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Comparison of NLR, PLR, SII, and SIRI for Discriminating Severe Primary Open-Angle Glaucoma in a Cross-Sectional Study

Herabaradena Putri[1*], Prima Maya Sari[1], Nurmalia Purnama Sari[2], Erial Bahar[3]

[1]Department of Ophthalmology, Faculty of Medicine, Universitas Sriwijaya, Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia
[2]Department of Clinical Pathology, Faculty of Medicine, Universitas Sriwijaya, Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia
[3]Department of Public Health and Biostatistics, Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia

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Corresponding author:
Herabaradena Putri
E-mail address:
herabaradenap@gmail.com

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ABSTRACT

Introduction. Primary open-angle glaucoma (POAG) is a leading cause of irreversible blindness, with a 3.0% national blindness prevalence. Chronic low-grade inflammation is increasingly implicated in POAG, but few studies compare how these indices track severity rather than detect it. Objective. To compare the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and systemic inflammatory response index (SIRI) in discriminating severe from mild/moderate POAG. **Methods.** This cross-sectional study enrolled 45 patients (90 eyes) at Dr. Mohammad Hoesin Hospital. Severity was staged by the Hodapp-Parrish-Anderson classification and dichotomized as severe (48 eyes) versus mild/moderate (42 eyes), with the four indices derived from complete blood counts. Analyses used generalized estimating equations (GEE) for within-patient eye clustering. **Results.** Patients averaged 57.4±10.3 years, 60.0% female, with 53.3% of eyes (48/90) severe. All four indices remained associated with severity under GEE ($p<0.05$; SIRI $p=0.043$, the narrowest margin). On non-clustered ROC analysis, SII showed the highest AUC (0.803) and accuracy (80.0%), ahead of NLR (0.785), PLR (0.729), and SIRI (0.622). Bootstrap validation (500 replications) confirmed these cut-offs and AUCs; only the NLR-SIRI AUC gap reached significance ($p=0.032$–0.052), with SII-SIRI borderline ($p=0.044$–0.060). **Conclusion.** All four indices remained associated with severity after clustering adjustment, with SIRI's margin consistently the narrowest. SII showed the highest apparent discriminative performance, and bootstrap validation supports a real AUC disadvantage for SIRI versus NLR; broader superiority among the other three remains unestablished pending external validation. None of the four markers should replace intraocular pressure measurement or structural-functional evaluation.

1. Introduction

Primary open-angle glaucoma (POAG) causes progressive damage to the optic nerve and retinal ganglion cells, driven mainly by impaired aqueous humor outflow through the trabecular meshwork despite an anatomically open anterior chamber angle.[1,2] As of 2020, among adults aged 50 and older worldwide, glaucoma as a group of diseases, not POAG specifically, accounted for an estimated 3.6 million of the 33.6 million cases of blindness, a measure of blindness attributable to glaucoma rather than glaucoma prevalence itself.[1–4] POAG specifically, as distinct from glaucoma overall, has a pooled global prevalence of 2.4% (95% CI 2.0–2.8%) among the general adult population, based on a 2021 meta-analysis of 50 population-based studies conducted between 2000 and 2020, corresponding to an estimated 68.56 million people currently living with POAG worldwide.[5] In Indonesia, a Rapid Assessment of Avoidable Blindness (RAAB) survey conducted among adults aged 50 and older (fieldwork 2013–2017) found an all-cause blindness prevalence of 3.0%.[1]

Elevated intraocular pressure (IOP) remains the best-established risk factor, but a growing line of research suggests that inflammation also plays a meaningful role in how the disease progresses. Disruption of the blood–retina and blood–brain barriers appears to trigger pro-apoptotic signalling in retinal ganglion cells once optic nerve head perfusion is compromised, and disturbed vascular autoregulation can set up repeated cycles of ischemia and reperfusion injury.[6,7] Interleukin-6 (IL-6), tumor necrosis factor (TNF), and C-reactive protein (CRP) have been proposed as potential biomarkers of disease severity. However, their routine clinical application remains limited by the relatively high costs of testing and the need for specialized

laboratory facilities, particularly in resource-limited healthcare settings.[8,9]

Among these inflammatory markers, the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been extensively investigated.[10] Several studies have reported significantly higher NLR values in patients with primary open-angle glaucoma (POAG) compared with healthy controls.[11–13] However, the findings remain inconsistent. A case-control study reported no statistically significant differences in NLR among patients with open-angle glaucoma, angle-closure glaucoma, and healthy controls ($p = 0.076$).[14] In contrast, PLR has demonstrated more consistent associations with glaucoma, with several studies reporting elevated PLR values in patients with glaucoma compared with healthy controls.[14–16]

Two additional composite inflammatory indices, the systemic immune-inflammation index (SII) and systemic inflammatory response index (SIRI), have recently gained attention as potentially useful biomarkers due to their accessibility and ease of calculation using routinely available hematological parameters. However, evidence regarding their associations with glaucoma remains limited and inconsistent across studies. A large population-based study reported significantly elevated SII levels among individuals with glaucoma or cataract.[17] Similarly, an analysis of data from the National Health and Nutrition Examination Survey (NHANES) identified a modest but statistically significant association between SIRI and glaucoma.[12,18] Nevertheless, the reported diagnostic performance of these indices has varied considerably. One case-control study reported an exceptionally high area under the receiver operating characteristic curve (AUC) of 0.986 for SII,[19] substantially exceeding the values reported in other studies. Such discrepancies may reflect differences in sample size, study populations, and methodological approaches, highlighting the need for further validation in larger, well-designed studies.

What has been largely missing from this literature is a direct, within-population comparison of all four indices (NLR, PLR, SII, and SIRI) specifically for grading disease severity, rather than simply separating POAG patients from healthy controls. The distinction matters clinically: a marker that helps confirm the presence of glaucoma is not necessarily the marker that helps a clinician judge how advanced a given patient's disease already is, which is usually the more immediate question once the diagnosis itself is no longer in doubt. To our knowledge, no previous study has made this particular comparison in an Indonesian population, where limited access to perimetry and optical coherence tomography outside major cities makes an inexpensive, blood-based severity marker a genuinely attractive option.

