



# Association of systemic inflammation indices with visual field loss progression in patients with primary angle-closure glaucoma: potential biomarkers for 3P medical approaches

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## Abstract

**Relevance** Accumulating evidence suggests a dysfunction of the para-inflammation in the retinal ganglion cell layer and the optic nerve head in patients with glaucoma. Currently, circulating blood platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), and lymphocyte-to-monocyte ratio (LMR) are regarded as novel indicators of systemic inflammation. Biomarkers allow early identification of patients with visual field (VF) loss progression and timely implementation of replacement therapies.

**Objective** This study aimed to investigate whether higher inflammatory indices (PLR, NLR, and LMR) were associated with VF loss progression in patients with primary angle-closure glaucoma (PACG) for the predictive diagnostics, targeted prevention, and personalization of medical services.

**Methods** This prospective cohort study followed up 277 patients with PACG for at least 24 months, with clinical examination and VF testing every 6 months. Inflammatory cell quantification, including platelets, neutrophils, lymphocytes, and monocytes, was measured using the Sysmex XN-A1 automated inflammatory cells quantification system. Three systemic inflammatory indices, PLR, NLR, and LMR, were determined on the basis of baseline neutrophil, lymphocyte, monocyte, and platelet counts in patients with PACG. The risk factors for PACG were analyzed using logistic regression, Cox proportional hazards regression, and the Kaplan–Meier curve.

**Results** Our results revealed that 111 (40.07%) patients showed VF loss progression. The PLR was significantly higher ( $P=0.046$ ) in the progression group than in the non-progression group. A higher PLR (OR 1.05, 95% CI 1.01–1.08,  $P=0.004$ ) was a risk factor for PACG progression. In multivariate analyses, PLR independently predicted VF loss progression (HR 1.01, 95% CI 1.00–1.01,  $P=0.04$ ). Kaplan–Meier curve analysis showed that higher PLR indicated significantly higher rates of VF loss progression (66.91% vs. 52.90%,  $P=0.03$ ). Comparable results were observed in the male and female subgroups.

**Conclusion** Our findings revealed the significant association between a high PLR and a greater risk of VF loss progression in patients with PACG. PLR may be highly recommended as a novel predictive/diagnostic tool for the assessment of VF loss progression from the perspectives of predictive, preventive, and personalized medicine in vulnerable populations and for individual screening.

**Keywords** Predictive preventive and personalized medicine (PPPM/3PM) · Glaucoma · Primary angle-closure glaucoma · Visual field · Cohort study · Systemic inflammation indices · Platelet-to-lymphocyte ratio · Neutrophil-to-lymphocyte ratio · Lymphocyte-to-monocyte ratio · Progression · Risk assessment · Prediction/prognostic assessment · Biomarker · Predictive diagnostics · Targeted prevention · Personalization of medical services

## Introduction

### World statistics on glaucoma

Glaucoma is characterized by visual field defects, optic nerve head (ONH) cupping, and increased intraocular

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pressure (IOP) and is the most frequent cause of irreversible blindness worldwide [1]. The number of people with glaucoma will increase from approximately 80 million to more than 100 million by 2040 [2]. The risk and subtypes of glaucoma vary among races and countries [2]. Asia accounts for approximately 60% of all glaucoma patients worldwide [3]. Based on a population-based study, there will be 59.51 million people with glaucoma by 2020 in Asia alone [4]. Primary angle-closure glaucoma (PACG) is the most prevalent form of glaucoma in Asian countries and carries a threefold increased risk of severe, bilateral visual impairment than primary open-angle glaucoma (POAG), which accounts for over 70% of PACG cases worldwide [5–7]. With the increasing number of glaucoma patients, a novel approach for the early identification of a high risk of progression/degeneration in patients with PACG is urgent, which is in line with the principles of predictive, preventive, and personalized medicine (PPPM).

### Economic and clinical burden of glaucoma

Early identification and treatment of patients with glaucoma are essential to slow down visual field (VF) loss progression to avoid irreversible blindness, which can result in greater clinical and economic burden [8]. VF loss in patients with glaucoma is associated with a decreased quality of life [9], such as higher susceptibility to falls and fractures [10], compared to that in patients without glaucoma. Thus, early identification and treatment of patients with PACG are likely to reduce an individual's loss of health-related quality of life as well as the clinical, personal, and societal economic burdens [11].

However, the increasing prevalence of glaucoma contributes to significant personal and societal economic burdens, both directly and indirectly [12]. Direct economic burden is the main burden that includes the costs of ocular hypotensive medications to prevent and/or slow down VF loss progression, transportation, government health insurance programs, and nursing care [11]. In a 2006 US study by Rein et al. [12], the annual total financial burden of major adult visual disorders was \$35.4 billion (\$16.2 billion in direct medical costs, \$11.1 billion in other direct costs, and \$8 billion in productivity losses), and the annual governmental budgetary impact was \$13.7 billion. In Australia, vision disorders cost an estimated A\$9.85 billion in 2004 [13]. Tang et al. [14] reported that compared with no screening, combined screening of POAG and PACG in China was predicted to result in an incremental cost–utility ratio of US\$569 (95% confidence interval [CI] 17 to 4180) and an incremental cost-effectiveness ratio of \$1280 (95% CI – 58 to 7940).

Existing studies evaluating the economic burden by disease stage conclude that direct medical costs increase with increasing disease severity [8, 15, 16]. A US claims-based

analysis reported that patients with severe POAG had higher eye-related outpatient costs than patients with moderate and mild POAG (median, \$639 vs. \$546 vs. \$476, respectively;  $P < 0.0001$ ) as well as higher glaucoma-related pharmacy costs (median, \$493 vs. \$244 vs. \$139, respectively;  $P < 0.0001$ ) [8]. Thus, a novel approach for the early predictive diagnostics, targeted prevention, and personalization of medical services in patients with glaucoma are likely to be effective methods to reduce economic and clinical burdens.

### Molecular mechanisms of inflammation in glaucoma

Inflammation is a defensive response to stimulation, and short-term inflammation is beneficial and an automatic defense response of the human body [17]. Chronic inflammation is a hallmark of the majority of non-communicable diseases (cancer, degenerative disease, autoimmune disease, etc.) [18–20] and is harmful. Inflammation can promote the occurrence and development of cancer by various ways (blood vessel growth, proliferation and invasiveness, et c.), which indicated that monitoring of the causes and inflammatory factors in chronic inflammation processes is a useful way to predict cancer and assess the efficiency of cancer prevention [17, 21]. Furthermore, inflammatory cytokine storm is associated with severe COVID-19 and unfavorable outcomes in hospitalized patients [22]. Thus, anti-inflammatory therapy would enable effective management of COVID-19-associated complications in primary, secondary, and tertiary care in the context of PPPM [23]. Considering these previous observations, to explore the relationship between inflammation alterations and risk of progression/degeneration in patients with glaucoma is urgent, which is in line with the principles of PPPM.

A gradual accumulation of evidence from human glaucoma samples and animal glaucoma models suggests impaired para-inflammation in the retinal ganglion cell (RGC) layer and the ONH in patients with glaucoma [24–26]. Mechanosensitive channels on RGCs are stimulated by high IOP, which leads to pro-apoptotic and paracrine signals for glial and microglial activation via toll-like receptors. Glial activation releases pro-inflammatory cytokines and tumor necrosis factor- $\alpha$ , which participate in the immune-mediated degeneration of RGC. Moreover, activation of the toll-like receptor upregulates the synthesis of nuclear factor- $\kappa$ B, which, in turn, stimulates the synthesis of pro-inflammatory cytokines (interleukin [IL]-1  $\beta$ , IL-6, and tumor necrosis factor- $\alpha$ ) [27].

The complement system and autophagy are also involved in the neuroinflammation of glaucoma. Upregulation of several complement factors, such as the complement components (C) 1q, C3, and C5 and the membrane attack complex, has been demonstrated in patients with glaucoma as well as in animal glaucoma models [28, 29]. It has recently been

demonstrated that autophagy is dysregulated in the trabecular meshwork and in RGC somas with aging and in animal glaucoma models [30, 31]. For example, LC3B-II and p62/SQSTM1 were found to be upregulated upon hyperbaric insult in a model of acute ocular hypertension[32].

### **PLR, NLR, and LMR as systemic inflammatory indices for glaucoma health status**

Systemic inflammatory biomarkers predicting clinical outcome would allow early identification of patients with faster VF loss progression and timely use of replacement therapies and may be useful tools for PPPM in patients with PACG. Circulating blood cell interactions are essential in the pathophysiology of inflammation, immune responses, and hemostasis.

