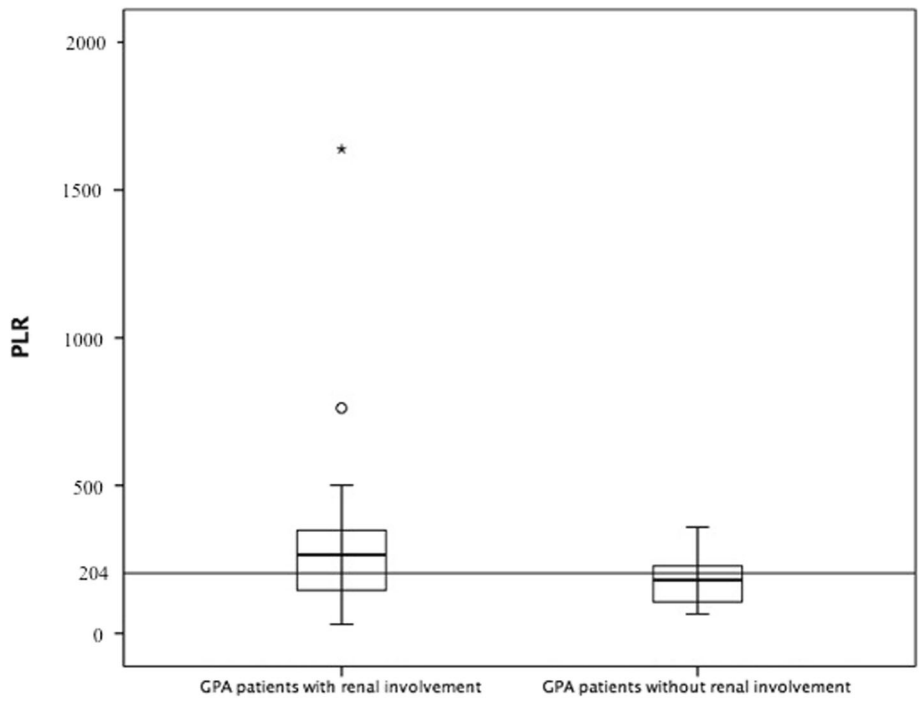

Fig. 2 Characteristics of PLR

therapy and help to determine those patients at high risk of relapse. Available markers, including ANCA titers, and commonly used inflammatory markers, ESR and CRP, are not adequate. Although these markers substantially elevated in active stages of disease their values are not correlated with disease activity and lack of prognostic information and prediction of relapses.

Systemic inflammation is associated with alterations in circulating peripheral blood cells quantity and composition. Normochromic anemia, thrombocytosis, neutrophilia and lymphocytopenia usually accompanies many inflammatory conditions [15]. In acute inflammation number and volume of platelets increase. Therefore, these features of circulating blood cell components can be used for the assessment of inflammatory activity [16, 17]. One of these, PLR has emerged as a marker of activity and as a prognostic marker in many diseases.

In our study, we found that PLR is significantly elevated in patients with GPA and correlated with other commonly used acute phase reactants. There is no correlation between PLR and BVAS/WG indicating that PLR might not reflect overall activity of disease. However, those patients with renal involvement had remarkably higher levels and PLR was significantly correlated with GFR. Therefore, we suggest that PLR might be a marker for renal activity of GPA.

In recent years, utility of PLR was evaluated in numerous studies. It has been reported to be elevated in patients with chronic renal failure (CRF) and is associated with increased mortality among the end stage CRF patients [18, 19]. Another striking evidence is correlation between PLR and disease activity of dermatomyositis which is widely accepted as a vasculitic process [20]. In addition, previous studies show that PLR is positively correlated with inflammatory indices such as CRP and ESR, and PLR is also associated with disease activity in psoriasis, RA and systemic lupus erythematosus [21–24]. Systemic lupus erythematosus (SLE) patients with nephritis had higher PLR levels than those without nephritis [24].

MPV was significantly lower in patients with GPA compared to healty control and negatively correlated witih ESR and CRP. There was no correlation between BVAS/WG, GFR and MPV. MPV values have previously been studied in various inflammatory conditions, such as familial mediterranean fever, rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease, juvenile SLE, psoriasis, systemic sclerosis and acute rheumatic fever [16, 25–31]. But the results are contradictory. It would seem that the size of circulating platelets is dependent on the intensity of systemic inflammation. Low-grade inflammatory conditions are associated with high levels of MPV and high-grade inflammatory diseases are associated with low levels of MPV [32, 33].

Herein, we presented 56 patients with GPA and tried to analyze the relation between PLR, MPV and disease activity. These costs may change from country to country, but the cost-effectiveness of these new parameters is valid worldwide. We have some limitations in our study.

First, our study is cross sectional and long term prognosis of patients are largely unknown. Second, number of patients is relatively small. Hence, our results must be confirmed in large scale longitudinal prospective studies.

Conclusions

Patients with GPA had significantly higher PLR and lower MPV compared to healthy controls. We have demonstrated a significant correlation between ESR, CRP, MPV and PLR. GPA patients with renal involvement had higher PLR levels than those without renal involvement and PLR was significantly correlated with GFR. Newer biomarkers detected in urine or blood could greatly assist with diagnosis, disease activity assessment, and prognosis of patients with GPA; however, at present there is a need for prospective and longitudinal studies followed by validation in different groups of GPA patients to confirm their clinical value [34].

Abbreviation

ACR: American College of Rheumatology; ANCA: Antineutrophil cytoplasmic antibodies; BVAS:/WG: Birmingham Vasculitis Activity Score for WG vasculitis; CBC: Complete blood count; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; GPA: Granulomatosis with polyangiitis; IQR: Inter-quartile range; MPV: Mean platelet volume; PLR: Platelet to lymphocyte ratio; PR-3: Proteinase-3; SD: Standard deviation; SPSS: Statistical Package for Social Science; WG: Wegener's granulomatosis

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None

Authors' contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study protocol was approved by the Committee on Human Research Ethics

Consent for publication

A well written informed consent and consent to publish was obtained from all the partipicants included in this study.

Competing interests

All co-authors are aware of your journal's conflict-of-interest policy; none of the co-authors has any direct or indirect conflicts of interest, financial or otherwise, relating to the subject of our report.

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