• Clinical Research •

Proliferative vitreoretinopathy and its relationship with inflammatory serum biomarkers

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Abstract

● **AIM:** To analyze if a relationship between levels of inflammatory serum biomarkers and severity of primary proliferative vitreoretinopathy (PVR) exists.

● **METHODS:** A retrospective case-control study. The healthy adult patients with rhegmatogenous retinal detachment and primary PVR were included in the PVR group. For the control group, healthy adults who underwent cataract surgery were included. The grade of PVR was classified according to the Retinal Society Terminology Committee. Blood samples were obtained before surgery, and processed in MYTHIC 18. Measures of interest were neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR), the time between the decrease in visual acuity and surgery, PVR grade, type of surgery, final best corrected visual acuity, and rate of re-detachment.

● **RESULTS:** Totally 240 patients were included, 120 in each group, 79 (65.8%) and 56 (46.7%) were male in the PVR and control group, respectively. PVR A had greater levels of monocytes (0.28±0.18 *vs* 0.12±0.32, *P*=0.002), neutrophils (4.59±1.51 *vs* 3.92±1.27, *P*=0.006), and LMR (9.32±4.42 *vs* 7.43±3.90, *P*=0.01). PVR B had a greater monocyte count (0.30±0.13 *vs* 0.12±0.32, *P*=0.001), and PVR C demonstrated higher levels in monocytes (0.27±0.12 *vs* 0.12±0.32, *P*=0.004), neutrophils (4.39±1.13 *vs* 3.92±1.27, *P*=0.004), and LMR (9.63±3.24 *vs* 7.43±3.90, *P*=0.002) compared to control, respectively. An LMR cut-off value of 9.38 predicted PVR with a sensibility of 54.2% and specificity of 77.5% and NLR cut-off of 1.70 predicted PVR with a sensibility of 62% and specificity of 54.2%.

● **CONCLUSION:** Patients with primary PVR demonstrate greater neutrophil, monocyte, and LMR levels than the control group. Cut-off values obtained from ratios could be useful in a clinical setting when no posterior view of the fundus is possible due to media opacity.

● **KEYWORDS:** biomarkers; proliferative vitreoretinopathy; retinal detachment; inflammation; serum

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INTRODUCTION

Neutrophils, lymphocytes, and monocytes are responsible for mounting a cellular inflammatory response in different pathologies, recently it has been demonstrated that their levels are related to severity and prognosis in different types of cancer, rheumatic, and cardiovascular diseases[1-6]. Furthermore, different levels of neutrophil-to-lymphocyte (NLR), platelet-to-lymphocyte (PLR), and lymphocyte-to-monocyte ratios (LMR) have been studied and related to ocular pathologies like age-related macular degeneration (AMD), vein and artery occlusions, uveitis, non-arteritic anterior ischemic optic neuropathy (AION), keratoconus, dry eye, glaucoma, thyroid eye disease, central serous chorioretinopathy, epiretinal membrane, retinopathy of prematurity, and diabetes[7-18].

Preoperative proliferative vitreoretinopathy (PVR), silicone oil time, photocoagulation energy, retinal tear size, and hypertension are significant risk factors for postoperative PVR formation in patients with primary rhegmatogenous retinal detachment (RRD)[19].

PVR is characterized by the growth and contraction of cellular membranes in the vitreous cavity in the epi-, sub-retinal plane, and intraretinal contraction. It is one of the major causes of failure in retinal detachment surgery in up to 10% of the cases. Two factors in the pathophysiology of PVR take place in RRD: retinal hypoxia, and breakdown of the blood-retina barrier; this leads to an increase in the mitogenic and chemotactic activity in the vitreous cavity, release of cytokines, growth factors,

and inflammatory cells that interact with hyalocytes, glial, and retinal pigment epithelium (RPE) cells[6]. The primary role of lymphocytes, monocytes, neutrophils, and fibroblasts in the pathogenesis of PVR has been observed in histology and cytology analysis of epiretinal membranes, vitreous, and aqueous samples in multiple studies[20-22]. To our knowledge no study has reported if levels of serum biomarkers like NLR, PLR, and LMR are related to PVR. Our study aims to analyze if there is a relationship between levels of these ratios and the severity of PVR.