We therefore designed this study to compare the accuracy of NLR, PLR, SII, and SIRI in predicting POAG severity among patients treated at Dr. Mohammad Hoesin General Hospital, Palembang, with the broader aim of identifying which of these readily available markers might best support severity-based risk stratification in settings where more sophisticated diagnostic tools are not always within reach.

2. Methods

This observational analytic study employed a cross-sectional design and was conducted at the Glaucoma Clinic of Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia, between July and December 2025. Consecutive sampling was used to recruit patients with primary open-angle glaucoma (POAG) who met the eligibility criteria during the study period. The minimum required sample size was estimated at 69 patients using a diagnostic sensitivity-based calculation, assuming an expected sensitivity of 90%, an absolute precision of 10%, a 95% confidence level, and an estimated prevalence of severe POAG of 50.3% based on a previous study.[20]

Patients aged 40–80 years with a confirmed diagnosis of POAG were eligible for inclusion. The diagnosis was established by a glaucoma subspecialist based on gonioscopy confirming an open anterior chamber angle, fundus examination, optical coherence tomography (OCT), and visual field testing.[2] Additional inclusion criteria were reliable visual field results, willingness to undergo complete blood count testing, and provision of written informed consent. Patients with ocular infections or intraocular surgery within the preceding six months, active systemic infections or acute illnesses, hematological or immunological disorders, chronic systemic diseases (including hypertension, diabetes mellitus, chronic kidney disease, chronic liver disease, and rheumatoid arthritis), current chemotherapy or corticosteroid treatment, or pregnancy were excluded. Patients unable to complete visual field testing or unwilling to provide informed consent were also excluded. Patients with normal-tension glaucoma were excluded, and only those with POAG associated with elevated intraocular pressure were included. Both eyes were assessed independently for eligibility and disease severity.

POAG severity was classified as mild, moderate, or severe according to the Hodapp–Parrish–Anderson (HPA) classification, based on visual field mean deviation (MD), pattern deviation, and central visual field defects.[21] Mild glaucoma was characterized by an MD better than −6 dB, moderate glaucoma by an MD between −6 and −12 dB, and severe glaucoma by an MD worse than −12 dB or advanced visual field loss, with the remaining HPA criteria also considered. Visual field examinations were performed using the Henson 9000 perimeter (Elektron Technology, Cambridge, UK) with a 24-2 testing pattern and the Zippy Adaptive Threshold Algorithm (ZATA). Visual field reliability was assessed using fixation loss, false-positive, and false-negative response indices, and

unreliable examinations were repeated. Previous evidence supporting agreement between Henson and Humphrey perimetry in HPA severity classification was considered in applying this grading system.[22]

The inflammatory indices evaluated were the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and systemic inflammatory response index (SIRI). These indices were calculated from absolute blood cell counts using the following formulas: NLR = neutrophil count/lymphocyte count; PLR = platelet count/lymphocyte count; SII = (platelet count × neutrophil count)/lymphocyte count; and SIRI = (neutrophil count × monocyte count)/lymphocyte count. All calculations were performed using unrounded absolute cell counts. NLR and PLR were expressed as dimensionless ratios, whereas SII and SIRI were expressed in $\times 10^3$ cells/μL.

Ophthalmological examinations included visual acuity assessment using a Snellen chart, intraocular pressure measurement using a Tomei FT-700 non-contact tonometer, anterior segment examination using a Carl Zeiss slit lamp, and optic nerve head assessment using a Topcon DRI OCT Triton. Intraocular pressure was measured three times in each eye, and the mean value was used for analysis. Measurements were obtained while patients continued their prescribed glaucoma medications.

Venous blood samples were collected into tubes containing tripotassium ethylenediaminetetraacetic acid (K3EDTA) and analyzed using a Sysmex XN-20 automated hematology analyzer (Sysmex Corporation, Kobe, Japan). All samples were processed on the day of collection in the hospital's clinical pathology laboratory under routine quality-control procedures. Absolute neutrophil, lymphocyte, monocyte, and platelet counts were obtained from the complete blood count results.

Clinical and laboratory data were collected during a single study visit. Demographic characteristics, medical history, glaucoma duration, and treatment history were obtained through structured interviews and clinical examinations. Ophthalmological assessments and severity grading were completed before venous blood collection. No formal blinding was implemented between clinical severity assessment and biomarker measurement.

Descriptive data were presented as frequencies and percentages for categorical variables and as means with standard deviations or medians with ranges for continuous variables, according to their distributions. Patient-level characteristics and eye-level clinical findings were reported separately according to their respective units of observation.

For statistical analysis, POAG severity was dichotomized into severe and mild/moderate categories, with mild/moderate POAG serving as the reference group. Categorical comparisons were performed using the chi-square test or Fisher's exact test, as appropriate. Generalized estimating equations (GEE) with a binomial distribution and logit link were used to evaluate associations between inflammatory indices and POAG severity while accounting for within-patient correlation between fellow eyes. Patients were specified as the clustering units, with an exchangeable working correlation structure applied to the final models. Robust standard errors were used to estimate confidence intervals and statistical significance.

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the ability of NLR, PLR, SII, and SIRI to discriminate severe POAG from mild/moderate POAG. The area under the ROC curve (AUC) was calculated for each biomarker, and optimal cut-off values were determined using the Youden index. Sensitivity, specificity, positive predictive value, negative predictive value, and overall diagnostic accuracy were calculated at the corresponding cut-offs. Patient-level bootstrap resampling was used to estimate 95% confidence intervals for diagnostic performance measures while accounting for within-patient clustering.

