ORIGINAL RESEARCH

Complete Blood Cell Count-Derived Inflammation Biomarkers and the Need for Laser Capsulotomy Due to Posterior Capsule Opacification Following Cataract Surgery

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Background: Inflammation plays a significant role in the proliferation, migration, and differentiation of lens epithelial cells after cataract surgery, clinically manifested as posterior capsule opacification (PCO). This condition is typically treated with neodymium: yttrium-aluminum-garnet (Nd:YAG) laser capsulotomy. Our objective is to evaluate the association between blood-derived inflammatory markers and the development of clinically significant PCO necessitating treatment with laser capsulotomy.

Materials and Methods: We conducted a retrospective review of charts for all patients who underwent Nd:YAG laser capsulotomy in our department between January 2021 and December 2022. The study included 70 patients who diagnosed with clinically significant PCO requiring treatment with Nd:YAG laser capsulotomy following cataract surgery, as well as 70 pseudophakic controls with no signs of PCO. Complete blood cell count parameters were obtained from medical records and the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR) were calculated.

Results: The mean age of the Nd:YAG laser capsulotomy and control group was 71.83±8.46 and 72.27±9.98 years, respectively. The preoperative NLR scores for the Nd:YAG laser capsulotomy group (mean rank = 34.43) were statistically significantly higher than those of the control group (mean rank = 25.41) (p = 0.044). However, after adjusting for preoperative measurements, no statistically significant differences were observed between the groups for the other parameters.

Conclusion: Preoperative NLR scores were higher in patients who developed clinically significant PCO requiring treatment with Nd: YAG laser capsulotomy. This finding suggests that patients with elevated systemic inflammation may be at an increased risk of developing PCO following cataract surgery. Further research is needed to evaluate the role of systemic inflammation in the pathogenesis of PCO.

Keywords: cataract, inflammation, nd:YAG laser capsulotomy, neutrophil-to-lymphocyte ratio, posterior capsular opacification

Introduction

Posterior capsule opacification (PCO), which causes significant visual symptoms including light scatter and reduced visual quality, is the most frequent complication of cataract surgery.[1] This secondary cataract is typically treated with neodymium:yttrium-aluminum-garnet (Nd:YAG) laser capsulotomy, a non-invasive and gold standard treatment procedure.[2] Despite its simplicity, reliability, and effectiveness, potential complications, such as increased intraocular pressure (IOP), cystoid macular edema, retinal hemorrhages or detachment, and intraocular lens (IOL) dislocation, along with the unnecessary burden on healthcare systems, highlight the importance of PCO prevention as a crucial goal.[2,3]

The pathophysiology of PCO is multifactorial. Factors such as the cataract surgery technique, the material and design of the IOL, the patient's age, coexisting ocular and systemic diseases contribute to the incidence of PCO.[4] Following cataract surgery, remaining lens epithelial cells (LECs) proliferate, migrate and differentiate to develop PCO, and inflammation plays a crucial role in initiation of wound-healing response and transdifferentiation of LECs into

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a myofibroblast phenotype.[5,6] These differentiated myofibroblastic cells secrete extracellular matrix proteins, that are not typically present in the lens. Among these proteins are matrix metalloproteinases, which play a role in cell migration, and inflammatory cytokines such as transforming growth factor-beta (TGF-β) and fibroblast growth factor 2 (FGF-2). Both TGF-β and FGF-2 are implicated in the development of PCO and the epithelial-to-myofibroblast transition. Additionally, oxidative stress activates TGF-β1 through the production of reactive oxygen species, further contributing to this process.[6,7] Given the role of inflammation in the development of PCO, various anti-inflammatory drugs, including triamcinolone acetonide, diclofenac, and dexamethasone, have been investigated in both clinical and experimental studies for their possible benefits in preventing PCO.[8,9]

Potential inflammatory biomarkers calculated from complete blood cell count (CBC) including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR), have been proposed as prognostic indicators in various systemic diseases.[10] These markers have also been widely studied in several ocular diseases such as different types of glaucoma, retinal vascular diseases, age-related macular degeneration, ocular surface diseases, and keratoconus.[11,12] The degradation of the blood-aqueous humor barrier during cataract surgery causes cytokine-mediated immune response; therefore the influence of systemic inflammation in the pathogenesis of PCO should not be neglected.[13] Ozates et al reported a high incidence (50.9%) of PCO as a complication of cataract surgery in patients with systemic disease–associated uveitis. They emphasized that eyes with early and frequent recurrences were more susceptible to developing PCO.[14] To the best of our knowledge, previous studies have not demonstrated an association between inflammatory biomarkers derived from CBC and PCO. This study aims to assess the relationship between these inflammatory indicators and the development of clinically significant PCO requiring treatment with Nd: YAG laser capsulotomy.