SUBJECTS AND METHODS

Ethical Approval This study conformed to the tenets of the Declaration of Helsinki and was approved by the Institutional Research Board of Fundación Hospital de Nuestra Señora de la Luz, National Autonomous University of Mexico. All patients included in this study accepted *via* oral and written informed consent.

This was a retrospective case-control study. Inclusion criteria were all adult patients with a recent diagnosis of RRD and primary PVR who underwent surgery for repair in our institution, no prior retinal or cataract surgery, myopia with spherical equivalent >-6.00 D, negative past medical history for cancer, renal disease, diabetes, hypertension, alcohol consumption or smoking. Ocular diseases like uveitis, glaucoma, AMD, or trauma may influence cytokine levels in serum, so patients with these pathologies were excluded, also patients with follow-up less than 1mo after surgery were excluded. Healthy patients who underwent uneventful cataract surgery without ocular pathology were used as control. The extent of PVR was classified according to the Retinal Society Terminology Committee 1991. Blood samples were obtained from patients before surgery as part of the preoperative tests. Data was retrieved from electronic medical records, and subjects with missing data were excluded. The blood test included: hemoglobin (Hb), hematocrit (Hct), white blood count (WBC), absolute neutrophil count, absolute lymphocyte count, absolute monocyte count, absolute eosinophil count, absolute basophil count, platelet count and mean platelet volume (MPV) and glucose. NLR, PLR, and LMR were obtained by dividing the total count of neutrophils by lymphocytes, platelets by lymphocytes, and lymphocytes by monocytes, respectively; values were obtained from the preoperative blood tests of RRD and cataract surgery patients, and samples were collected in EDTA tubes (BD Vacutainer, New Jersey) and processed in MYTHIC 18 (C2 diagnostics, France). Analyzed variables were age, sex, basal best corrected visual acuity, the time between the decrease in visual acuity and surgery, PVR grade, type of surgery: scleral buckle, three-port pars plana vitrectomy with or without phacoemulsification, and phaco vitrectomy plus buckle; final best corrected visual acuity, severe visual impairment (SVI; >1.0 logMAR), days of follow-up, and rate of re-detachment (RE-D).

Table 1 Descriptive values for PVR and control groups mean±SD

Characteristics	PVR group (*n*=120)	Control (*n*=120)	*P*
Gender, male, *n* (%)	79 (65.8)	56 (46.7)	0.003
Age, y	52±14	61±13	<0.001
Final BCVA, logMAR	1.01±0.61	NA	NA
Vision loss to surgery (d)	52.28±55.30	NA	NA
White blood cells	7.06±1.63	6.63±1.44	0.33
Lymphocytes	2.29±0.52	2.23±0.53	0.405
Monocytes	0.29±0.15	0.12±0.32	<0.001
Neutrophils	4.43±1.33	3.92±1.27	0.003
Platelets	231.54±53.53	237.83±64.81	0.413
NLR	2.02±0.79	1.83±0.71	0.054
PLR	106.20±36.30	111.16±40	0.316
LMR	9.24±3.62	7.43±3.90	<0.001
Glucose	100.33±9.72	101.71±13.35	0.362

BCVA: Best corrected visual acuity; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; LMR Lymphocyte to monocyte ratio; NA: Not applicable; PVR: Proliferative vitreoretinopathy.