Multivariable GEE logistic regression analyses were performed separately for each inflammatory index to assess its association with POAG severity after adjustment for potential confounding factors, including age, sex, intraocular pressure, glaucoma duration, and treatment history. Inflammatory indices were entered as continuous variables, and glaucoma duration was categorized as <1 year, 1–5 years, and >5 years, with <1 year as the reference category. Backward elimination was applied using a removal criterion of $p > 0.10$. An independence working correlation structure was used during variable selection when the initial exchangeable models failed to converge, and the final models were refitted using an exchangeable correlation structure. All statistical analyses were performed using SPSS version 29.0, with statistical significance set at $p < 0.05$.

The study was approved by the Health Research Ethics Committee of Dr. Mohammad Hoesin General Hospital, Palembang (No. DP.04.03/D.XVIII.06.08/ETIK/243/2025). Written informed consent was obtained from all participants before enrollment.

3. Results

Of the 154 patients with primary open-angle glaucoma (POAG) who presented to the Glaucoma Clinic during the six-month study period, 45 patients (90 eyes) met the eligibility criteria and were enrolled. Patient-level characteristics, including age, sex, POAG duration, and treatment history, were assessed in 45 patients, whereas eye-level characteristics, including disease severity and intraocular pressure, were assessed in 90 eyes (Table 1). The mean age was 57.38 ± 10.34 years, with the largest proportion of patients aged 51–60 years (44.4%). Female patients accounted for 60.0% of the

study population, while male patients accounted for 40.0%. Severe POAG was the most common severity grade (48 eyes, 53.3%), followed by mild (22 eyes, 24.4%) and moderate POAG (20 eyes, 22.2%).

The median duration of POAG was 1 year (range: 0–6 years). Most patients (57.8%) had been diagnosed 1–5 years before enrollment, while 33.3% had been diagnosed less than 1 year earlier and 8.9% more than 5 years earlier. Treatment adherence was assessed based on patients' reported compliance with their prescribed glaucoma medication regimens.23 Patients were classified as having regular adherence if they consistently followed their prescribed treatment and irregular adherence if they reported repeated missed doses or treatment discontinuation without medical advice. Regular treatment adherence was reported in 73.3% of patients (33/45), while 26.7% (12/45) reported irregular adherence. The mean intraocular pressure across 90 eyes was 22.43 ± 4.06 mmHg (Table 1).

Bilateral concordance in POAG severity was assessed using a binary classification (severe vs. mild/moderate) to account for potential differences in disease severity between the two eyes of the same patient. Of the 45 patients, 35 (77.8%) had concordant severity classifications in both eyes, whereas 10 (22.2%) had discordant classifications. Severe POAG was present in at least one eye in 29 patients (64.4%), including 19 (42.2%) with bilateral severe POAG and 10 (22.2%) with unilateral severe POAG. The remaining 16 patients (35.6%) had no severe POAG in either eye. Table 1b presents baseline characteristics stratified by the severity of the worse-affected eye, categorized as severe or non-severe. This patient-level classification complements the subsequent eye-level analyses.

Current glaucoma medications are summarized in Table 1c. Topical timolol, a non-selective beta-blocker, was the most frequently prescribed medication (41/45 patients, 91.1%), followed by latanoprost, a prostaglandin analog (34/45, 75.6%), and brinzolamide, a topical carbonic anhydrase inhibitor (26/45, 57.8%). Other medications included oral acetazolamide (6/45, 13.3%), topical brimonidine (1/45, 2.2%), and topical pilocarpine (1/45, 2.2%). Combination therapy involving two or more medication classes was used by 33 patients (73.3%), most commonly comprising three medication classes (17/45, 37.8%). The remaining 12 patients (26.7%) received monotherapy.

Table 1. General Characteristic of Study Subjects

Variable	Subject, n (%)	Mean ± SD	Median (Min-Max)
Age (years)		57.38 ± 10.34	
Age Group			
40-50 years	10 (22.2)		
51-60 years	20 (44.4)		
61-70 years	10 (22.2)		
>70 years	5 (11.1)		
Sex			
Male	18 (40)		
Female	27 (60)		
POAG Severity (90 eyes)			
Mild POAG	22 (24.4)		
Moderate POAG	20 (22.2)		
Severe POAG	48 (53.3)		
POAG Duration			1 (0-6)
<1 years	15 (33.3)		
1-5 years	26 (57.8)		
>5 years	4 (8.9)		
POAG Treatment History			
Regular	33 (73.3)		
Irregular	12 (26.7)		
Intraocular Pressure (90 Eyes)		22.43 ± 4.06	

Table 1b. Characteristics by Worse-Eye POAG Severity Status (n=45 patients)

Worse-eye status	n	Age, mean±SD	Sex M/F	NLR, median (range)	PLR, median (range)	SII, median (range)	SIRI, median (range)
Non-severe (mild/ moderate)	16	55.9 ± 9.7	7 / 9	2.08 (1.75–2.38)	138.8 (88.9–174.7)	581.2 (437.5–910.0)	1.18 (0.80–1.97)
Severe	29	58.2 ± 10.8	11 / 18	2.26 (1.50–3.29)	150.3 (113.7–204.3)	684.1 (518.3–1409.6)	1.30 (0.58–3.28)

Table 1c. Current Glaucoma Medication (n=45 patients)

Variable	Patients, n (%)*
Medication class in use — 45 patients*	
Beta-blocker (timolol)	41 (91.1)
Prostaglandin analog (latanoprost)	34 (75.6)
Topical carbonic anhydrase inhibitor (brinzolamide)	26 (57.8)
Oral carbonic anhydrase inhibitor (acetazolamide)	6 (13.3)
Alpha-2 agonist (brimonidine)	1 (2.2)
Cholinergic agonist / miotic (pilocarpine)	1 (2.2)
Number of concurrent medication classes — 45 patients	
1 (monotherapy)	12 (26.7)
2	9 (20.0)
3	17 (37.8)
4	7 (15.6)

** Percentages for medication class do not sum to 100% because most patients used more than one class concurrently; see combination-therapy breakdown below.*