Currently, as simple, rapid, and reliable parameters, the platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), and lymphocyte-to-monocyte ratio (LMR) are regarded as novel indicators of systemic inflammation [33, 34]. PLR, NLR, and LMR, as circulating hematologic parameters, have emerged as informative markers revealing shifts in platelet, lymphocyte, neutrophil, monocyte, and lymphocyte counts due to acute and chronic inflammation [35]. Thus, we hypothesized that determining the PLR, NLR, and LMR before glaucoma treatment may be a novel approach for the early identification of a high risk of progression/degeneration in patients with PACG from the perspectives of PPPM in vulnerable populations and for individual screening [36].

The role of systemic inflammatory indices as possible biomarkers of PPPM has recently been investigated. PLR, NLR, and LMR are the most tested diagnostic, predictive, preventive, and personalized indices and have been associated with the prognosis of various diseases[37–39]. For example, Krenn-Pilko et al. [39] reported that an increased PLR was significantly associated with decreased overall survival in patients with breast cancer (hazard ratio [HR] 1.92, 95% CI 1.01–3.67,  $P=0.047$ ). Willim et al. [40] found that a high PLR at admission predicted in-hospital and long-term major adverse cardiac events and mortality. Our previous large sample ( $n=771$ ) case–control study of patients with glaucoma revealed a significant difference in PLR, NLR, and LMR between patients with PACG [41] and POAG [42] and normal controls. Comparable results were also reported by other researchers in patients with different types of glaucoma, including PACG[43], POAG [43, 44], normal-tension glaucoma [45], and pseudoexfoliation glaucoma[46]. Despite evidence that patients with PACG have abnormal PLR, NLR, and LMR, knowledge regarding the role of PLR, NLR, and LMR in VF loss progression in patients with PACG for the predictive diagnostics, targeted prevention, and personalization of medical services is limited.

### **Working hypothesis**

For these reasons, to propose a novel approach for the early identification of a high risk of VF loss progression in patients with PACG would be of interest to ophthalmologists, in line with the principles of PPPM. Recently, several studies have attempted to explore whether subcellular imaging and expression patterns in blood as the reliable platform for early/predictive glaucoma diagnosis[47–49]. Golubnitschaja O et al. [48] reported that many types of glaucoma-specific molecular alterations can be potentially used for development of advanced tools for early and predictive diagnosis. The levels of endothelin-1 (ET-1) were able to predict post-surgery intraocular pressure in patients undertaking POAG eye surgery. Furthermore, papillomacular bundle defect on fundus photography might be a personalized indicator representing ischemia-associated diseases and a predictive factor for diagnosis and preventive management of glaucoma[49].

The current study hypothesized that elevated levels of systemic inflammatory indices (PLR, NLR, and LMR) would be related to a hyperinflammatory state, leading to faster rates of VF damage in patients with PACG, and may be regarded as novel biomarkers to predict the progression of PACG. If being valid, this study could provide two benefits: (1) early identification of patients with faster VF loss progression ahead of the disease and (2) timely use of personalized treatment or replacement therapies based on the baseline levels of systemic inflammatory indices. These results may facilitate the development of PPPM in patients with PACG.

### **Materials and methods**

This study was conducted at the Department of Ophthalmology and Visual Sciences, Eye, Ear, Nose, and Throat Hospital of Fudan University, Shanghai, China. The Ethics Committee of the Eye and ENT Hospital of Fudan University approved this study (EENT2015011), and the study adhered to the principles of the Declaration of Helsinki. Informed consent was obtained from all subjects.

### **Patients**

A total of 476 patients were recruited from the Department of Ophthalmology and Visual Sciences at the Eye and ENT Hospital of Fudan University from June 2016 to June 2018. All participants visited the institution once every 6 months to allow the regular assessment of the progression of PACG. The minimum follow-up period in this study was set to 24 months.

## Diagnostic criteria

PACG was diagnosed by glaucoma specialists. Previously described diagnostic criteria were used to diagnose PACG [50–53] and include the following conditions: narrow anterior chamber angles with glaucomatous optic neuropathy and corresponding VF loss. VF loss was determined by including a cluster of at least three non-edge contiguous points on a pattern deviation plot, which does not cross the horizontal meridian, and with a probability of being present in age-matched controls at less than 5% (one of which was less than 1%). It had an abnormal standard deviation pattern with a  $P < 0.05$  when plotted in the normal population and should fulfill the following test reliability criteria:  $< 20\%$  fixation loss,  $< 1\%$  false positives, and/or  $< 15\%$  false negatives. Additionally, PACG was diagnosed in eyes that have narrow angles; patients with elevated IOP ( $> 21$  mmHg); patients with at least  $180^\circ$  of angle-closure, obliterating the pigmented segment of the trabecular meshwork, whether synechial, appositional, segmented, or continuous; and in patients where the degree of peripheral anterior synechiae was too extensive to be managed via laser peripheral iridotomy.

## Inclusion and exclusion criteria

The selection criteria of patients with PACG were described previously [50–53], including the absence of secondary glaucoma or any other eye disease that could potentially affect visual acuity or the VF; did not undergo intraocular surgery within the previous 2 months; absence of hematologic diseases; absence of coagulation disorders; did not receive drugs that can affect blood components; and absence

of any systemic diseases, including acute infectious diseases, metabolic syndrome, autoimmune disease, or cancer. In this study, no patients with PACG were treated with laser peripheral iridectomy, laser iridotomy, and surgery before study enrollment. Most of the patients with PACG received topical glaucoma medications.

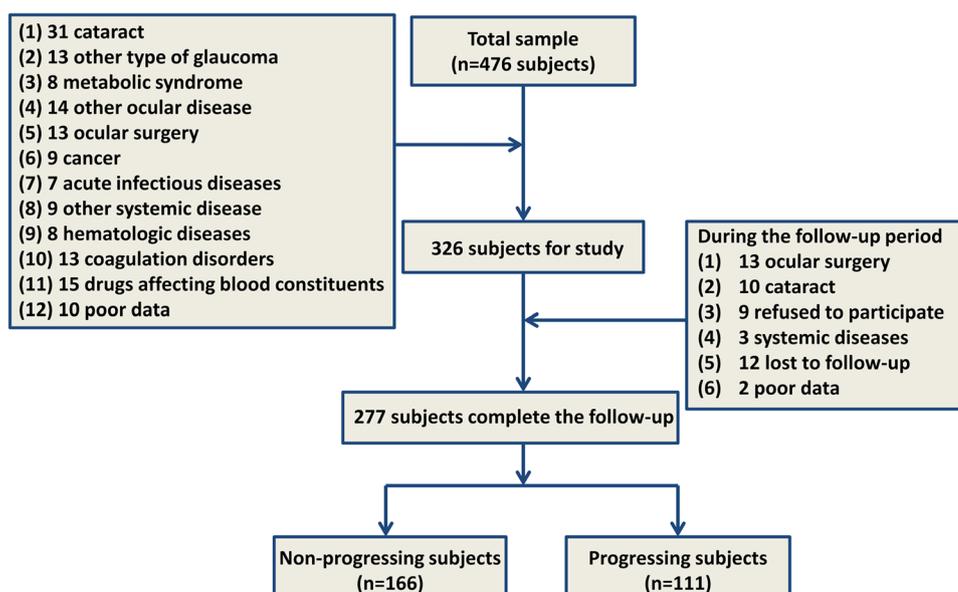
This study recruited a total of 476 patients with glaucoma; however, 150 patients were subsequently excluded based on their failure to fulfill the diagnostic and inclusion criteria, they did not complete the required examination, or they had missing data. During the follow-up period, 35 and 12 patients with PACG were excluded and were lost to follow-up, respectively. Two patients with PACG with missing data were also excluded. Finally, a total of 277 subjects with PACG were enrolled in this study. Figure 1 depicts the flowchart of the study regarding patient recruitment.

## Ophthalmic examinations

The ophthalmic examination included an assessment of the anterior chamber angle via gonioscopy (Haag-Streit, Bern, Switzerland) and three IOP measurements using Goldmann applanation tonometry (Haag-Streit, Bern, Switzerland), which were then averaged. Their fundi were analyzed using a digital retinal camera (TRC-NW200, Topcon). An A-scan ultrasound (A-Scan Pachymeter, Ultrasonic, Exton, PA, USA) was used to measure the central corneal thickness (CCT), axial length (AL), and anterior chamber depth (ACD), and the vertical cup-disk ratio (VCDR) was evaluated by two doctors based on the analysis of the obtained fundus photographs, which was then averaged.

All subjects underwent these medical examinations as performed by their respective specialty physicians at the

**Fig. 1** Flowchart of the cohort study



Eye and ENT Hospital of Fudan University. These medical examinations, including the assessment of electrocardiograms, radiographs, liver function, blood glucose, infectious disease diagnoses, renal function, blood pressure, heart rate, disease duration, diabetes, hypertension, use of IOP-lowering medications, body temperature, height, and weight, were performed for all subjects. The body mass index (BMI) of the subjects was calculated as their weight in kilograms divided by the square of their height in meters.