Statistical Analysis Descriptive statistics were assessed by central tendency values and dispersion such as mean, median, standard deviation, and minimum and maximum values. For inferential statistics, categorical variables were analyzed with Chi-squared tests, numerical variables were analyzed by student *t*-test for independent groups, and analysis of variance (one-way ANOVA) for three or more groups. The area under the curve (AUC) with compatibility intervals (95%CI) was assessed by sensitivity and specificity values with cut-off points with the highest value of the Youden index. Binary logistic regressions were analyzed to assess odds ratios. We used Microsoft Excel and IBM Corp. (released in 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp, USA). Statistical significance was $P<0.05$.

RESULTS

We included 240 patients, 120 in each group, 79 (65.8%) and 56 (46.7%) were male in the PVR and control groups, respectively (Laboratory values such as monocytes, neutrophils, and LMR between PVR as a whole and control group, Table 1). Supporting this finding groups of PVR A, B, and C had greater monocyte, neutrophil counts, and a higher LMR compared with the control; PVR A had greater levels in monocytes (0.28±0.18 *vs* 0.12±0.32, $P=0.002$), neutrophils (4.59±1.51 *vs* 3.92±1.27, $P=0.006$) and LMR (9.32±4.42 *vs* 7.43±3.90, $P=0.01$); PVR B had a greater monocyte count (0.30±0.13 *vs* 0.12±0.32, $P=0.001$); furthermore, PVR C demonstrated higher levels in monocytes (0.27±0.12 *vs* 0.12±0.32, $P=0.004$) neutrophils (4.39±1.13 *vs* 3.92±1.27, $P=0.004$) and LMR (9.63±3.24 *vs* 7.43±3.90, $P=0.002$) compared to control, respectively. Comparisons among PVR groups were shown in Table 2.

Table 2 Proliferative vitreoretinopathy grades mean±SD

Characteristics	PVR total (*n*=120)	PVR grade A (*n*=40)	PVR grade B (*n*=40)	PVR grade C (*n*=40)	*P*
Gender, Male, *n* (%)	79 (65.8)	25 (62.5)	26 (66.7)	28 (68.3)	0.862
Age (y)	52±14	52±13.8	51±15	54±14	0.551
Final BCVA logMAR	1.01±0.61	0.74±0.39	1.00±0.60	1.29±0.69	<0.001
White blood cells	7.06±1.63	7.22±1.90	6.97±1.46	6.99±1.52	0.684
Lymphocytes	2.29±0.52	2.28±0.45	2.30±0.51	2.29±0.60	0.988
Monocytes	0.29±0.15	0.28±0.18	0.30±0.13	0.27±0.12	0.564
Neutrophils	4.43±1.33	4.59±1.51	4.30±1.34	4.39±1.13	0.495
Platelets	231.54±53.53	234.37±55.79	244.23±50.42	216.26±51.63	0.075
NLR	2.02±0.79	2.05±0.60	2.01±1.10	1.99±0.57	0.905
PLR	106.20±36.30	106.76±31.73	112.47±44.73	99.51±30.87	0.322
LMR	9.24±3.62	9.32±4.42	8.75±3.06	9.63±3.24	0.462
Glucose	100.33±9.72	101.83±6.91	98.26±11.48	100.80±10.22	0.123
Vision loss to surgery (d)	52.28±55.30	16.63±18.60	32.92±23.36	107.93±59.59	<0.001

ANOVA test for independent groups was applied to analyse the difference between PVR grades A, B, and C. PVR: Proliferative vitreoretinopathy; BCVA: Best corrected visual acuity; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; LMR: Lymphocyte to monocyte ratio.

Surgery Types Among all patients, 120 (50%) phacoemulsification and implantation of intraocular lens without complications were performed in the control group. In the PVR group, buckle was made in 24 (20%), phacoemulsification and implantation of intraocular lens plus vitrectomy in 14 (5.8%), vitrectomy plus buckle in 38 (31.6%), phaco vitrectomy plus buckle in 33 (27.5%), and vitrectomy in 11 (9.2%).