Table 2. Laboratory Characteristic of Study Subjects

Parameter	Mean ± SD	Median (Min-Max)	Normality p-value*
Neutrophil ($\times 10^3/\mu L$)	4.57 ± 0.85		0.127
Lymphocyte ($\times 10^3/\mu L$)	2.06 ± 0.32		0.200
Monocyte ($\times 10^3/\mu L$)	0.57 ± 0.13		0.200
Platelet ($\times 10^3/\mu L$)		287 (209–429)	0.005
NLR	2.23 ± 0.31		0.082
PLR	147.11 ± 23.13		0.200
SII		628.33 (437.5–1409.5)	0.029
SIRI	1.30 ± 0.42		0.074

*Kolmogorov-Smirnov normality test; p>0.05 indicates a normal distribution

Table 3. Bivariate association, optimal cut-off, and diagnostic accuracy of NLR, PLR, SII, and SIRI for severe POAG

Parameter	Cut-off	OR (95% CI)	AUC (95% CI)	Se (%)	Sp (%)	PPV (%)	NPV (%)	Accuracy (%)	Youden Index
NLR	≥2.38	16.714 (4.530–61.665)	0.785 (0.688–0.882)	56.3	92.9	90.0	65.0	73.3	49.2
PLR	≥138.21	5.246 (2.037–13.507)	0.729 (0.624–0.834)	81.3	54.8	67.2	71.9	68.9	36.1
SII	≥637.00	18.000 (6.092–53.185)	0.803 (0.705–0.901)	75.0	85.7	85.7	75.0	80.0	60.7
SIRI	≥1.36	5.023 (1.929–13.076)	0.622 (0.503–0.740)	54.2	81.0	76.5	60.7	66.7	35.2

Laboratory characteristics are presented in Table 2. The mean NLR, PLR, and SIRI values were 2.23 ± 0.31, 147.11 ± 23.13, and 1.30 ± 0.42, respectively. The median SII was 628.33 (range: 437.5–1409.5).

Chi-square analysis revealed significant associations between all four inflammatory biomarkers and POAG severity (all $p < 0.001$). SII demonstrated the strongest bivariate association (OR = 18.000; 95% CI: 6.092–53.185; $\chi^2 = 33.176$), followed by NLR (OR = 16.714; 95% CI: 4.530–61.665), PLR (OR = 5.246; 95% CI: 2.037–13.507), and SIRI (OR = 5.023; 95% CI: 1.929–13.076).

Further analysis using generalized estimating equations (GEE) to account for within-patient correlation confirmed significant associations between all four biomarkers and POAG severity. SII remained the most strongly associated biomarker (OR = 17.86; 95% CI: 5.32–62.50; $p < 0.001$), followed by NLR (OR = 16.67; 95% CI: 3.24–83.33; $p < 0.001$), PLR (OR = 5.24; 95% CI: 1.86–14.71; $p = 0.002$), and SIRI (OR = 5.03; 95% CI: 1.50–16.67; $p = 0.009$).

The optimal cut-off values and corresponding diagnostic performance measures, including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, and Youden index, are presented in Table 3. These estimates were derived from the study population without adjustment for within-patient correlation between fellow eyes.

To account for within-patient correlation, a patient-level cluster bootstrap analysis was performed using 500 replications. In each replication, patients were randomly resampled with replacement, with both eyes retained as a single cluster. The

optimal cut-off values and areas under the receiver operating characteristic curves (AUCs) were recalculated for all four biomarkers. Pairwise AUC differences were evaluated using the same bootstrap samples to preserve the correlation between biomarker estimates. Bootstrap 95% confidence intervals for the cut-off values and AUCs were calculated using the percentile method and are presented in Table 3b.

The bootstrap analysis also provided 95% confidence intervals for sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy (Table 3d). NLR showed an apparent sensitivity of 56.3%, with a bootstrap mean of 64.8% (95% CI: 41.5–86.1%). PLR demonstrated an apparent specificity of 54.8%, with a bootstrap 95% CI of 37.0–97.2%. The relatively wide confidence intervals indicated considerable uncertainty in the diagnostic performance estimates. Among the six pairwise AUC comparisons (Table 3c), a statistically significant difference was observed between NLR and SIRI (ΔAUC = 0.160; 95% CI: 0.011–0.305; p = 0.032). The comparison between SII and SIRI showed a difference of 0.179 (95% CI: −0.003–0.345), although statistical significance varied across bootstrap analyses (p = 0.044–0.060). No statistically significant differences were observed in the remaining comparisons (NLR vs. PLR, NLR vs. SII, PLR vs. SII, and PLR vs. SIRI; p = 0.21–0.71).

ROC curve analysis demonstrated statistically significant results for all four biomarkers (p < 0.001 for NLR, PLR, and SII; p = 0.048 for SIRI). SII exhibited the highest AUC (0.803), overall accuracy (80.0%), and Youden index (60.7%), whereas SIRI had the lowest AUC (0.622). The AUCs of SII and NLR were comparable (0.803 vs. 0.785; ΔAUC = 0.018). Pairwise AUC comparisons using patient-level cluster bootstrap analysis with 500 replications (Table 3c) revealed a statistically significant difference only between NLR and SIRI (p = 0.032). The comparison between SII and SIRI yielded inconsistent statistical significance across bootstrap analyses (p = 0.044–0.060), while the remaining comparisons showed no statistically significant differences. NLR demonstrated the highest specificity (92.9%) and positive predictive value (PPV; 90.0%), whereas PLR showed the highest sensitivity (81.3%) but lower specificity (54.8%). SII demonstrated a PPV of 85.7% and a negative predictive value (NPV) of 75.0%.