### Collection and analysis of blood samples

In this study, three inflammatory indexes were determined on the basis of baseline values of neutrophils, lymphocytes, monocytes, and platelets in patients with PACG. Laboratory testing was performed at the Department of Clinical Laboratory, Eye and ENT Hospital of Fudan University. Blood samples were obtained in the morning through standard venipuncture from the antecubital fossae (anterior elbow veins) after the participants had fasted for 8 h. Then, 2 ml of blood samples was collected in ethylenediaminetetraacetic acid tubes. Laboratory parameters were measured within 0.5 h after blood collection. Inflammatory cells quantification, which included neutrophils, lymphocytes, monocytes, and platelets, was measured with the Sysmex XN-A1 automated blood counting system (Kobe, Japan). The NLR, PLR, and LMR were calculated. Internal controls were also analyzed daily for 5 years, with typical monthly coefficients of variation (CVs) of 4–8% (platelets), 5–8% (monocytes), 2–4% (neutrophils), and 2–5% (lymphocytes), and no significant changes were found in the CVs.

### VF analysis

VF loss progression was analyzed as previously described [50, 51]. The Glaucoma Department of the Eye and ENT Hospital of Fudan University performed perimetry in patients with glaucoma, unless they were unable to see any light with both eyes open or if they experienced an eye infection. The mean deviation (MD) and mean sensitivity of the VFs were measured using an Octopus automated perimeter. All patients underwent a minimum of three VF tests. After considering the learning effect from the VF tests, the results of the first two tests were excluded. Only reliable (false-positive/false-negative rate < 15% and reliability factor < 20%) and compatible VF results were included. VF testing was performed at baseline and every 6 months throughout the follow-up period. Patients with PACG were required to have at least five reliable VF results within the follow-up period of more than 2 years. Previously described methods [51, 54] were applied to determine the functional VF loss progression in PACG according to an event-based analysis modified for Octopus

perimetry [51, 55], satisfying at least one of the following criteria: (1) development of a new scotoma of at least three worsening non-edge points  $\geq 5$  dB or one worsening non-edge point  $\geq 10$  dB, (2) a cluster of  $\geq 3$  non-edge points with  $\geq 10$  dB deterioration within a preexisting scotoma, (3) development of a new cluster of  $\geq 3$  non-edge points with  $15^\circ$  around a preexisting scotoma, or (4) worsening of the global MD value by  $\geq 2$  dB/year. In each patient, the first eye with VF loss progression was included in the analyses. If both eyes had VF loss progression, the eye with the greater progression was included in the analyses.

### Statistical analyses

All analyses were performed using the SPSS version 13.0 (SPSS Inc., Chicago, IL, USA). Figures were created using GraphPad Prism 6 software (La Jolla, CA, USA). Values are presented as means  $\pm$  standard deviations. Normality was assessed using the Kolmogorov–Smirnov test. Independent Student's *t* test and  $\chi^2$  tests were used to compare patient characteristics between groups, as appropriate.

Given the potentially increased risk of blindness in women caused by PACG [56, 57], those with PACG were categorized into female and male subgroups to investigate the role of PLR, NLR, and LMR in PACG development between sexes. Moreover, we categorized participants into two groups based on their median levels of PLR, NLR, and LMR.

Univariate and multivariate logistic regression analyses were performed to identify the risk factors of PACG progression. The odds ratios (ORs) and their corresponding 95% CIs were calculated using logistic regression models and were adjusted for age, sex, systolic blood pressure (SBP), diastolic blood pressure (DBP), disease duration, medications, IOP, VCDR, CCT, ACD, AL, MD, body mass index (BMI), presence of diabetes (yes = 1, no = 0), and presence of hypertension (yes = 1, no = 0).

Univariate and multivariate Cox proportional hazards analyses were performed to analyze the association of the baseline parameters with PACG progression. Cox proportional hazards models were employed to obtain the HRs and to identify the baseline factors that would help classify participants into the non-progression group during the follow-up period and were adjusted for age, sex, SBP, DBP, duration, medications, IOP, VCDR, CCT, ACD, AL, MD, BMI, presence of diabetes (yes = 1, no = 0), and presence of hypertension (yes = 1, no = 0). Survival outcomes (time to confirmed VF loss progression) were assessed using Kaplan–Meier plots, and the log-rank test was used to assess the differences among the constructed plots. A *P*-value of < 0.05 was considered significant.

## Results

### Characteristics of the participants

This study enrolled a total of 277 patients with PACG (male = 100, female = 177). Only one eye was randomly selected in patients with bilateral PACG. Among them, 111 (40.07%) showed progressive glaucoma based on VF loss progression. Table 1 summarizes the demographic and ocular characteristics of the progression and non-progression groups at baseline.

### Comparison of systemic inflammation levels between progression and non-progression groups

No significant intergroup differences were found in age, sex, BMI, SBP, DBP, diabetes, hypertension, duration, number of topical glaucoma medications, IOP, VCDR, CCT, ACD, AL,

or MD ( $P > 0.05$ ). The mean PLR level in the progression group was significantly higher than that in the non-progression group ( $P = 0.046$ ) (Table 1, Fig. 2A). Meanwhile, no significant differences were found in NLR (Table 1, Fig. 2B) and LMR (Table 1, Fig. 2C) levels between the progression group and non-progression group ( $P = 0.42$ ,  $P = 0.66$ , respectively).

### Comparison of systemic inflammation levels between the progression and non-progression groups stratified by sex

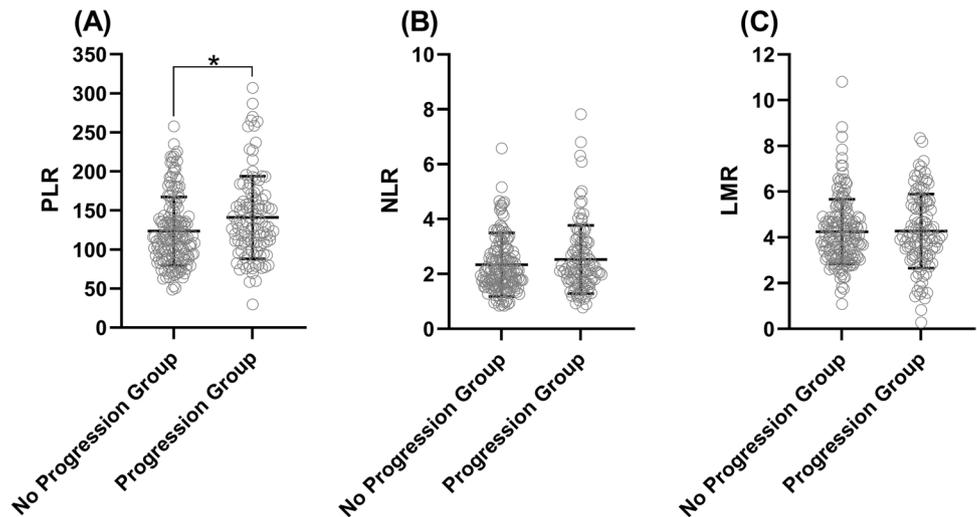
Patients with PACG were categorized into female and male subgroups. In these subgroups, the mean PLR level was significantly higher in the progression group than in the non-progression group ( $P = 0.046$ ,  $P = 0.035$ , respectively) (Table 2, Fig. 3A, B). Furthermore, no significant difference was observed in the NLR (Fig. 3C, D) and LMR (Fig. 3E, F) levels between the progression group and non-progression