Re-Detachment In our series 18 (15%) had RE-D, 3 in each group PVR grade A and B, and 12 in PVR grade C (*P*=0.005), with a median of 18 (2-145)d to develop. Even though higher NLR (2.25±0.78 *vs* 1.97±0.78) and PLR (118±34.88 *vs* 104±36.30) values were found in the RE-D group compared with single operation success group (SOS) respectively, it was not statistically significant. In the PVR grade C, the RE-D group had a significantly higher PLR compared with the SOS group with the same PVR grade (*P*=0.047). Patients with RE-D presented with worse final visual acuity compared with the SOS group (1.69±0.83 *vs* 0.89±0.48; *P*<0.001). Comparison between ratios of SOS and RE-D groups are depicted in Table 3.

Visual Acuity As expected, worse final visual acuity (logMAR 1.29±0.69; 0.74±0.39; 1.00±0.60; *P*<0.001) and higher time interval (107.93±59.59, 16.63±18.60, 32.92±23.36d; *P*<0.001) between visual loss and surgery were observed in PVR group C compared with groups A and B. Half of the patients with PVR 62 (51.6%), presented with SVI in the last follow-up, and no statistical relationship was found with serum biomarkers. A comparison between biomarkers was shown in Table 4.

Predictive Values Cut-off values were obtained to predict PVR and RE-D. NLR with a cut-off value of 1.70 predicted PVR with a sensibility of 62% and specificity of 54.2% with an AUC 0.590 (0.518-0.662, *P*=0.016) and LMR with a value of 9.38 predicted PVR with a sensibility of 54.2% and specificity 77.5% with an AUC 0.686 (0.617-0.754, *P*<0.001). Other predictive values were depicted in Figure 1.

Table 3 Rate of re-detachment and NLR, PLR, LMR mean±SD

Ratios	SOS group (*n*=102)	Re-detachment (*n*=18)	*P*
NLR	1.97±0.78	2.25±0.78	0.159
PLR	104.10±36.30	118.04±34.88	0.134
LMR	9.25±3.51	9.12±4.30	0.889

SOS: Single operation success; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; LMR: Lymphocyte to monocyte ratio.

Table 4 Comparison of visual acuity and days to surgery between PVR groups

PVR grade	Mean difference between grades (95%CI)	*P*
Grade A *vs* B		
LogMAR	-0.26 (-0.58 to 0.05)	0.134
Days to surgery	-16.29 (-37.39 to 4.80)	0.189
Grade B *vs* C		
LogMAR	-0.29 (-0.60 to 0.02)	0.082
Days to surgery	-75 (-96.1 to -53.91)	<0.0001
Grade A *vs* C		
LogMAR	-0.55 (-0.87 to -0.24)	<0.0001
Days to surgery	-91.30 (-112.26 to -70.34)	<0.0001

DISCUSSION

To our knowledge, this is the first study to demonstrate a relationship between PVR and an increase in serum inflammatory biomarkers. In 2019 Kurtul and Ozer[23] published a systematic review of ocular disease and NLR, where different cut-off and total values predicted the severity and presence of ocular disease compared with controls in patients with retinopathy of prematurity, AMD, retinal vein occlusion, chronic central serous chorioretinopathy, primary open and closed angle glaucoma, pseudoexfoliation, non-