Table 3b. Internal Validation of Cut-offs and AUC via Cluster Bootstrap (500 Replications)

Biomarker	Cut-off, bootstrap 95% CI	AUC, bootstrap 95% CI
NLR	≥2.32 (2.21–2.48)	0.781 (0.647–0.897)
PLR	≥146.48 (131.80–163.56)	0.734 (0.613–0.842)
SII	≥636.22 (623.07–677.23)	0.805 (0.675–0.910)
SIRI	≥1.40 (1.30–1.57)	0.621 (0.473–0.760)

Table 3b. Internal Validation of Cut-offs and AUC via Cluster Bootstrap (500 Replications)

Biomarker	Se (%), bootstrap 95% CI	Sp (%), bootstrap 95% CI	PPV (%), bootstrap 95% CI	NPV (%), bootstrap 95% CI	Accuracy (%), bootstrap 95% CI
NLR	64.8 (41.5–86.1)	89.5 (65.3–100.0)	89.0 (66.1–100.0)	69.8 (54.2–85.7)	76.4 (66.7–86.7)
PLR	73.4 (40.9–97.2)	70.3 (37.0–97.2)	75.7 (54.7–95.5)	72.4 (52.6–94.4)	71.9 (61.1–82.2)
SII	79.5 (62.5–93.6)	83.6 (68.2–96.7)	84.7 (71.4–97.2)	78.3 (60.9–92.9)	81.3 (71.1–90.0)
SIRI	54.5 (33.3–74.2)	82.9 (64.3–97.5)	79.0 (60.4–95.8)	61.8 (47.1–77.3)	67.8 (57.8–78.9)

Table 3c. Pairwise AUC Comparison via Cluster Bootstrap (500 Replications)

Comparison	ΔAUC	95% CI (bootstrap)	p (bootstrap)
NLR vs. PLR	0.055	−0.093 to 0.186	0.500
NLR vs. SII	−0.018	−0.146 to 0.106	0.712
NLR vs. SIRI	0.160	0.011 to 0.305	0.032*
PLR vs. SII	−0.073	−0.202 to 0.041	0.212
PLR vs. SIRI	0.106	−0.106 to 0.304	0.316
SII vs. SIRI	0.179	−0.003 to 0.345	0.060

** p < 0.05, two-sided bootstrap p-value. ΔAUC = AUC of the first-named biomarker minus AUC of the second. p-values shown are from the SPSS-executed bootstrap; the independent Python re-implementation gave consistent conclusions (NLR vs. SIRI p=0.052; SII vs. SIRI p=0.044), with exact values differing slightly because the two implementations use different pseudo-random number generators for resampling, as expected for a Monte Carlo method.*

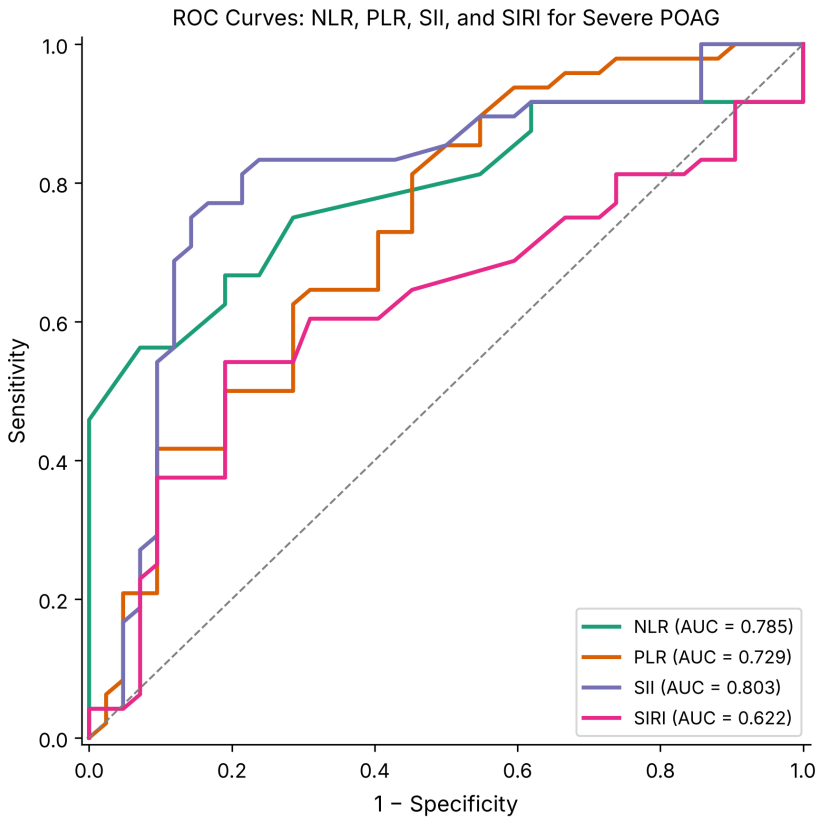


Figure 1. *Receiver operating characteristic (ROC) curves for NLR, PLR, SII, and SIRI in discriminating severe from mild/moderate POAG (90 eyes), computed directly from the authentic dataset (the same .sav file underlying the GEE and bootstrap analyses reported above), not from the manually transcribed placeholder used in an earlier draft. The dashed diagonal marks the line of no discrimination (AUC=0.5). The AUC shown beside each marker's curve (NLR 0.785, PLR 0.729, SII 0.803, SIRI 0.622) matches Table 3 to three decimal places, confirming the curves were generated from the same source data and the same Youden-based cut-off procedure used throughout this manuscript.*

Table 4. Summary of the Four Backward Multivariable Logistic Regression Models, Original and GEE-Clustered

Parameter	OR (95% CI) — original	p	OR (95% CI) — GEE-clustered*	p (GEE)	Retained covariates	Nagelkerke R^2 (original)	Classif. accuracy (%)
NLR	55.652 (8.133–380.799)	<0.001	58.82 (7.04–500)	<0.001	Age, IOP	0.600	78.9
PLR	9.546 (2.272–40.103)	0.002	8.70 (1.60–47.62)	0.012	IOP, duration, treatment	0.590	83.3
SII	12.615 (3.609–44.099)	<0.001	12.20 (2.93–50.0)	<0.001	IOP, duration	0.619	82.2
SIRI	4.584 (1.402–14.987)	0.012	4.83 (1.05–22.22)	0.043	IOP, duration	0.516	77.8