**Table 1** Comparison of characteristics of No progression group and progression group in PACG patients

Variable	No progression ( $n = 166$ )	Progression ( $n = 111$ )	<i>t</i> -value	<i>P</i> -value
Age(year), mean $\pm$ SD	64.14 $\pm$ 10.19	64.10 $\pm$ 9.96	0.03	0.98 <sup>a</sup>
Male/female, <i>n</i>	65/101	35/76	1.68	0.20 <sup>b</sup>
BMI (kg/m <sup>2</sup> ), mean $\pm$ SD	23.08 $\pm$ 3.27	22.50 $\pm$ 3.19	1.45	0.15 <sup>a</sup>
SBP (mmHg), mean $\pm$ SD	128.54 $\pm$ 18.64	128.20 $\pm$ 18.39	0.15	0.88 <sup>a</sup>
DBP (mmHg), mean $\pm$ SD	72.19 $\pm$ 9.88	71.14 $\pm$ 10.63	0.84	0.40 <sup>a</sup>
Diabetes, <i>n</i> (yes/no)	15/151	11/100	0.06	0.81 <sup>b</sup>
Hypertension, <i>n</i> (yes/no)	36/130	26/85	0.12	0.73 <sup>b</sup>
Duration (month), mean $\pm$ SD	14.10 $\pm$ 18.44	15.67 $\pm$ 21.94	0.64	0.52 <sup>a</sup>
Follow up period (month), mean $\pm$ SD	24.00 $\pm$ 0.00	24.00 $\pm$ 0.00	0	1 <sup>a</sup>
Time of VF progression occurrence	-	12.32 $\pm$ 6.05	-	-
Topical glaucoma medications, <i>n</i> (%)				
0–2	43 (25.90%)	37 (33.33%)		
> 2	123 (74.10%)	74 (66.67%)	1.79	0.18 <sup>b</sup>
IOP (mmHg), mean $\pm$ SD	19.87 $\pm$ 10.07	23.20 $\pm$ 23.44	1.41	0.16 <sup>a</sup>
VCDR, mean $\pm$ SD	0.64 $\pm$ 0.30	0.59 $\pm$ 0.23	1.59	0.11 <sup>a</sup>
CCT (mm), mean $\pm$ SD	545.65 $\pm$ 41.89	541.38 $\pm$ 41.14	0.82	0.42 <sup>a</sup>
ACD (cm), mean $\pm$ SD	1.91 $\pm$ 0.53	1.92 $\pm$ 0.43	0.11	0.92 <sup>a</sup>
AL (cm), mean $\pm$ SD	22.44 $\pm$ 1.15	22.56 $\pm$ 1.07	0.88	0.38 <sup>a</sup>
MD (dB), mean $\pm$ SD	13.41 $\pm$ 8.80	12.46 $\pm$ 7.96	0.93	0.35 <sup>a</sup>
Platelet count (10 <sup>9</sup> /L), mean $\pm$ SD	206.99 $\pm$ 50.09	211.43 $\pm$ 54.97	0.69	0.49 <sup>a</sup>
Neutrophil count (10 <sup>9</sup> /L), mean $\pm$ SD	3.93 $\pm$ 1.41	3.76 $\pm$ 1.22	1.06	0.29 <sup>a</sup>
Lymphocyte count (10 <sup>9</sup> /L), mean $\pm$ SD	1.80 $\pm$ 0.56	1.69 $\pm$ 0.67	1.36	0.18 <sup>a</sup>
Monocyte count (10 <sup>9</sup> /L), mean $\pm$ SD	0.45 $\pm$ 0.13	0.47 $\pm$ 0.52	0.51	0.61 <sup>a</sup>
PLR, mean $\pm$ SD	126.12 $\pm$ 49.43	138.78 $\pm$ 54.73	2.00	0.046 <sup>a</sup>
NLR, mean $\pm$ SD	2.37 $\pm$ 1.16	2.49 $\pm$ 1.24	0.80	0.42 <sup>a</sup>
LMR, mean $\pm$ SD	4.22 $\pm$ 1.42	4.30 $\pm$ 1.60	0.44	0.66 <sup>a</sup>

BMI body mass index; SBP systolic blood pressure; DBP diastolic blood pressure, IOP intraocular pressure, VCDR vertical cup-to-disc ratio, AL axial length, CCT central corneal thickness, ACD anterior chamber depth, MD mean deviation, NLR neutrophil to lymphocyte ratio, PLR platelet to lymphocyte ratio, LMR lymphocyte to monocytes ratio, PACG primary angle closure glaucoma <sup>a</sup>Independent sample *t* test. <sup>b</sup> $\chi^2$  test

**Fig. 2** Comparison of levels of PLR (A), NLR (B), and LMR (C) in patients with PACG. Each data point represents one subject. Middle of the plot represents the mean value and the up and down bar represents the standard deviation. NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; LMR, lymphocyte to monocytes ratio. \* $P < 0.05$



**Table 2** Comparison of PLR, NLR, and LMR levels in subjects with PACG, stratified according to sex

Subgroup	No progression	Progression	t-value	P-value
<b>PLR</b>				
Male	122.33 ± 45.14	142.44 ± 63.66	2.02	0.046
Female	125.57 ± 42.74	140.22 ± 47.53	2.12	0.035
<b>NLR</b>				
Male	2.58 ± 1.47	2.75 ± 1.52	0.56	0.58
Female	2.18 ± 0.87	2.43 ± 1.08	1.64	0.10
<b>LMR</b>				
Male	3.82 ± 1.36	3.88 ± 1.67	0.22	0.82
Female	4.53 ± 1.38	4.46 ± 1.57	0.33	0.74
<b>Platelet count (10<sup>9</sup>/L)</b>				
Male	195.18 ± 44.07	206.91 ± 59.47	1.12	0.27
Female	214.86 ± 50.52	216.64 ± 47.17	0.24	0.81
<b>Neutrophil count (10<sup>9</sup>/L)</b>				
Male	4.09 ± 1.43	3.96 ± 1.33	0.45	0.66
Female	3.82 ± 1.39	3.71 ± 1.17	0.53	0.60
<b>Lymphocyte count (10<sup>9</sup>/L)</b>				
Male	1.79 ± 0.61	1.73 ± 0.97	0.37	0.71
Female	1.83 ± 0.51	1.66 ± 0.50	2.17	0.03
<b>Monocyte count (10<sup>9</sup>/L)</b>				
Male	0.49 ± 0.14	0.47 ± 0.16	0.57	0.57
Female	0.42 ± 0.12	0.47 ± 0.63	0.73	0.47

NLR neutrophil to lymphocyte ratio, PLR platelet to lymphocyte ratio, LMR lymphocyte to monocytes ratio, PACG primary angle closure glaucoma

group in male ( $P = 0.58$ ,  $P = 0.82$ , respectively) and female ( $P = 0.10$ ,  $P = 0.74$ , respectively) subgroups (Table 2).

**Associations of PLR with ocular parameters**

The Spearman analysis showed that PLR was significantly positively associated with MD ( $r = 0.12$ ,  $P = 0.04$ ) (Table 3).

After adjustment for age, sex, SBP, DBP, duration, medications, BMI, diabetes, and hypertension, the linear regression analysis suggested that PLR was also associated with the MD level ( $B = 0.02$ ,  $P = 0.009$ , 95% CI 0.96–1.33) (Table 3).

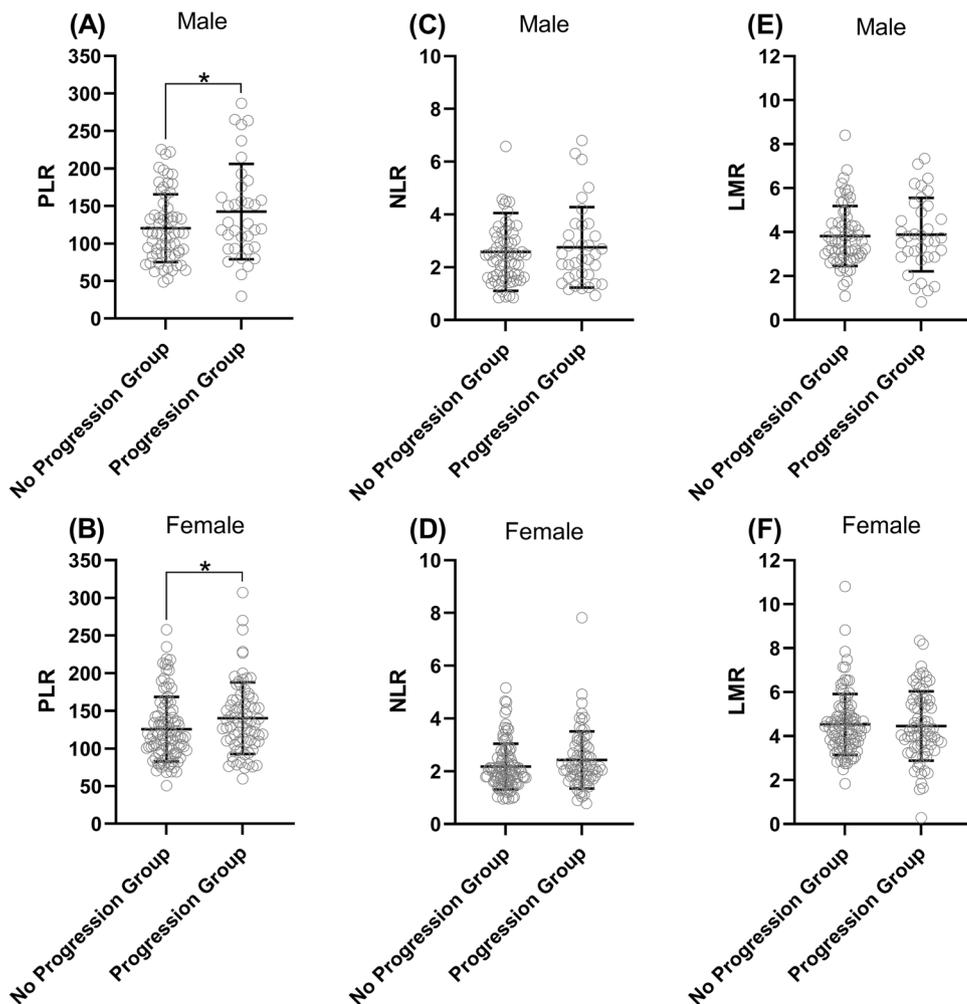
**Comparison of the MD and mean change in MD between the groups at different points**