Materials and Methods

This retrospective study was conducted at a tertiary university hospital and institutional ethical committee approval (IRB No:49838221–050.01.04–54) was obtained before the study commenced. Researchers participating in the study adhered to the principles of the Declaration of Helsinki, and all participants provided written informed consent.

The medical charts of patients with age-related cataracts who developed clinically significant PCO after cataract extraction surgery and underwent Nd:YAG laser capsulotomy between January 2021 and December 2022 were retrospectively reviewed (Nd:YAG laser group). The control group was selected from age- and sex-matched patients with age-related cataracts who also had cataract extraction surgery and did not develop PCO during the same time period.

The exclusion criteria for our study were as follows: 1) a history of any other ocular disease or ocular surgery; 2) intraoperative complications; and 3) cataract etiologies other than age-related cataracts. Additionally, since CBC-derived inflammatory biomarkers are influenced by various systemic conditions,[15] patients with a history of diseases such as diabetes mellitus, hypertension, hyperlipidemia, malignancy, active or chronic inflammatory diseases, or allergic diseases were also excluded.

The demographic characteristics of the patients in our clinic's registry, medical history, ocular comorbidities, preoperative ocular measurements, preoperative and postoperative CBC, enzyme-linked immunosorbent assay (ELISA), coagulation test results, surgical events, complications and postoperative results were accessed through a secure web-based RedCAP system by trained researchers.

Phacoemulsification surgery was performed under topical anesthesia by the same single surgeon using ultrasound technology (CENTURION® Vision System), and the same type of hydrophobic acrylic IOL (Acriva, 6 mm optical and 13 mm haptical size with a sharp edge and no haptic angulation) was implanted into the capsular bag. All patients received the same postoperative treatment: 0.5% moxifloxacin drops, 0.1% nepafenac drops, and 1% prednisolone acetate drops were applied every two hours for a week, then gradually reduced and stopped over three weeks. Only one eye per patient, with the indication for cataract surgery, was included in the study.

At each follow-up, measurements of best-corrected visual acuity (BCVA), anterior and posterior segment slit lamp examinations (SL-1800, Nidek Co., Ltd., Aichi, Japan), IOP measurements (NT-2000, Nidek Co., Ltd., Aichi, Japan) and examination of posterior capsule were performed. Clinically significant PCO was considered present when Elschnig pearls or fibrosis were detected in the central zone of the posterior capsule. The requirement of Nd:YAG laser

capsulotomy (YC-1800, Nidek Co., Ltd., Aichi, Japan) was determined when the BCVA decreased by at least 20%, and the patient complained of blurred vision.

Blood samples were collected from all participants after 6–8 hours of fasting. Preoperative CBC testing is routinely conducted prior to cataract surgery, while postoperative CBC results were obtained from routine tests conducted during visits to primary care. Hematology analyzers were used to conduct a complete blood count, and the results were collected. Subsequently, the NLR, PLR, and MLR were calculated by dividing the neutrophil, platelet, and monocyte count by the lymphocyte count, respectively.

Statistical Analysis

The minimum required sample size was determined using G*Power software, based on an effect size of 0.5 and a power of 0.9, resulting in a calculation that 70 patients per group were necessary to achieve statistical significance. Statistical analyses were conducted using SPSS version 23.0 for Windows (SPSS, Inc., Chicago, IL). The Shapiro–Wilk test was used to assess the normality of the data distribution. Descriptive statistics were reported as mean ± standard deviation (SD) for normally distributed variables. Categorical variables were analyzed using the chi-square test. An independent-samples t-test was performed to compare parameters between the groups, with a Welch t-test applied if the assumption of homogeneity of variances was violated. For non-normally distributed variables, a Mann–Whitney U-test was used to assess differences between the Nd:YAG laser capsulotomy group and the control group. Additionally, an analysis of covariance (ANCOVA) was conducted to evaluate the significance of changes in CBC parameters between preoperative and postoperative measurements, controlling for baseline scores. All analyses were performed with a 95% confidence interval, and a p-value of less than 0.05 was considered statistically significant.