** GEE: generalized estimating equations with a robust, patient-clustered covariance estimator (45 clusters, 90 observations). For NLR and SII, backward elimination was carried out under an independence working correlation because the full six-covariate model would not converge under exchangeable; for PLR and SIRI, the full model converged under exchangeable correlation throughout. Once pared down, every final model was re-fit (or, for PLR/SIRI, already stood) under an exchangeable working correlation (removal criterion p>0.10, Wald test, at each elimination step). Retained covariates match the original logistic-regression models in every case; odds ratios are close to, but not numerically identical to, the original point estimates, since the GEE and ordinary-logistic fitting algorithms converge to slightly different coefficient values even on the same retained covariate set. Full parameter estimates (including intercepts and every covariate considered, not only those retained) and the covariate-by-covariate backward-elimination log underlying this table are reproduced in the accompanying SPSS analysis record. Classification accuracy in this table was computed from each model's predicted probabilities using the standard 0.50 cut-off applied by SPSS's logistic regression classification table; the corresponding confusion matrix (true/false positive and negative counts) for each of the four models is likewise provided in that same accompanying SPSS analysis record.*

Multivariable logistic regression with backward elimination was performed separately for each biomarker, adjusting for age, sex, intraocular pressure (IOP), POAG duration, and treatment history. All four biomarkers remained significantly associated with severe POAG in their respective adjusted models (Table 4). NLR demonstrated the highest adjusted odds ratio (OR = 55.652; 95% CI: 8.133–380.799; $p < 0.001$), with age and IOP retained in the final model. SII exhibited the highest Nagelkerke R^2 (0.619), with IOP and POAG duration retained as covariates. The PLR model achieved the highest overall classification accuracy (83.3%), with IOP, POAG duration, and treatment history retained. In contrast, the SIRI model showed the lowest odds ratio, Nagelkerke R^2, and classification accuracy. IOP was the only covariate retained across all four models.

Generalized estimating equation (GEE) analysis accounting for within-patient correlation confirmed significant associations between all four biomarkers and severe POAG. The covariates retained in the final models were consistent with those identified by conventional logistic regression. SIRI demonstrated the weakest statistical association ($p = 0.043$), whereas NLR exhibited the widest confidence interval (95% CI: 7.04–500), followed by PLR and SIRI, with SII showing the narrowest interval (95% CI: 2.93–50.0) in relative terms. The results of both conventional logistic regression and GEE analyses are presented in Table 4.

4. Discussion

The mean age of participants was 57.38 ± 10.34 years, with the largest proportion aged 51–60 years (44.4%). These findings are consistent with previous studies identifying increasing age as an established risk factor for POAG.[24] Age-related changes, including progressive stiffening of the lamina cribrosa and gradual loss of retinal ganglion cells, may contribute to increased susceptibility to glaucomatous optic nerve damage.[3,5,25]

Female patients accounted for 60.0% of the study population. In contrast, a meta-analysis by Zhang et al. identified male sex as a significant risk factor for POAG (RR = 1.28; 95% CI: 1.12–1.45; $p < 0.01$).[5] Meanwhile, Ehrlich et al. reported comparable age-standardized glaucoma prevalence between men and women in a US population-based study.[26] These differences may reflect variations in study populations, glaucoma subtypes, and study designs. The female predominance observed in the present study may also be influenced by clinic attendance patterns and may not reflect the sex distribution of POAG in the general population.

The mean intraocular pressure (IOP) was 22.43 ± 4.06 mmHg across 90 eyes. Elevated IOP is a major modifiable risk factor for POAG; however, glaucomatous optic neuropathy may also occur in patients with IOP below 22 mmHg.[2,27] The role of IOP in glaucomatous optic nerve damage can be explained by mechanical and vascular mechanisms. According to the mechanical theory, elevated IOP increases stress on the lamina cribrosa and disrupts axoplasmic transport, whereas the vascular theory suggests that reduced ocular perfusion may contribute to ischemic injury and oxidative stress. Furthermore, vascular dysregulation and alterations in blood–retinal barrier integrity may contribute to inflammatory responses involving neutrophils, platelets, and monocytes.[6,7] These mechanisms suggest a potential relationship between elevated IOP and systemic inflammation, consistent with the significant association of IOP with POAG severity across all four multivariable models in the present study.

The median duration of POAG was 1 year (range: 0–6 years), reflecting the time since clinical diagnosis rather than the actual onset of disease. Despite the relatively short recorded disease duration, severe POAG was observed in 53.3% of eyes. Similarly, a study conducted at a tertiary care center in South India reported severe glaucoma in more than 40% of newly diagnosed patients.[18,28] However, differences in patient characteristics and referral patterns may limit direct comparisons between studies. The high proportion of severe POAG in the present study may be attributed to the tertiary referral setting, where patients with more advanced disease are more likely to receive specialized care.

Neutrophil-to-lymphocyte ratio

The optimal NLR cut-off identified in this study was ≥2.38 (AUC = 0.785; 95% CI: 0.688–0.882), which falls within the gray zone of 2.3–3.0 proposed by Zahorec, indicating low-grade systemic inflammation.[30] This cut-off was higher than the threshold of 1.998 (AUC = 0.627) previously reported for distinguishing POAG patients from healthy controls and the reference range of 1–2 observed in healthy adults.[13,29] These differences may be attributed to variations in study populations, outcome measures, and disease severity. Similarly, a study involving 771 patients with primary angle-closure glaucoma reported an association between elevated NLR and glaucoma severity, with an AUC of 0.719.[30] These findings suggest that NLR may reflect inflammatory processes associated with glaucoma severity, although differences in glaucoma subtypes and study populations should be considered when interpreting cut-off values.

Elevated NLR in patients with severe POAG may reflect increased systemic inflammation associated with neutrophil activation and lymphocyte apoptosis. Delayed neutrophil apoptosis may prolong cytokine release and promote the formation of neutrophil extracellular traps (NETs),[31,32] which can contribute to endothelial dysfunction, vascular inflammation, and platelet aggregation.[33] However, a previous study reported no significant differences in NLR among patients with POAG, angle-closure glaucoma,

and healthy controls (p = 0.076).[14] These inconsistent findings may reflect differences in study populations, glaucoma subtypes, and clinical outcomes.