Figure 4A represents the MD between the groups at different points during the follow-up period. No significant difference ( $P > 0.05$ ) was noted in the MD between the low and high PLR groups (Fig. 4B); comparable results were also observed in the male (Fig. 4C) and female (Fig. 4D) subgroups. During the follow-up period, the mean change in MD in the progression group (Fig. 4E) was greater than that in the non-progression group throughout the follow-up period ( $P < 0.05$ ). The mean change in MD in the high PLR group was significantly greater than that in the low PLR group ( $P < 0.05$ ) at 12, 18, and 24 months (Fig. 4F). Comparable results were observed in the male subgroup ( $P < 0.05$ , Fig. 4G) and female subgroup ( $P < 0.05$ , Fig. 4H).

**Logistic regression analyses of the risk factors for PACG progression**

Univariate logistic regression analyses showed that a higher PLR level (OR 1.01, 95% CI 1.00–1.01,  $P = 0.04$ ) was a risk factor for PACG progression; comparable results were observed in male and female subgroups. After adjusting for confounding factors, multivariate logistic regression analyses also demonstrated that a lower PLR level (OR 1.05, 95% CI 1.01–1.08,  $P = 0.004$ ) was a risk factor for PACG progression, and comparable results were observed in the male and female subgroups (Table 4).

**Fig. 3** Comparison of levels of PLR, NLR, and LMR in patients with PACG, stratified according to sex (male: **A, C, E**; female: **B, D, F**). Each data point represents one subject. Middle of the plot represents the mean value and the up and down bar represents the standard deviation. NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; LMR, lymphocyte to monocytes ratio. \* $P < 0.05$



**Table 3** Associations between PLR levels and ocular parameters in patients with primary angle closure glaucoma

	B/R value	P-value	95%CI
Spearman analysis			
IOP	0.10	0.91	
VCDR	0.11	0.08	
ACD	0.04	0.55	
CCT	0.10	0.12	
AL	0.05	0.38	
MD	0.12	0.04	
Linear regression*			
MD	0.02	0.09	0.96–1.33

IOP intraocular pressure, VCDR vertical cup-to-disc ratio, AL axial length, CCT central corneal thickness, ACD anterior chamber depth, MD mean deviation, NLR neutrophil to lymphocyte ratio, PLR platelet to lymphocyte ratio, LMR lymphocyte to monocytes ratio, PACG primary angle closure glaucoma. \*Adjusted for age, sex, SBP, DBP, duration, medications, BMI, diabetes (yes = 1, no = 0), and hypertension (yes = 1, no = 0)

**Cox regression analysis to explore the association of PLR with VF loss progression**

A Cox proportional hazards regression analysis was performed to assess the value of baseline parameters associated with PACG progression (Table 5). The univariate Cox analysis showed that baseline PLR level was associated with glaucoma progression. After adjusting for confounding factors, the baseline PLR (HR 1.01, 95% CI 1.00–1.01,  $P = 0.04$ ) level was significantly associated with glaucoma progression based on VF loss progression in the multivariate Cox analysis, and comparable results were also observed in the male and female subgroups. Furthermore, the multivariate Cox analysis showed that baseline IOP level (HR 1.01, 95% CI 1.00–1.02,  $P = 0.007$ ) was associated with glaucoma VF loss progression.

**Kaplan–Meier survival analysis**

Survival analysis indicated that a significantly higher proportion of patients with PLR levels > 120 (log-rank test,

$P=0.03$ , Fig. 5A) caused PACG progression. No significant difference was noted in patients with VF loss progression between the  $NLR < 2.11$  and  $NLR > 2.11$  subgroups ( $P=0.96$ ) (Fig. 5B) and between  $LMR < 4.04$  and  $LMR > 4.04$  subgroups ( $P=0.49$ ) (Fig. 5C).

Comparable results were also observed in that a higher proportion of patients with  $PLR > 116$  (log-rank test,  $P=0.04$ , Fig. 6A) in the male subgroup and  $PLR > 123$  (log-rank test,  $P=0.03$ , Fig. 6B) in the female subgroup experienced PACG progression. In the female and male subgroups, no significant difference was found in the proportion of patients who had VF loss progression between the high NLR and low NLR subgroups (Fig. 6C, D) and between the high LMR and low LMR subgroups (Fig. 6E, F).

## Discussion

### Data interpretation

This study highlighted potential biomarkers in patients with PACG, as well as our suggestion that PPPM should be considered in the prevention/prediction of VF loss progression and therapy procedures. Neuroinflammation is emerging as an increasingly important risk factor for the development and progression of PACG [58, 59]. Currently, the PLR is regarded as a novel indicator of inflammation [34]. In this study, the mean PLR was significantly higher in the progression group than in the non-progression group. Furthermore, our study revealed that a higher PLR was a risk factor for PACG progression and that a higher baseline PLR was associated with prospective glaucoma VF loss progression in a large sample cohort of patients with PACG. Patients with higher PLR showed more rapid VF loss progression and were more likely to demonstrate progressive RGC damage. This association was also observed in the male and female subgroups. Our results indicate that systemic inflammation plays an important role in the emergence and progression of PACG and PLR may be considered as a novel effective biomarker to predict VF loss progression in patients with glaucoma.

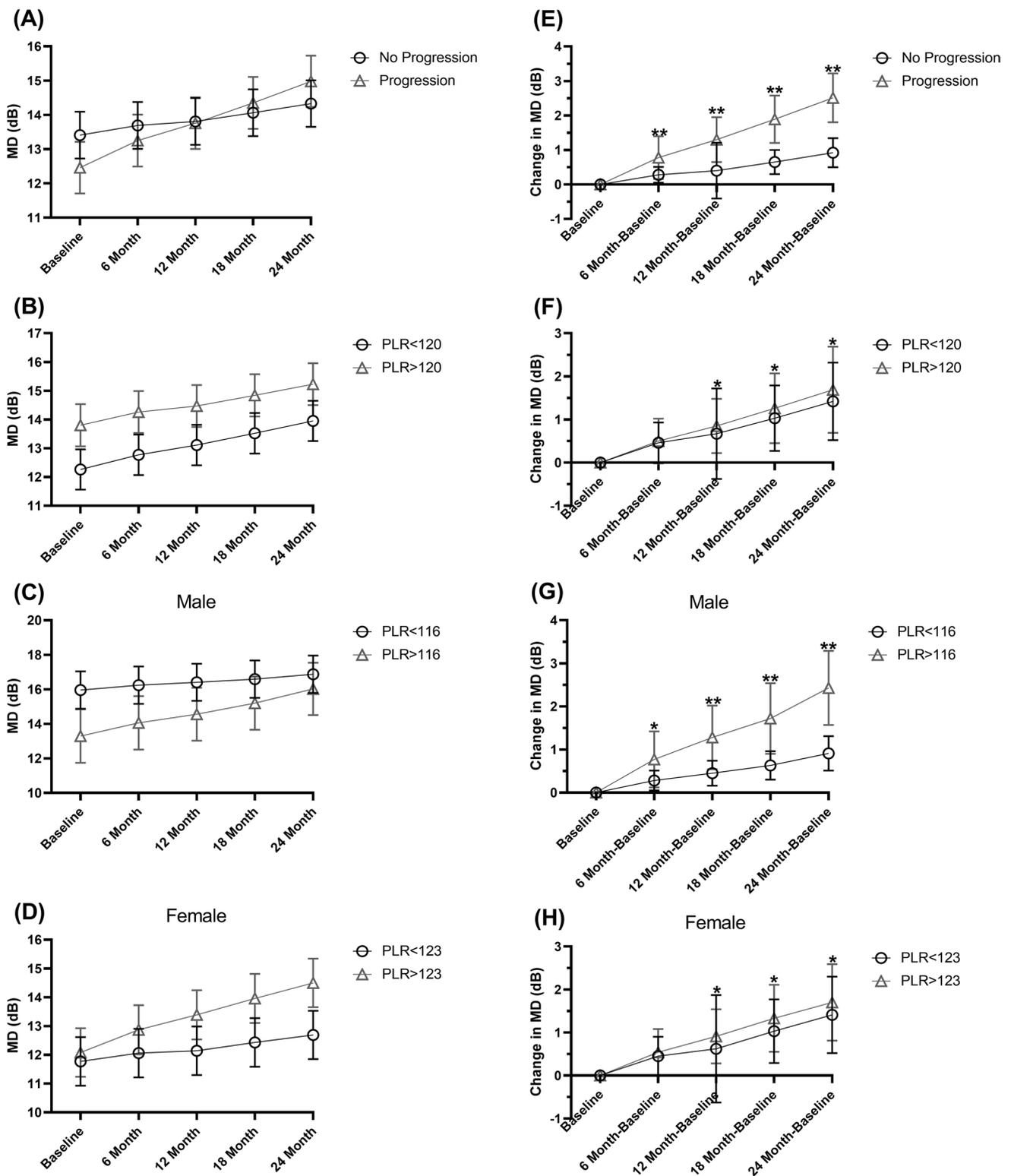
In this study, PLR was measured using an automated inflammatory cells quantification system (Sysmex XN-A1, Kobe, Japan). Sample stability is a crucial aspect of the quality of results. Sysmex XN has been reported to have good reliability for inflammatory cells quantification [60]. Meanwhile, internal controls were analyzed daily for 5 years, with typical monthly CV values within the range of 4–8% (platelets) and 2–5% (lymphocytes), and no significant changes were found in the CV values. Moreover, in this study, the platelet and lymphocyte counts were stable on different days in the same participants. Venous blood sampling was conducted four times on different days to quantify the number of