Results

A total of 124 patients who developed clinically significant PCO after cataract extraction surgery and underwent Nd: YAG laser capsulotomy between January 2021 and December 2022 were identified in our electronic medical record system. Fifty-four patients were subsequently excluded based on both the exclusion criteria and missing blood test data. Finally, a total of 70 patients were included in the Nd:YAG laser capsulotomy group. The control group consisted of 70 pseudophakic patients who did not develop any signs of PCO during the same period.

The mean age of patients and controls was 71.83±8.46 and 72.05±9.15 years, respectively. The mean interval for the Nd:YAG laser capsulotomy group (the period from the day of cataract surgery to the day of laser capsulotomy) and the control group (the period from the day of cataract surgery to the last visit within the study time frame) were 25.59±12.66 and 21.78±10.13 months, respectively. All demographic data of the subjects are listed in Table 1, and no significant differences were observed in terms of age, sex, or mean interval.

An independent-samples t-test was run to determine if there were differences in parameters between the groups (Table 2). Data are mean ± SD, unless otherwise stated. There were no outliers in the data, as assessed by inspection of a boxplot. The data for each group level were normally distributed, as confirmed by the Shapiro–Wilk test (p>0.05). However, the assumption of homogeneity of variances was not met for four variables, as assessed by Levene's test for equality of variances. Consequently, a Welch t-test was used to evaluate differences in preoperative white blood cell counts and postoperative

Table 1 Demographic Distribution of the Patients in Both Groups

	Nd:YAG Laser Group (n=70)	Control Group (n=70)	p value
Age (years)	71.83±8.46	72.27±9.98	0.855[a]
Sex (n) *Male* *Female*	44 (62.9%) 26 (37.1%)	43 (61.4%) 27 (38.6%)	0.981[b]
Mean Interval (range) (months)	25.59±12.66 (12–45)	21.78±10.13 (11–42)	0.874[a]

Notes: a:Independent samples t-test, b: chi-square test.

Table 2 The Comparison of Pre- and Postoperative Complete Blood Count Parameters Between the Groups (Independent *t* Test)

Parameters		Nd:YAG Laser Group	Control Group	p value
White blood cells	**Preop** **Postop**	7.31±2.03 7.23±2.06	6.84±1.46 7.08±1.43	0.306 0.756
Lymphocytes	**Preop** **Postop**	1.89±0.57 1.98±0.69	2.16±0.70 2.23±0.72	0.063 0.182
Monocytes	**Preop** **Postop**	0.47±0.15 0.51±0.19	0.48±0.11 0.49±0.11	0.746 0.687
Neutrophils	**Postop**	4.52±1.78	4.13±1.24	0.338
Red Blood cells	**Preop** **Postop**	4.47±0.43 4.44±0.47	4.59±0.49 4.65±0.44	0.313 0.09
Hemoglobin	**Postop**	13.07±1.51	13.40±1.33	0.37
Hematocrit	**Preop** **Postop**	39.47±3.44 39.92±3.85	40.52±3.31 40.85±3.62	0.24 0.34
Platelets	**Preop** **Postop**	236.30±63.79 248.06±76.13	246.06±58.00 249.82±61.68	0.541 0.923
Mean platelet volume	**Preop** **Postop**	9.64±1.051.22 9.93±1.31	9.61±1.38 10.04±1.42	0.924 0.747
Mean corpuscular volume	**Preop** **Postop**	88.6±4.80 88.80±4.16	88.53±5.73 90.14±6.98	0.959 0.747

monocyte, neutrophil, and mean corpuscular volume scores due to the violation of homogeneity of variances (Table 2). No statistically significant differences were found between the groups for any of the parameters (Table 2).

A Mann–Whitney *U*-test was run to assess differences in non-normally distributed variables between the Nd:YAG laser capsulotomy group and the control group. Distributions of the variables for both groups were similar, as assessed by visual inspection. The preoperative NLR scores for the Nd:YAG laser capsulotomy group (mean rank = 34.43) were statistically significantly higher than those of the control group (mean rank = 25.41) (p = 0.044). However, no significant differences were found for the other parameters (Table 3). An ANCOVA was run to examine the effect of changes in CBC parameters between the groups after controlling for preoperative scores. After adjusting for preoperative measurements, no statistically significant differences were observed between the groups for any of the parameters (Table 4).

