

Arachidonic acid pathway in proliferative vitreoretinopathy: the study of the vitreous biomarker in rhegmatogenous retinal detachment



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ABSTRACT

Background: While prompt surgical intervention is still the gold standard, controlling the inflammation may prevent or reduce the progression of PVR, thus increasing the surgical success rate. The arachidonic acid pathway has been reported to play a significant role in the development of PVR. This study aims to investigate the role of the arachidonic acid pathway and assess the related vitreous inflammatory biomarkers in cases of RRD with PVR.

Methods: Thirty patients scheduled for a pars plana vitrectomy for RRD with PVR were included in the study. At the beginning of surgery, a sample of undiluted vitreous was collected in each patient to assess vitreous levels of inflammatory biomarkers, including PGE₂, COX-2, TGF- β , monocytes (comparison of CD14 and CD45), and total protein. The vitreous inflammatory biomarkers were also analyzed based on the severity of PVR and the onset of RRD.

Results: The mean of PGE₂ level was 91.77 ± 31.87 pg/mL, the median (range) of COX-2 level was 1.32 (1.25–1.55) ng/mL; TGF- β was 51.83 (15.61–319.58) pg/mL; monocytes were 90.25 (24.85–95.24) %; and total protein was 4.81 (0.19–20.4) mg/dL. A noticeable trend was found towards the elevation of PGE₂, COX-2, TGF- β , monocytes, and total protein vitreous levels in conjunction with the severity of PVR, although no significant differences between the groups ($p > 0.05$ in each group).

Conclusion: Inflammation, particularly the arachidonic acid pathway, plays a vital role in the early stage of the pathogenesis of PVR. Inhibition of the arachidonic pathway by the anti-inflammatory agent at the early stage may provide a therapeutic approach for PVR prevention.

Keywords: arachidonic acid pathway, inflammatory biomarker, proliferative vitreoretinopathy, rhegmatogenous retinal detachment, vitreous.

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INTRODUCTION

Proliferative vitreoretinopathy (PVR) significantly contributes to surgical failures in retinal detachment. PVR is characterized by the formation of fibro cellular membranes that cause retinal scarring, contraction, and diminished flexibility, thereby reducing the vitality of the retina.¹⁻² It occurs quite frequently, affecting approximately 5 to 10% of individuals diagnosed with rhegmatogenous retinal detachment (RRD).³ Currently, there are no available data on the overall incidence of PVR in Indonesia. However, Lukmana *et al.* reported the incidence rate of PVR

affecting 21% to 31.7% of rhegmatogenous retinal detachment (RRD) cases in Dr. Soetomo General Academic Hospital, Surabaya.⁴ There is no established standard therapy for preventing PVR, except for surgical intervention in managing retinal detachment. Attempts have been made to utilize adjunctive treatments with anti-proliferative agents to prevent PVR, but the outcomes have demonstrated limited efficacy.⁵ Wong *et al.* reported rapid onset of inflammation within the initial two weeks after PVR induction and remained elevated for up to four weeks in a rabbit PVR model.⁶ After rhegmatogenous retinal detachment occurs, retinal

ischemia and blood-retinal barrier disruption are the two key events that play a vital role in initiating PVR development. These events subsequently trigger an inflammatory response involving the migration of cytokines, growth factors, and inflammatory cells into the vitreous and retina.⁷ Multiple inflammatory markers are reported to be overexpressed in the vitreous fluid of PVR patients, including transforming growth factor beta (TGF- β), cyclooxygenase enzymes (COX), prostaglandins, and monocytes.⁸⁻¹⁰ Monocytes/macrophages, RPE cells, and glial cells undergo proliferation and transformation into myofibroblasts.

TGF- β plays a role in the development of PVR, particularly during the initial clinical stage associated with the fibrotic process.¹¹

In addition to direct regulation by cytokines and growth factors, cell proliferation in PVR is also mediated through an indirect mechanism, namely the arachidonic acid pathway.⁸ The arachidonic acid pathway is a metabolism pathway in which an essential fatty acid, arachidonic acid, is converted into prostaglandin using isoenzymes cyclooxygenase, known as COX-1 and COX-2. It is also converted into other substrates, such as thromboxane and leukotrienes. Prostaglandin is considered one of the factors that initiate and sustain the inflammatory response in PVR.¹²

Therefore, while prompt surgical intervention remains the established approach, effective control of inflammation can potentially prevent or reduce the advancement of PVR, leading to improved surgical outcomes.^{13,14} Identifying the specific inflammatory components involved can help determine the appropriate anti-inflammatory agent. Early detection of inflammatory markers that can reliably indicate the future occurrence of PVR would represent a significant advancement in clinical practice.² Therefore, this study aims to investigate the early vitreous inflammatory response, including the arachidonic acid pathway, in cases of RRD with PVR.