inflammatory cells in the same participant ( $n=467$ ), revealing that the mean intraindividual CV was below 10% in the complete blood count [61]. Tahir et al. [62] also reported that no significant difference was noted on different days. The CVs of PLR on different days in the same patient were small, which did not lead to bias in the results. Thus, our analysis on the PLR is comparable and stable and can be reliably used in the present study. In summary, our findings revealed that PLR has potential clinical application in the prediction and prevention of VF loss progression for the predictive diagnostics, targeted prevention, and personalization of medical services.

### Achievements in the previous studies

Eye examination and blood biomarkers as the reliable platform played important role in early/predictive glaucoma diagnosis [47–49, 53, 63]. For example, Golubnitschaja O et al. [48] reported that many types of glaucoma-specific molecular alterations, such as chromosomal and mitochondrial DNA (oxidative damage, mutations, polymorphism, methylation status of CpG islands), mRNA, proteins, and metabolites (signaling molecules, amino acids, plasma hormones, etc.) that can be potentially used for development of advanced tools for early and predictive diagnosis. Chen et al. [63] found that an elevated red blood cell distribution width was associated with PACG and its severity which indicated that the use of a red blood cell distribution width assessment may help to predict the PACG severity in each patient in order to better customize effective prevention treatments. Our previous study also found that the AL was positively and significantly related to the severity of PACG and suggested the use of AL assessment in glaucoma monitoring, diagnosis, and progression [53]. Considering these previous observations, the levels of certain systemic inflammation indices may serve as novel predictive/diagnostic tool for early/predictive glaucoma diagnosis.

PLR, as a simple, rapid, inexpensive, stable, and reliable parameter, has been widely used to diagnose and/or predict the prognosis of various diseases. Jaaban et al. [64] reported that a high PLR was significantly correlated with diabetic nephropathy and that PLR may serve as a predictor and prognostic risk marker of diabetic nephropathy. Liu et al. [65] performed a meta-analysis and suggested that PLR was significantly elevated in retinal vein occlusion, with pooled mean differences of 21.49 (95% CI 10.03–32.95) and pooled area under the receiver operating characteristic curve of 0.621 (95% CI 0.452–0.741). Gong et al. [66] reported that PLR (OR 1.013, 95% CI 1.009–1.016,  $P=0.001$ ) was an independent factor for early neurological deterioration post-thrombolysis. Chen et al. [67] found that PLR was an independent predictor of 3-month functional outcomes in patients with acute ischemic stroke.



Recently, several cross-sectional studies have attempted to explore the PLR in patients with glaucoma. Our previous study reported that the mean PLR was significantly higher in patients with PACG [41] and POAG [42] than in normal controls. Consistent with our previous study, Karahan et al.

[43] reported that both POAG and PACG groups exhibited higher PLR than the control group. Ozgonul et al. [44] reported that the PLR was higher ( $P=0.049$ ) in patients with POAG than in the controls, suggesting that PLR may be useful as a biomarker in patients with POAG. In agreement

**Fig. 4** Comparison of the mean levels of visual field mean deviation (MD) and mean change in MD between groups at different follow-up times. (A) The MD between the progression group and the non-progression group. (B) The MD between the PLR < 120 group and the PLR > 120 group. (C) The MD between the PLR < 116 group and the PLR > 116 group in male patients. (D) The MD between the PLR < 123 group and the PLR > 123 group in female patients. (E) The mean change in MD between the progression group and the non-progression group. (F) The mean change in MD between the PLR < 120 group and the PLR > 120 group. (G) The mean change in MD between the PLR < 116 group and the PLR > 116 group in male patients. (H) The mean change in MD between the PLR < 123 group and the PLR > 123 group in female patients. NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; LMR, lymphocyte to monocytes ratio. The results were presented as means  $\pm$  standard deviations. \* $P < 0.05$ . \*\* $P < 0.001$

with previous studies, we found that increased baseline PLR was significantly associated with a greater risk of VF loss progression in patients with PACG.

### Result interpretation of PLR in VF loss progression

Data regarding the association between PLR and VF loss progression in patients with PACG are limited. In this study, we found that a higher PLR was a risk factor for PACG progression and that a higher baseline PLR was associated with prospective glaucoma VF loss progression in a large sample cohort of patients with PACG. Patients with higher PLR showed more rapid VF loss and were more likely to demonstrate progressive RGC damage.

The pathophysiology of glaucoma involves complex inflammatory responses at various levels, with the interaction of various pathways [24, 47]. ET-1 was involved in inflammatory events and also plays a crucial role in age-associated diseases such as glaucoma or age-related macular degeneration [47]. Several studies using animal models [28, 68] and glaucoma human ONH specimens [69, 70] have supported the role of neuroinflammation in glaucoma. In patients with PACG, a high PLR indicates an impairment of para-inflammation in the RGC layer and the ONH. In agreement with previous studies, the present study suggested that a higher PLR at baseline was significantly associated with a greater risk of VF loss progression in patients with PACG.

### PLR as an effective tool for predicting VF loss progression

In this study, the OR/HR was 1.05/1.01, which is close to 1. Possible reasons for this value are as follows: (1) PLR reflects the levels of inflammation throughout the body, which may not substitute the existing PLR in the retina/optic nerve. The HR for IOP was also 1.01, which was equal to the PLR, highlighting the clinical significance of PLR in PACG progression. (2) The pathophysiology of glaucoma

is complex, multifactorial, and not completely understood. Oxidative stress, mitochondrial dysfunction, excitotoxicity, and neuroinflammation are involved in the progression of glaucoma. (3) Multivariate Cox regression and multivariate logistic regression analyses were performed to adjust for several factors, including disease duration and topical glaucoma medications, which may lead to a small OR/HR for PLR.

Although the OR/HR for PLR was 1.05/1.01, we demonstrated that a higher PLR was a risk factor for VF loss progression and that a higher PLR at baseline was significantly associated with VF loss progression in patients with PACG. Briefly, PLR, as a novel biomarker to predict VF loss progression, has clinical significance in patients with PACG.

### Result interpretation of clinical parameters in VF loss progression

In addition to PLR, other potential risk factors were investigated in this study. Multivariate Cox regression analysis also suggested that patients with PACG and higher IOP levels at baseline had faster VF loss progression (HR 1.01, 95% CI 1.00–1.02,  $P = 0.007$ ), which is consistent with the results of previous studies [71, 72]. Given that baseline IOP was linked with VF loss progression, we considered that the higher PLR may be a result of a secondary change attributed to IOP. One possibility is the poorer response to IOP treatment in those with higher PLR or that more aggressive (and successful) IOP-lowering drugs are associated with lower PLR. Therefore, adjusting treatment with regard to the IOP is important when analyzing PLR. After adjustment for medications, IOP, and other confounding factors, baseline PLR was found to be independently and significantly associated with glaucoma progression, as measured using VF loss in the multivariate Cox analysis. Furthermore, older age and moderate disease severity are risk factors for glaucomatous progression [73, 74]. However, in the present study, older age and moderate disease severity were not associated with VF loss progression. A possible explanation for this difference is that in this study, the disease duration ranged from 0 months to 7 years; although multivariate Cox regression analysis was performed to adjust for this factor, a huge difference in the disease course may have also affected these risk factors. Moreover, patients with PACG were treated at the discretion of the treating clinicians, who were expected to delay VF loss progression. Although multivariate Cox regression and multivariate logistic regression analyses were adjusted for the number of eyes that received topical glaucoma medications, therapeutic schedules modified based on the patients' current conditions may have also affected these risk factors.