At a cut-off of ≥2.38, NLR demonstrated a sensitivity of 56.3%, specificity of 92.9%, positive predictive value (PPV) of 90.0%, negative predictive value (NPV) of 65.0%, and overall accuracy of 73.3%, with the highest specificity and PPV among the four biomarkers. These findings are consistent with previous reports suggesting the potential clinical utility of NLR in chronic inflammatory conditions.[10] Furthermore, a prospective study involving 277 patients with primary angle-closure glaucoma found that elevated baseline NLR was associated with subsequent visual field progression.[34] The high specificity and PPV observed in the present study suggest that NLR may serve as a complementary marker for identifying severe POAG. However, its relatively low sensitivity limits its utility for excluding severe disease, emphasizing the importance of conventional ophthalmological assessments and further validation before clinical implementation.[10]

Platelet-to-lymphocyte ratio

The optimal PLR cut-off identified in this study was ≥138.21 (AUC = 0.729; 95% CI: 0.624–0.834), indicating moderate discriminative ability in distinguishing severe POAG from mild/moderate disease. Ozgonul et al. reported significantly higher PLR values in patients with POAG compared with healthy controls (p = 0.049), although no specific PLR cut-off was established.[16] Similarly, a meta-analysis examining PLR and the lymphocyte-to-monocyte ratio in glaucoma reported elevated PLR levels among glaucoma patients, with variations across studies potentially attributable to differences in study populations, designs, and laboratory methods.[14]

Elevated PLR may reflect platelet activation and its involvement in inflammatory processes associated with glaucomatous optic nerve damage. Activated platelets contribute to inflammation through the release of inflammatory mediators, including platelet factor 4, serotonin, and interleukin-1β, as well as P-selectin-mediated interactions with neutrophils.[35,36] Previous studies have reported significantly elevated PLR in patients with POAG and angle-closure glaucoma compared with healthy controls.[14] Furthermore, a prospective study involving 277 patients with primary angle-closure glaucoma identified elevated PLR as a potential predictor of visual field progression, supporting its possible association with glaucoma severity and progression.[34]

At a cut-off of ≥138.21, PLR demonstrated a sensitivity of 81.3%, specificity of 54.8%, positive predictive value (PPV) of 67.2%, negative predictive value (NPV) of 71.9%, and overall accuracy of 68.9%. PLR exhibited the highest sensitivity among the four biomarkers, although its relatively low specificity may limit its ability to distinguish severe POAG from mild/moderate disease. These findings suggest that PLR may serve as a complementary inflammatory marker in assessing POAG severity. However, its diagnostic performance should be interpreted cautiously, as PLR alone may not reliably exclude severe disease and requires further validation before clinical application.

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Although a stepwise approach combining PLR with NLR or SII may have potential clinical utility in assessing POAG severity, its diagnostic performance has not been evaluated in the present study. Further studies are needed to determine the validity and clinical applicability of such an approach.The earlier suggestion of a stepwise PLR-to-NLR/SII diagnostic strategy has accordingly been removed, since its joint performance and clinical consequences have not been evaluated or validated in this or any other study to our knowledge; such a strategy would need dedicated evaluation before

being recommended.

Systemic immune-inflammation index

The systemic immune-inflammation index (SII) demonstrated the highest numerical discriminative performance among the four biomarkers, with an AUC of 0.803 (95% CI: 0.705–0.901), the strongest bivariate association (χ^2 = 33.176; OR = 18.000; 95% CI: 6.092–53.185), the highest overall accuracy (80.0%), and the highest Youden index (60.7). The optimal SII cut-off of ≥637.00 was higher than the threshold of 449.4 previously reported for distinguishing patients with pseudoexfoliation syndrome from healthy controls.[37] However, differences in disease characteristics and study objectives limit direct comparisons between these thresholds. Similarly, Tang et al. reported a substantially higher AUC of 0.986 for distinguishing patients with POAG from healthy controls.[13] These differences may reflect variations in study populations, disease severity, and methodological approaches, highlighting the need for further validation.

SII incorporates neutrophil, platelet, and lymphocyte counts, potentially reflecting multiple components of the systemic inflammatory response associated with glaucomatous optic nerve damage. However, its inclusion of three hematological parameters does not necessarily indicate greater measurement stability or precision than NLR or PLR. A previous study involving patients with keratoconus reported higher discriminative performance for SII than for NLR and PLR.[17,38] Furthermore, a large population-based cross-sectional study identified associations between elevated SII and several ocular diseases, supporting its potential relevance as a marker of ocular inflammatory processes.[17]

At a cut-off of ≥637.00, SII demonstrated a sensitivity of 75.0%, specificity of 85.7%, positive predictive value (PPV) of 85.7%, negative predictive value (NPV) of 75.0%, and overall accuracy of 80.0%. These findings suggest that SII may serve as a complementary biomarker for assessing POAG severity, although its numerical advantage over the other inflammatory indices does not establish statistically significant superiority. A population-based study in the United States also reported an association between SII and cataract, further suggesting a potential relationship between systemic inflammation and ocular diseases.[39] Nevertheless, further studies involving larger, independent populations are needed to validate the optimal cut-off and determine the additional clinical value of SII alongside conventional ophthalmological assessments.