METHODS

Study Design

A prospective, cross-sectional study included consecutive patients with RRD and PVR from April 2021 to December 2021 at Cipto Mangunkusumo Kirana Hospital. The estimated sample size for the present study was calculated based on Ghezala *et al.*, with a prevalence of RRD of 2.37%.¹⁵ With a confidence level of 90% and a margin of error of 5%, the minimum sample size would be 26.

This study was conducted based on the Declaration of Helsinki and was approved by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia and Cipto Mangunkusumo Hospital (KET-87/UN2.F1/ETIK/PPM.00.02/2021) on February 8th, 2021. All subjects provided written informed consent.

Eligibility criteria

We recruited participants from consecutive patients with rhegmatogenous retinal detachment and proliferative vitreoretinopathy undergoing pars plana vitrectomy (PPV) at the Cipto Mangunkusumo Kirana Hospital. The inclusion criteria were patients 18 years old and above with macula-off rhegmatogenous retinal detachment, grade A or B proliferative vitreoretinopathy, and RRD onset upon examination to 30 days. The exclusion criteria were RRD patients with media opacification, a history of intraocular surgery in less than three months, and other eye disease comorbidities (i.e., macular hole, epiretinal membrane).

Preoperative Evaluation

A complete ocular examination was done as a preoperative evaluation, including best-corrected visual acuity (BCVA), slit-lamp examination, and funduscopy using condensing 78-dioptic lenses and IOP measurement. Fundus photography using a Visucam 200 camera from Carl Zeiss Meditec AG, Germany, was used to classify PVR.

Vitreous Sampling

A conventional 3-port pars plana vitrectomy (PPV) was performed using a 23-gauge transconjunctival trochar-cannula (Constellation Vision System; Alcon, FortWorth-TX) under retrobulbar anesthesia. At the beginning of the surgery, before starting the infusion of balanced salt solution, 0.5 mL to 1.0 mL of undiluted vitreous was collected from the mid-vitreous cavity in front of the posterior pole. Samples were immediately frozen and stored at -80°C until analysis.

Measurements of PGE2, COX-2, TGF- β , Monocytes

Vitreous samples were thawed and subjected to quantitative analysis of PGE2, COX-2, TGF- β , and monocyte levels. PGE2, COX-2, and TGF β -1 levels were measured using a commercially available ELISA kit (Prostaglandin E2 Monoclonal ELISA Kit [Cayman, Ann Arbor, MI]; Human Cyclooxygenase 2 ELISA Kit [Cayman, Ann Arbor, MI]; Quantikine ELISA Human TGF β -1 [R&D

System, MN, USA]). Measurement of monocyte levels was performed using flow cytometry, detecting CD14 as a marker of monocytes. The measurement obtained compared monocyte count (CD14) with leukocyte cell count (CD45) in percentage. The total protein level was measured using the Bradford protein assay.

Statistical analysis

Clinical and imaging data were analyzed with descriptive statistics. T-independent and Mann-Whitney U tests were used to compare vitreous biomarkers mean values between groups. P values < 0.05 were considered statistically significant. Data analysis was performed using IBM SPSS, version 26 (IBM Corp) and GraphPad Prism 9.0 (GraphPad Software, Inc., San Diego, CA).

RESULT

Baseline characteristics

Thirty prospective patients with clinical diagnoses of ARR and PVR were recruited into the study. The mean age of the patients was 47.6 years, ranging from 18-69 years, with males (63.33%) and females (36.67%). RRD onset ranges between 3 to 30 days, with 46.67% of patients having less than 14 days of onset. Examinations of best-corrected visual acuity (BCVA), intraocular pressure (IOP), and grading of PVR were performed before vitrectomy. The median of BCVA was 2.48, ranging from 0.7 – 2.48. Seventy percent of the subjects had single retinal breaks, and 80% were grade B PVR cases. Baseline characteristics are summarized in [Table 1](#).

Vitreous Biomarker Levels

The vitreous biomarker levels between the two groups were summarized in [Table 2](#). The mean (SD) of PGE2 was 91.77 ± 30.87 pg/mL. The median (range) COX-2 was 1.32 (1.25–1.55) ng/mL; TGF- β was 51.83 (15.61–319.58) pg/mL; monocytes (comparison of CD14 and CD45) was 90.25 (24.85–95.24) %; and total protein was 4.81 (0.19–20.4) mg/dL. The vitreous biomarker levels of PVR subjects are described in [Table 2](#).

The subjects were divided based on the PVR grade: PVR grade A and grade B. [Figure 1](#) showed a noticeable trend towards the elevation of PGE2, COX-2,

TGF- β , monocytes, and total protein in conjunction with the severity of PVR, although not statistically significant ($p > 0.05$ in all groups).