**Table 4** Univariate and multivariate logistic regression analyses to identify risk factors for progression of PACG

	Univariate		Multivariate	
	P-value	OR (95%CI)	P-value	OR (95%CI)
Age	0.97	1.00 (0.98–1.02)		
Sex	0.20	1.40 (0.84–2.32)		
Diabetes	0.81	1.11 (0.49–2.51)		
Hypertension	0.73	1.11 (0.62–1.96)		
BMI	0.15	0.95 (0.88–1.02)	0.12*	0.77 (0.55–1.07)
SBP	0.88	1.00 (0.99–1.01)		
DBP	0.40	0.99 (0.97–1.01)		
Duration	0.52	1.00 (0.99–1.02)		
Medications	0.45	0.97 (0.93–1.01)		
IOP	0.14	1.01 (1.00–1.03)	0.21**	1.04 (0.98–1.11)
VCDR	0.12	0.44 (0.16–1.23)	0.42**	0.20 (0.01–9.73)
CCT	0.41	1.00 (0.99–1.00)		
ACD	0.92	1.03 (0.62–1.70)		
AL	0.38	1.10 (0.89–1.37)		
MD	0.36	0.99 (0.96–1.02)		
PLR	0.04	1.01 (1.00–1.01)	0.049 <sup>⊗</sup>	1.01 (1.00–1.01)
			0.004 <sup>#</sup>	1.05 (1.01–1.08)
Male	0.05	1.01 (1.00–1.02)	0.05 <sup>#</sup>	1.01 (1.00–1.02)
Female	0.04	1.01 (1.00–1.01)	0.03 <sup>#</sup>	1.01 (1.00–1.02)
NLR	0.42	1.09 (0.89–1.33)	0.42 <sup>⊗</sup>	1.01 (0.89–1.33)
			0.15 <sup>#</sup>	2.02 (0.77–5.29)
Male	0.57	1.08 (0.82–1.42)	0.40 <sup>#</sup>	1.14 (0.84–1.56)
Female	0.11	1.30 (0.94–1.80)	0.17 <sup>#</sup>	1.26 (0.91–1.75)
LMR	0.66	1.04 (0.88–1.22)	0.66 <sup>⊗</sup>	1.04 (0.88–1.22)
			0.51 <sup>#</sup>	1.23 (0.67–2.23)
Male	0.82	1.03 (0.78–1.37)	0.63 <sup>#</sup>	1.09 (0.78–1.52)
Female	0.74	0.97 (0.79–1.19)	0.89 <sup>#</sup>	0.99 (0.80–1.22)

*BMI* body mass index; *SBP* systolic blood pressure; *DBP* diastolic blood pressure, *IOP* intraocular pressure, *VCDR* vertical cup-to-disc ratio, *AL* axial length, *CCT* central corneal thickness, *ACD* anterior chamber depth, *MD* mean deviation, *NLR* neutrophil to lymphocyte ratio, *PLR* platelet to lymphocyte ratio, *LMR* lymphocyte to monocytes ratio, *PACG* primary angle closure glaucoma

\*Multivariate logistic regression was adjusted for age, sex, SBP, DBP, duration, medications, IOP, VCDR, CCT, ACD, AL MD, diabetes (yes=1, no=0), and hypertension (yes=1, no=0) \*\*Multivariate logistic regression was adjusted for age, sex, SBP, DBP, duration, medications, CCT, ACD, AL MD, BMI, diabetes (yes=1, no=0), and hypertension (yes=1, no=0). <sup>#</sup>Multivariate logistic regression was adjusted for age, sex, SBP, DBP, duration, medications, IOP, VCDR, CCT, ACD, AL MD, BMI, diabetes (yes=1, no=0), and hypertension (yes=1, no=0). <sup>⊗</sup>Multivariate logistic regression was adjusted for age

## Strength and limitations

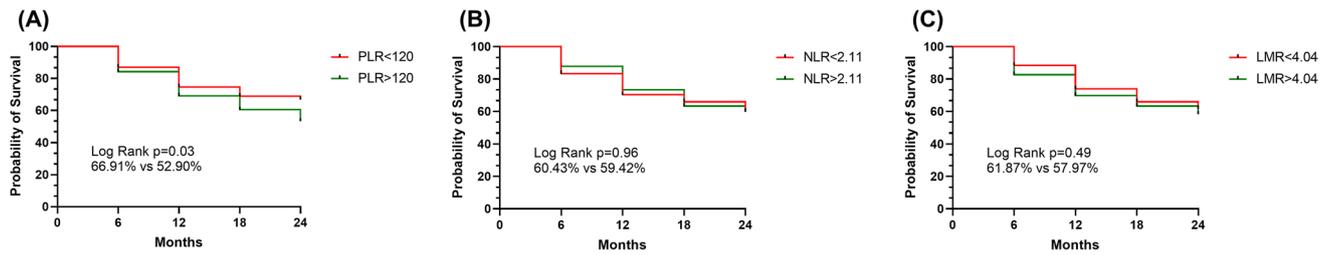
In this study, the relationship between PLR and VF loss progression was systematically analyzed to promote PPPM-attitude-based glaucoma management. Our study has several strengths. First, we used a large sample with a

**Table 5** Univariate Cox proportional hazards regression analysis and multivariate Cox proportional hazards regression analysis to assess the value of baseline parameters associated with progression of PACG

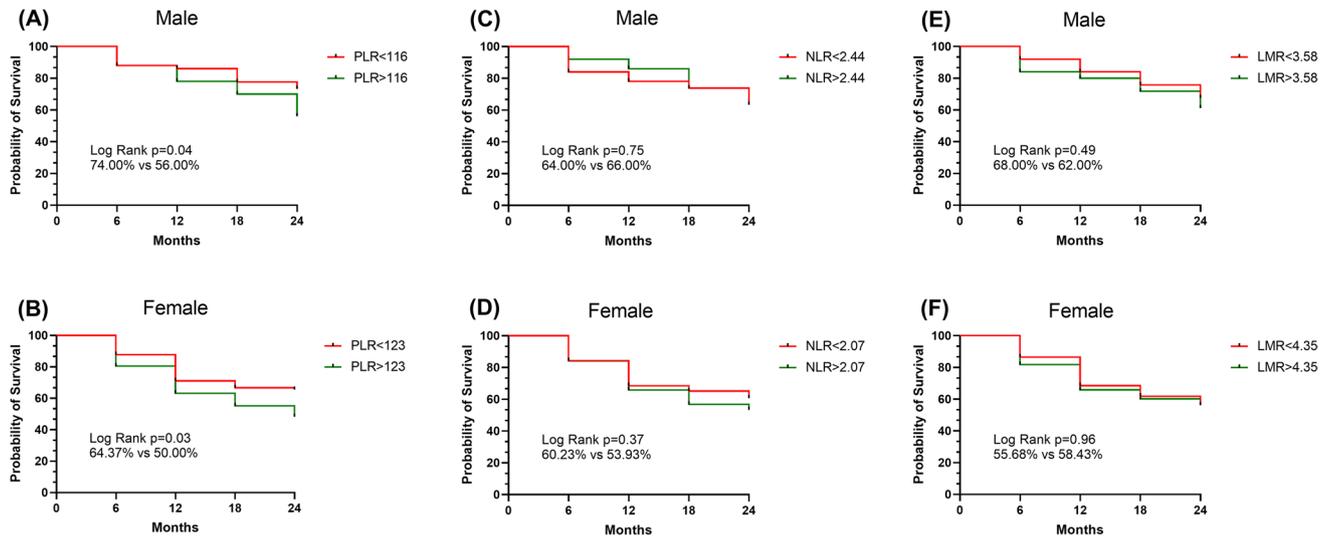
	Univariate		Multivariate	
	P-value	HR (95%CI)	P-value	HR (95%CI)
Age	0.94	1.00 (0.98–1.02)		
Sex	0.19	1.31 (0.88–1.95)	0.77*	1.07 (0.68–1.69)
Diabetes	0.84	1.07 (0.57–1.99)		
Hypertension	0.76	1.07 (0.69–1.66)		
BMI	0.18	0.96 (0.90–1.02)	0.53*	0.98 (0.91–1.05)
SBP	0.86	1.00 (0.99–1.01)		
DBP	0.33	0.99 (0.97–1.01)		
Duration	0.44	1.00 (0.99–1.01)		
Medications	0.42	1.01 (0.97–1.04)		
IOP	0.05	1.01 (1.00–1.02)	0.007**	1.01 (1.00–1.02)
VCDR	0.15	0.56 (0.25–1.24)	0.12**	0.47 (0.18–1.21)
CCT	0.42	1.00 (0.99–1.00)		
ACD	0.93	1.02 (0.70–1.48)		
AL	0.55	1.05 (0.90–1.22)		
MD	0.46	0.99 (0.97–1.01)		
PLR	0.09	1.00 (1.00–1.01)	0.04 <sup>⊗</sup>	1.00 (1.00–1.01)
			0.04 <sup>#</sup>	1.01 (1.00–1.01)
			0.043 <sup>§</sup>	1.005 (1.00–1.011)
Male	0.08	1.01 (1.00–1.01)	0.046 <sup>#</sup>	1.01 (1.00–1.01)
Female	0.048	1.01 (1.00–1.01)	0.049 <sup>#</sup>	1.01 (1.00–1.01)
NLR	0.39	1.07 (0.92–1.24)	0.39 <sup>⊗</sup>	1.07 (0.92–1.24)
			0.60 <sup>#</sup>	1.06 (0.85–1.33)
			0.85 <sup>§</sup>	1.01 (1.00–1.03)
Male	0.56	1.06 (0.87–1.31)	0.24 <sup>#</sup>	1.20 (0.89–1.62)
Female	0.08	1.22 (0.98–1.52)	0.082 <sup>#</sup>	1.22 (0.98–1.02)
LMR	0.57	1.04 (0.92–1.17)	0.56 <sup>⊗</sup>	1.04 (0.92–1.18)
			0.72 <sup>#</sup>	1.03 (0.87–1.23)
			0.56 <sup>§</sup>	1.07 (0.85–1.35)
Male	0.81	1.03 (0.82–1.30)	0.34 <sup>#</sup>	1.17 (0.85–1.61)
Female	0.87	0.99 (0.84–1.16)	0.88 <sup>#</sup>	0.99 (0.84–1.16)