Table 3 The Comparison of Pre-and Postoperative Complete Blood Count Parameters Between the Groups (Mann–Whitney *U*-Test)

Parameters		Nd:YAG LaserGroup	Control Group			
		Mean Rank	Mean Rank	U	Z	P
Neutrophils	**Preop**	34.43	25.41	533	1.48	0.137
Eosinophils	**Preop**	29.6	30.41	423	−0.182	0.855
	Postop	32	27.93	495	0.911	0.362
Basophils	**Preop** **Postop**	28.72 29.38	31.33 30.64	396 416	−0.592 −0.288	0.554 0.773

(*Continued*)

Table 3 (Continued).

Parameters		Nd:YAG LaserGroup	Control Group			
Hemoglobin	**Preop**	27.9	32.17	372	−0.956	0.339
Mean corpuscular hemoglobin	**Preop**	30.27	29.72	443	0.121	0.903
	Postop	32.87	27.03	521	1.304	0.192
Mean corpuscular hemoglobin concentration	**Preop**	30.47	29.52	449	0.212	0.832
	Postop	30.0	30.0	435	0.000	1.0
Plateletcrit	**Preop**	28.13	31.93	368	−0.10	0.313
	Postop	27.53	32.55	361	−1.122	0.262
Platelet distribution width	**Preop**	30.77	29.21	458	0.35	0.726
	Postop	31.78	28.16	488	0.817	0.414
Neutrophil to Lymphocyte Ratio (NLR)	**Preop**	34.43	25.41	568	2.017	**0.044***
	Postop	33.10	26.79	528	1.410	0.159
Platelet to Lymphocyte Ratio (PLR)	**Preop**	32.67	27.24	515	1.213	0.225
	Postop	32.07	27.86	497	0.904	0.347
Monocyte to Lymphocyte Ratio (MLR)	**Preop**	31.83	28.10	490	0.834	0.404
	Postop	31.40	28.55	477	0.637	0.524

Note: *bold: Statistically significant.

Table 4 The Comparison of Differences in Pre- and Postoperative Values of Complete Blood Count Parameters (ANCOVA)

	Nd:YAG Laser Group	Control Group		
	Adjusted means ± SE	Adjusted means ± SE	partial η^2	p
White blood cells	7.07 ± 0.024	7.25 ± 0.024	0.004	0.617
Lymphocytes	2.12 ± 0.98	2.12 ± 0.98	0.009	0.484
Monocytes	0. 51± 0.22	0.49 ± 0.22	0.001	0.864
Neutrophils	4.28 ± 0.22	4.43 ± 0.23	0.004	0.644
Eosinophils	0.19 ± 0.02	0.16 ± 0.21	0.124	0.007
Basophils	0.33±0.02	0.31± 0.02	0.024	0.252
Red Blood cells	4.48±0.64	4.61±0.65	0.000	0.929
Hemoglobin	13.19±1.85	13.26±1.89	0.002	0.761
Hematocrit	40.26±0.53	40.4±0.54	0.005	0.618
Mean Corpuscular Hemoglobin	30.48±0.74	29.26±0.75	0.154	0.001
Mean Corpuscular Hemoglobin Concentration	35.98±2.03	32.83±2.06	0.118	0.009
Mean Corpuscular Volume	90.18 ±0.51	88.77±0.51	0.103	0.015
Platelets	251.82±8.98	245.53±9.13	0.003	0.703
Mean Platelet Volume	10.03±0.15	9.94+0.0.15	0.030	0.197
Plateletcrit	0.27±0.07	0.36±0.06	0.318	0.000

(Continued)

Table 4 (Continued).

	Nd:YAG Laser Group	Control Group		
	Adjusted means ± SE	Adjusted means ± SE	partial η^2	p
Platelet distribution width	16.22±0.108	16.13±0.109	0.003	0.674
Neutrophil to Lymphocyte Ratio (NLR)	2.35±0.17	2.42±0.20	0.001	0.807
Platelet to Lymphocyte Ratio (PLR)	134.47±6.78	125.94±6.99	0.024	0.245
Monocyte to Lymphocyte Ratio (MLR)	0.27±0.014	0.25±0.015	0.001	0.458

Abbreviation: SE, Standard Error.