Systemic inflammatory response index

The systemic inflammatory response index (SIRI) demonstrated the lowest discriminative performance among the four biomarkers, with an AUC of 0.622 (95% CI: 0.503–0.740), sensitivity of 54.2%, negative predictive value (NPV) of 60.7%, and overall accuracy of 66.7%. A population-based study using National Health and Nutrition Examination Survey (NHANES) data reported a significant association between SIRI and glaucoma (OR = 1.24; 95% CI: 1.07–1.44), with an AUC of 0.674 for the fully adjusted model.[12] However, direct comparison is limited by differences in study populations, outcomes, and analytical approaches. Similarly, a study involving patients with retinal vein occlusion reported lower predictive performance for SIRI than for NLR and SII.[40] These findings suggest that SIRI may have relatively limited discriminative ability compared with other inflammatory indices, although further studies are needed to establish its clinical relevance in POAG.[12]

The relatively limited performance of SIRI may be associated with the heterogeneous roles of monocytes in inflammatory responses. Monocytes can differentiate into macrophages with either pro-inflammatory or anti-inflammatory functions, depending on the cellular environment and disease context.[41,42] These mechanisms may influence the relationship between circulating monocyte counts and glaucomatous neuroinflammation, although circulating monocytes and resident retinal microglia represent distinct immune cell populations.[41] Despite its lower discriminative performance, SIRI remained significantly associated with severe POAG in both bivariate and multivariable analyses. However, its association was the weakest among the four biomarkers in the patient-clustered multivariable analysis (p = 0.043), with the lowest odds ratio (Tables 3 and 4). These findings suggest that SIRI may reflect inflammatory processes associated with POAG severity, although its clinical utility requires further investigation and validation in larger prospective studies.

Comparative performance and multivariable regression

Among the four inflammatory biomarkers, SII demonstrated the highest numerical discriminative performance, with an overall accuracy of 80.0% and a Youden index of 60.7, followed by NLR (73.3%; 49.2), PLR (68.9%; 36.1), and SIRI (66.7%; 35.2). Although these differences did not consistently reach statistical significance, the findings are broadly consistent with those of Tang et al., who identified SII and NLR as significant indicators of POAG in multivariable analysis, whereas PLR was not consistently significant.[13] Similarly, a large population-based study reported favorable associations between SII and several ocular diseases.[17] NLR demonstrated the highest specificity and positive predictive value (PPV), whereas PLR exhibited the highest sensitivity, consistent with findings previously reported by Ozgonul et al.[16]

Multivariable logistic regression analysis demonstrated that all four biomarkers remained significantly associated with severe POAG in their

respective adjusted models (Table 4). However, because each biomarker was evaluated in a separate model, these findings do not establish their independent contributions relative to one another. NLR, PLR, SII, and SIRI share overlapping hematological components and may therefore provide correlated information regarding systemic inflammation. Further studies incorporating correlation analyses and multivariable models evaluating the incremental discriminative value of individual biomarkers are needed to determine their independent clinical contributions.

NLR demonstrated the highest adjusted odds ratio in the conventional logistic regression analysis (OR = 55.652; 95% CI: 8.133–380.799), although the wide confidence interval suggests considerable uncertainty in the effect estimate, potentially related to the limited sample size and model instability. The initial GEE models for NLR and SII encountered convergence difficulties, which were resolved after variable selection. SII exhibited the highest Nagelkerke R^2 (0.619) and a relatively narrower confidence interval in the clustering-adjusted analysis (95% CI: 2.93–50.0), while the PLR model achieved the highest classification accuracy (83.3%). However, these measures reflect the performance of the respective multivariable models rather than the individual biomarkers alone. In the clustering-adjusted PLR model, irregular treatment adherence was significantly associated with severe POAG (OR = 5.92; 95% CI: 1.10–31.80). Intraocular pressure was consistently retained as a significant covariate across all four models, whereas POAG duration was retained in the PLR, SII, and SIRI models (Table 4).

This study has several limitations. Both eyes of each patient were included in the analysis, although systemic inflammatory biomarkers were measured once per patient. The potential correlation between fellow eyes was addressed using generalized estimating equations (GEE) and patient-level cluster bootstrap analysis. However, the relatively small sample size of 45 patients may have limited the precision of the estimates and statistical comparisons between biomarkers. Additionally, the optimal cut-off values were derived and evaluated using the same study population, potentially resulting in optimistic estimates of diagnostic performance. Although bootstrap analysis was performed to assess the precision of these estimates, external validation in an independent population remains necessary.

The use of backward elimination in multivariable regression models may have increased the risk of overfitting and unstable variable selection, particularly given the limited number of independent patients. Furthermore, inflammatory biomarkers were measured at a single time point, preventing assessment of their temporal variability and longitudinal associations with disease progression. The single-center design also limits the generalizability of the findings to broader populations. In addition, the exclusion of patients with common systemic comorbidities, including hypertension, diabetes mellitus, and chronic kidney or liver disease, may further restrict the applicability of these findings to patients encountered in routine clinical practice.

Treatment adherence was assessed through patient interviews rather than validated adherence instruments or objective measures, introducing potential recall and social desirability bias. The absence of detailed records regarding specific reasons for patient exclusion may also have limited the assessment of selection bias. Moreover, potential confounding factors, including subclinical systemic inflammation, medication effects, and biological variability in hematological parameters, could not be fully accounted for. Larger, multicenter prospective studies with independent external validation are therefore warranted to confirm the discriminative performance of these biomarkers, establish reliable cut-off values, and determine their potential clinical utility in assessing POAG severity.

5. Conclusion

NLR, PLR, SII, and SIRI were significantly associated with primary open-angle glaucoma (POAG) severity in both bivariate and patient-clustered multivariable analyses. Among the four biomarkers, SII demonstrated the highest numerical discriminative performance, with an AUC of 0.803, overall accuracy of 80.0%, and a Youden index of 60.7%. However, its discriminative performance was not significantly different from that of NLR or PLR. NLR exhibited the highest specificity and positive predictive value, whereas PLR demonstrated the highest sensitivity, suggesting potentially complementary roles in assessing POAG severity. SIRI showed the lowest discriminative performance, although its association with disease severity remained statistically significant. These findings suggest that hematological inflammatory indices, particularly SII, NLR, and PLR, may serve as complementary biomarkers for POAG severity assessment. Nevertheless, their clinical utility requires further validation through larger, multicenter prospective studies before they can be incorporated into routine clinical practice.

6. Author Contribution

H.P. designed the study, collected and analyzed the data, and drafted the manuscript. P.M.S. supervised the clinical and glaucoma-subspecialty aspects of the study and critically revised the manuscript. N.P.S. supervised the laboratory and clinical pathology aspects of the study. E.B. supervised the statistical analysis and methodology. All authors have reviewed and approved the final version of the manuscript.

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