When compared with the onset of RRD upon examination of < 14 days and ≥ 14 days, the mean of PGE2 levels and median of monocytes and total protein showed elevation in the ≥ 14 days onset group, whereas COX-2 and TGF- β levels were higher in the < 14 days onset group. However, no significant differences were found among the vitreous inflammatory biomarker (Table 3).

DISCUSSION

Strong connections have been observed between arachidonic acid metabolites and inflammation within the eye.^{7,8} In vivo, arachidonic acid can undergo metabolism

via pathways such as cyclooxygenase (COX), lipoxygenase, and cytochrome P450, leading to the production of prostaglandins, thromboxane, leukotrienes, epoxyeicosatrienoic acids, and other compounds. Prostaglandins have a role in regulating intraocular pressure and have also been linked to intraocular inflammation and the disruption of the blood-retinal barrier.^{8,12}

Kahler *et al.* demonstrated that the release of arachidonic acid metabolites significantly increased in human fibroblasts when exposed to vitreous from patients with proliferative vitreoretinopathy (PVR).⁸ Their experiments also revealed a significant elevation of prostaglandin E2 (PGE2) in PVR cases, which is known to induce the continuous breakdown of the aqueous blood-retinal barrier. It is in line with our study, in which there were

higher PGE2 values (91.77 ± 30.87 pg/mL) in PVR patients compared to patients with epiretinal membrane, macular hole, vitreous opacities, and dislocated intraocular lens (16.40 ± 7 pg/mL) who underwent pars plana vitrectomy in Schoenberger *et al.* using the same method of ELISA.¹⁶ This study demonstrated that PGE2, which is produced through the arachidonic acid pathway, was detected during the initial phases of PVR. Additionally, higher levels of vitreous PGE2 were observed as the severity of PVR and duration of RRD increased.

It has been mentioned that prostaglandins were produced in the arachidonic acid pathway using COX enzymes. However, it must be highlighted that prostaglandin had a positive feedback mechanism to COX enzymes, in which a higher prostaglandin level further increased COX-2 expression.¹⁷ This is also supported by our study, which showed an increase in COX-2 value in patients with PVR, particularly in less than 14 days period.

Another inflammatory biomarker that needs to be considered is TGF- β . TGF- β is a cytokine that regulates multiple biological responses, including apoptosis, migration, differentiation, immune cell function, and synthesis of extracellular molecules (ECM).¹⁸ In PVR, TGF- β has been shown to induce retinal pigment epithelium (RPE) cell influx to vitreous. A high level of TGF- β facilitates epithelial-to-mesenchymal transition (EMT), such as contractile myofibroblasts, which contribute to the fibrovascular membrane traction process.⁶ The roles of TGF- β in promoting EMT were supported by a previous study conducted by Palomares-Ordonez *et al.*, in which higher expression of TGF- β was observed during the initial stages of PVR.¹¹ Our study also showed a higher concentration of TGF- β during less than 14 days period ($51.83 [15.61 - 319.58]$ ng/mL) compared to the period of 14 days

Table 1. Baseline characteristics of proliferative vitreoretinopathy subjects

Characteristic	PVR* (n=30)
Mean age, SD [†] (years)	47.6 \pm 12.75
Gender	
• Male	20 (63.33%)
• Female	10 (16.67%)
BCVA [‡] (LogMAR [§])	2.48 (0.7-2.48)
Median (range)	
Intraocular pressure (mmHg)	10 (6-19.5)
Median (range)	
RRD [¶] Onset	
• < 14 days	14 (46.67%)
• ≥ 14 days	16 (53.33%)
Number of Breaks	
• Single	21 (70%)
• Multiple	9 (30%)
Lens Status	
• Phakic	26 (86.67%)
• Cataract	2 (6.67%)
• Pseudophakic	2 (6.67%)
PVR* Grade	
• A	6 (20%)
• B	24 (80%)

PVR: proliferative vitreoretinopathy; [†]SD: standard deviation; [‡]BCVA: best-corrected visual acuity; [§]LogMAR: logarithm of the minimum angle of resolution; [¶]RRD: rhegmatogenous retinal detachment.

Table 2. Vitreous inflammatory biomarkers in proliferative vitreoretinopathy subjects

Subjects	Vitreous Inflammatory Biomarkers				
	PGE2 (pg/mL)	COX-2 (ng/mL)	TGF- β (pg/mL)	Monocytes (%) Median (range)	Total protein (mg/dL)
PVR (n=30)	91,77 \pm 30,87	1.32 (1.25-1.55)	51.83 (15.61-319.58)	90.25 (24.85-95.24)	4.81 (0.19-20.4)

PVR: proliferative vitreoretinopathy; PGE2: Prostaglandin E 2; COX-2: Cyclooxygenase enzyme 2; TGF- β : transforming growth factor beta.

or more (46.74 [17.85 - 319.6] ng/mL). Higher expression during the early period showed that TGF- β is one of the main factors involved in EMT.