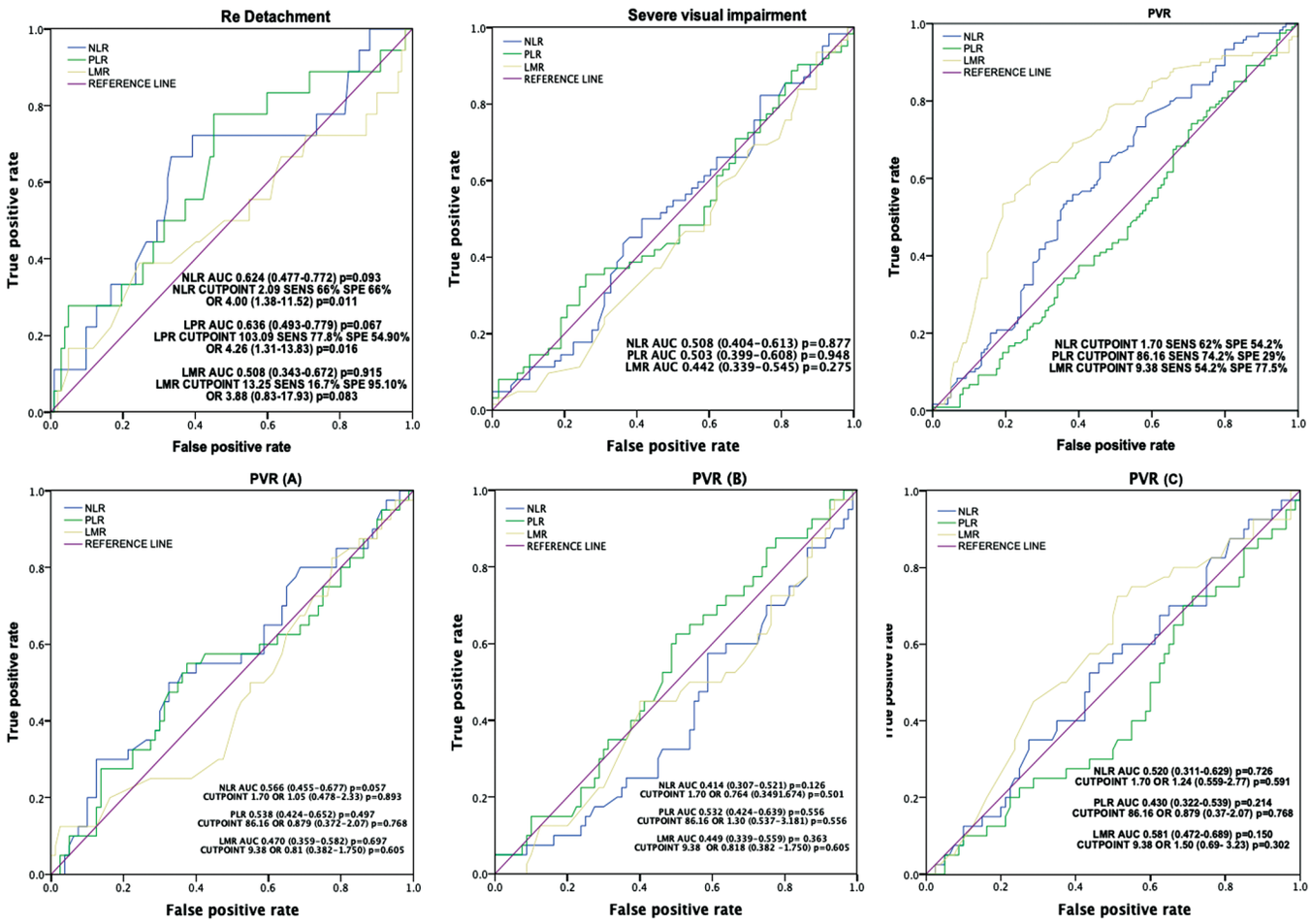

Figure 1 ROC curves with cut points for re-detachment, severe visual impairment, PVR group, PVR A, B, and C. ROC: Receiver operating characteristic; PVR: Proliferative vitreoretinopathy; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; LMR: Lymphocyte-to-monocyte ratio.

arteritic AION, multiple sclerosis, optic neuropathy, and keratoconus; no description of PVR was included. In this study patients with primary PVR demonstrated greater neutrophil, monocyte counts, and LMR levels than the control group. PVR is currently the major cause of failure after retinal detachment surgery and is estimated to occur in 5%-10% of all retinal detachment cases. While it can occur before surgery, it occurs more commonly after any surgical intervention; however, in our setting, many patients arrive with some grade of primary PVR due to the delay in diagnosis and patient resources. Supporting this, the average median time from initial symptoms to surgery was 52.28±55.30d in the PVR group and was more than doubled in patients with PVR type C, 107.93±59.59d.