Discussion

In the current study, we assessed the relationship between CBC-derived inflammatory biomarkers and the development of PCO. Our findings indicated that preoperative NLR was significantly higher in the Nd:YAG laser capsulotomy group compared to the control group. However, ANCOVA analysis did not reveal any significant changes over time between the groups. This suggests that elevated systemic inflammation before phacoemulsification surgery may predict PCO development. To the best of our knowledge, this is the first study to investigate the relationship between CBC-derived inflammation indicators and PCO.

PCO is a pathophysiological outcome of cataract surgery with multiple etiological factors.[16] Following cataract surgery, the remaining LECs in the capsular bag are primarily implicated in PCO development.[1] LECs can spread into the anterior chamber and capsular bag during cataract surgery, proliferate, migrate and transdifferentiate into myofibroblastic cells, resulting in PCO by forming fibrotic plaques in the posterior capsule.[17] The development of PCO has been associated with various cytokines, matrix metalloproteinases, and growth factors, with a primary focus on TGF-β. Inflammation is believed to modulate and accelerate LECs behaviour, given that inflammatory mediators can accumulate more readily in the eye after the breakdown of the blood-aqueous humor barrier.[18]

In recent years, as inflammatory reactions have been recognized as playing crucial roles in various diseases, inflammatory indices based on white blood cell counts have been extensively examined as a potential biomarkers or prognostic factors. The NLR is easily derived by dividing the neutrophil count by the lymphocyte count from CBC measurements. NLR reflects the balance between innate (nonspecific) and acquired (specific) immune responses. Given that neutrophils are primary mediators of the innate immune response, responsible for phagocytosis, and the release of various cytokines, and lymphocytopenia is indicative of stress during inflammation, NLR serves as an excellent composite indicator of inflammation and stress.[15] Ocular disorders associated with the anterior segment of the eye, such as dry eye, glaucoma, cataracts, pterygium and keratoconus entail a complex pathophysiology linked to oxidative stress and inflammation-mediated tissue damage.[19] Given that an increased NLR indicates an imbalance between myeloid and lymphocyte lineages, researchers have extensively examined its relevance in these conditions, investigating its potential as a risk factor, predictor of prognosis, or indicator of therapeutic response. Previous studies have consistently shown higher NLR values in patients with dry eye and pterygium compared to healthy subjects.[20–22] Karaca et al observed a significant increase in the NLR in patients with progressive keratoconus compared to stable and control groups.[23] Researchers have presented evidence supporting NLR as a potential biomarker for both diagnosing and predicting the prognosis of various glaucoma types.[24,25] Moreover, NLR has been associated with an elevated incidence and the prediction of complications during cataract surgery.[26,27] In our study, we found that the preoperative NLR scores for the Nd:YAG laser capsulotomy group (mean rank = 34.43) were statistically significantly higher than those in the control group (mean rank = 25.41) (p = 0.044). However, when comparing the differences between pre- and postoperative NLR scores, we did not observe a statistically significant change between the groups.

MLR and PLR, calculated by dividing the monocyte and platelet counts by the lymphocyte count, respectively, have emerged as novel inflammatory prognostic markers in various diseases.[28] Researcher have extensively explored the roles of the MLR and PLR across a wide range of ocular diseases, including diabetic retinopathy, Graves' orbitopathy, and keratoconus. These studies investigate their potential as risk factors and indicators of disease severity.[29–31] In this study, we

observed that both pre- and postoperative PLR values tended to be higher in the PCO group, with a p-value greater than 0.05. However, no significant difference was found in terms of MLR between the groups in our study.

This study has several limitations. We included a relatively small sample size of 70 patients in our study. Since CBC-based inflammatory markers can increase in a variety of diseases, we set broad exclusion criteria, which consequently limited the number of eligible patients. We did not evaluate other systemic inflammation markers such as C-reactive protein, beyond those derived from the CBC count. While it is possible that patients in the control group may develop PCO in subsequent years, the primary objective of this study was to investigate the potential relationship between PCO and blood-derived inflammatory parameters within the specified time period.

In conclusion, we observed that preoperative NLR scores were higher in patients who developed PCO. This finding suggests that elevated systemic inflammation may increase the risk of developing PCO following cataract surgery. Further research is needed to explore the role of systemic inflammation in the pathogenesis of PCO.

Ethics Approval

Institutional ethical committee approval (IRB No:49838221-050.01.04-54) was granted prior to the study, and researchers participating in the study were assured to follow the tenets of the Declaration of Helsinki.

Acknowledgments

Disclosure

The authors declare no conflicts of interest.

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