*BMI* body mass index; *SBP* systolic blood pressure; *DBP* diastolic blood pressure, *IOP* intraocular pressure, *VCDR* vertical cup-to-disc ratio, *AL* axial length, *CCT* central corneal thickness, *ACD* anterior chamber depth, *MD*=mean deviation, *NLR* neutrophil to lymphocyte ratio, *PLR* platelet to lymphocyte ratio, *LMR* lymphocyte to monocytes ratio, *PACG* primary angle closure glaucoma

\*Multivariate Cox regression analysis was adjusted for age, SBP, DBP, duration, medications, CCT, ACD, AL MD, diabetes (yes=1, no=0), and hypertension (yes=1, no=0). \*\*Multivariate Cox regression analysis was adjusted for age, sex, SBP, DBP, duration, medications, CCT, ACD, AL MD, BMI, diabetes (yes=1, no=0), and hypertension (yes=1, no=0). <sup>#</sup>Multivariate Cox regression analysis was adjusted for age, sex, SBP, DBP, duration, medications, IOP, VCDR, CCT, ACD, AL MD, BMI, diabetes (yes=1, no=0), and hypertension (yes=1, no=0). <sup>⊗</sup>Multivariate Cox regression analysis was adjusted for age. <sup>§</sup>Multivariate Cox regression analysis was adjusted for IOP



**Fig. 5** Kaplan–Meier curves stratified via the median value in terms of PLR (A), NLR (B), and LMR levels (C). NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; LMR, lymphocyte to monocytes ratio



**Fig. 6** Kaplan–Meier curves stratified via the median value in terms of PLR, NLR, and LMR levels in the male (A, C, E) and female (B, D, F) subgroups. NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; LMR, lymphocyte to monocytes ratio

well-characterized PACG diagnosis at baseline and performed standard protocols to measure VF loss progression during the entire follow-up period. Second, multivariate Cox regression analyses and multivariate logistic regression analyses were performed to adjust for many factors, including disease duration and topical glaucoma medications, to avoid bias. Furthermore, we also found that higher IOP was significantly associated with an increased risk of VF loss progression, which is consistent with the results of previous studies. Our findings exhibit strong predictive abilities of PLR for the early identification of faster VF loss progression in patients with PACG. Thus, PLR can be used as potential VF loss progression biomarker for the predictive diagnosis, population risk stratification, and personalized management towards glaucoma.

This study has several limitations. First, this study was conducted in a single center; thus, further multicenter studies including several different ethnicities are warranted. Second, although the baseline PLR was associated with VF loss progression, this parameter may interact with several other factors, including mediators; this does not necessarily imply that modifying them alone will have significant effects on the

results. Third, PLR, as a one-time blood level of molecules in the peripheral blood, may not substitute for the existing PLR in the retina/optic nerve. However, to the best of our knowledge, measuring the platelet and lymphocyte counts in the retina/optic nerve by current detection technology is difficult. Finally, although PLR is a comparable, stable, and reliable marker, whether the PLR was different before and after medical treatment for glaucoma is still unknown. Thus, further multicenter studies including several times blood level of molecules in the peripheral blood are warranted.

## Conclusions and expert recommendations

### Conclusions

The early identification of patients with rapid VF loss progression may be a cost-effective way for the targeted prevention and personalized therapy of glaucoma diseases. In this study, three system inflammation indices (PLR, NLR, and LMR) to predict the VF loss progression in patients with

PACG were analyzed. The present study clearly revealed the potential value of PLR for the predictive identification of higher risk of glaucoma VF loss progression from the perspective of PPPM.

We suggest that PLR should be taken into consideration for PPPM. The elevated PLR in the progression group indicated that systemic inflammation disorder plays a significant role in the progression of PACG. Furthermore, we demonstrated that a higher PLR was a risk factor for VF loss progression and that a higher PLR at baseline was significantly associated with VF loss progression in patients with PACG. Our results suggested that PLR may be used as a novel biomarker to predict VF loss progression. In this context, a simple, non-invasive, and reliable PACG VF loss progression risk assessment appears to be a plausible approach for early/predictive of progression of PACG, which may lead to a more efficient treatment tailored to the patient and prevent progression of glaucoma damage, especially in patients with PACG. These results may facilitate the development of PPPM in patients with PACG.

## Expert recommendations

In agreement with EPMA strategies, our findings determined the potential utility of system anti-inflammatory therapy for targeted prevention and personalized therapy of PACG, especially for patients with elevated PLR. Earlier prediction of glaucoma in patients with a higher risk of VF loss progression would enable the use of different treatment strategies to reduce the economic and clinical burden and avoid secondary effects associated with unnecessary treatments. Actually, systemic inflammation indices alterations are involved in the entire healthcare process of a glaucoma patient, including prediction/prevention, early-stage diagnosis/therapy, and prognostic assessment in the framework of PPPM/3P medicine [75].

To provide greater possibility of PPPM for personalized treatment, we also recommend that (1) the assessment of systemic inflammation indices should be mandatory in all 3PM (personalized medicine, targeted prevention, and predictive diagnostics) disciplines to get a global insight into an individual's current health condition[76]; (2) monitoring of systemic inflammation indices could be a personalized-preventive strategy for glaucomatous VF loss progression. Thus, clinicians would be establishing a customized treatment plan by monitoring systemic inflammation indices alterations to prevent further glaucomatous damage, which is a key concept in PPPM; (3) we recommend the utilization of multi-omics in PPPM-associated studies of glaucoma. Strengthen the studies of system inflammation in PACG using different omics strategies.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s13167-021-00260-3>.

**Author contribution** Shengjie Li and Wenjun Cao contributed to the study conception and design, data analysis, interpretation of the data, and drafting the manuscript. Yichao Qiu, Jian Yu, Yingzhu Li, and Mingxi Shao contributed to the interpretation of the data and critical revision of the manuscript. Shengjie Li, Yichao Qiu, Jian Yu, Yingzhu Li, Xinghuai Sun, and Mingxi Shao contributed to the collection of the data. All authors read and approved the final manuscript.

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**Data availability** The datasets generated in the current research can be obtained from the supplementary material.

**Code availability** Not applicable.

## Declarations

**Ethics approval and consent for participation** The Ethics Committee of the Eye and ENT Hospital of Fudan University approved this study (EENT2015011), and the study adhered to the principles of the Declaration of Helsinki. Informed consent was obtained from all subjects.

**Consent for publication** All individuals were informed about the purposes of the study and have signed their consent for publishing the data.

**Conflict of interest** The authors declare no competing interests.

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