The eye is a site of immune privilege, foreign tissues placed in the vitreous, anterior chamber or subretinal space experience extended survival compared with those similarly placed subcutaneously. This was believed to be due to absent or minimal lymphatic drainage from the eye.

In the process of RRD, there is an activation of immune and inflammatory systems; increased cytokine expression, gliosis, and subretinal infiltration of monocytes and macrophages have been identified in experimental and human retinal tissues[24]. Also, the presence of interleukin (IL)-8, -10, -13, tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ) has been noted in subretinal fluid in patients with RRD[25].

Apart from dystrophic intraocular changes and the development of RRD, the presence of bacteria such as *Chlamydia trachomatis* in intraocular structures may result in aggravation of the course of RRD due to chronic inflammation and may induce PVR[26]. The loss of the immune regulation mechanisms in RRD may underlie the pathologic changes that lead to the development of PVR.

Membrane formation in PVR requires an extra-cellular matrix scaffold in addition to other constituents: RPE cells, glial cells (mostly Müller cells), macrophages, monocytes, and fibroblasts, all responsible for considerable cellular dedifferentiation. This cellular proliferation is secondary to a break in the retina-blood barrier in which interleukins regulate a localized low-grade inflammatory reaction in addition to wound healing. Some cytokines and growth factors have been identified locally in vitreous samples of patients with PVR mentioned above[27-28].

PVR development may be more complex than we think, at least 516 proteins were detected by high-performance proteomic analysis of vitreous samples in patients with PVR grades C and D. In addition, increased expression of extracellular proteins in PVR samples and downregulation of cytoskeleton proteins such as actin family, opticin precursors, and the absence of tubulin compared to controls were demonstrated in the same study, this supports the idea that in PVR extracellular proteins drive the transcriptional regulation and protein activation[29].

In this study, the PVR group, excluding the platelet count, had greater values in the complete blood count overall, and greater levels of NLR and LMR compared to the control. PVR grades A, B, and C had greater values of monocytes, these findings support the important role of macrophages and monocytes in PVR development. Currently, there were no normal reference intervals defined in our population for these serum biomarkers, the only normative data described in the literature on these biomarkers was a large multi-center study from west China, in that study normal reference interval values of NLR was 0.88-4.0, LMR 2.63-9.9, and PLR 49-198, as we can observe, there is a wide range in the values considered as normal, and comparing the NLR and PLR values obtained in our PVR group with this study, they can be categorized as normal, nevertheless, the LMR can be classified in the upper limit of this values compared with our control group (9.24±3.62 *vs* 7.43±3.90)[30].

Patients with RRD and primary PVR demonstrated a significant increase in serum biomarkers especially in LMR compared to controls. An LMR cut-off value of 9.38 predicted PVR with a sensibility of 54.2% and specificity of 77.5% and an NLR ratio cut-off of 1.70 predicted PVR with a sensibility of 62% and specificity of 54.2%. This could be useful in the clinical setting in those were no posterior view of the fundus is possible due to media opacity. The pitfalls of our study are its retrospective nature and that although there is no information on the subject, the sole presence of RRD may be sufficient to modify these serum biomarkers. A prospective study analyzing serum biomarkers between patients with RRD without primary PVR and with primary PVR is necessary to support our findings.

The identification of extraocular pathways of inflammation can be key in identifying potential targets of intravitreal or systemic drugs for multiple diseases. Also, there is a clear need for the validation of diagnostic, prognostic, and predictive biomarkers to help accelerate the development of these new treatments. As our understanding of the underlying molecular mechanisms in PVR pathogenesis continues to expand, so does the list of novel drug targets[31].

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