In this study, the result showed high monocytes (CD14) compared to leukocyte cell count (CD14) with a median of 90.25 % (24.85-95.24). This finding suggests that monocytes are the primary inflammatory cells in the development of PVR. This result showed an increase in monocyte count when compared to macular hole patients reported by Urbancic *et al.*¹⁹ The study reported flow cytometric analysis of vitreous inflammatory cells in PDR patients compared to macular hole patients, with the CD14 in the macular hole patients being 52.75 % (17.9-83).

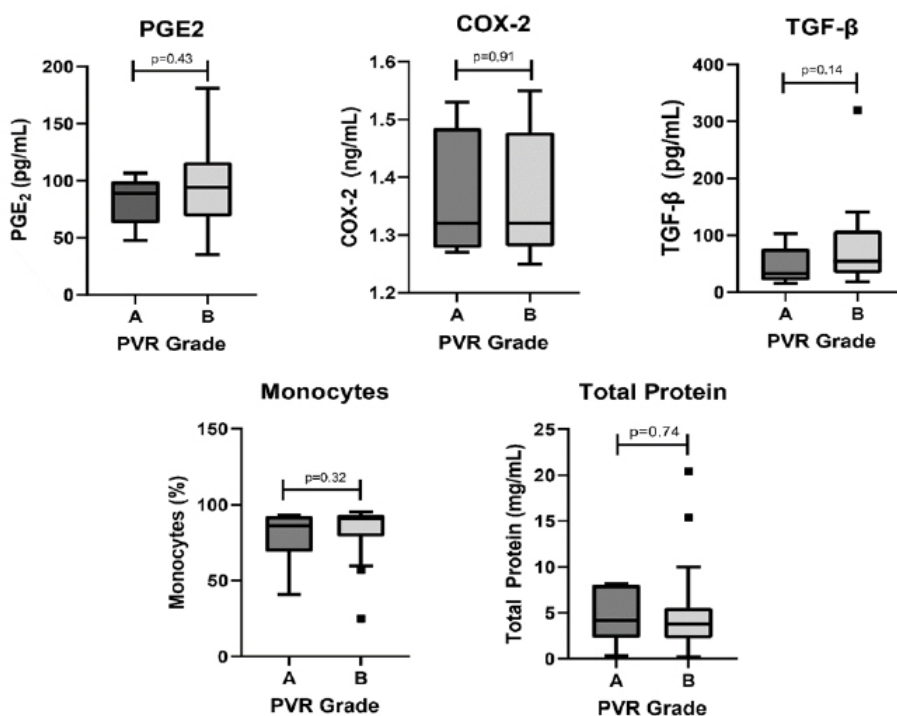
The normal vitreous protein concentration is 40 mg/dL or 0.4 mg/mL, with albumin as the major component (60-70%), followed by globulins, complement factors, and low-molecular-weight protein.²⁰ Yu *et al.* analyzed the vitreous proteomic in PVR and found that approximately 40% of the proteome were specific proteins in PVR, compared to the control group.²¹ Proteins involved in transcription and translation regulation showed an increase in the vitreous of PVR patients. Thus, it can be inferred that PVR is a complex pathological process characterized by the significant involvement of newly produced proteins related to metabolism dysfunction and immune responses. The total protein in

the vitreous of PVR patients was reported to be 1.8 mg/mL \pm 0.6 mg/mL in Ulrich *et al.*²⁰ This finding is in line with our study, as the median of total protein was higher than the normal vitreous protein concentration of 4.81 mg/dL, ranging from 0.19 to 20.4 mg/dL.

Surgery is still considered the gold standard approach in RRD. However, the redetachment rate is still frequently reported, with PVR as the main cause. Many attempts to prevent PVR by administering pharmacologic agents intra or post-operatively, such as anti-proliferative and anti-inflammatory agents, have been reported, but the outcomes have demonstrated limited efficacy.^{8,17,22-23}

An experimental study on PVR using an NSAID agent reported a favorable effect. Tikhonovich *et al.* reported that using nonsteroidal anti-inflammatory drugs (NSAID) of lornoxicam intravitreal injection during the early stages of experimental PVR reduces the severity of PVR development and is more effective than steroids.¹³ Administering in the first three days of inflammation can reduce the production of pro-inflammatory mediators by inhibiting the activity of COXs and decreasing the synthesis of the enzymes. Kahler *et al.* reported that acetylsalicylic acid as a cyclooxygenase inhibitor significantly inhibits the stimulatory effect of prostanoid release in PVR patients.¹¹

Our study had several limitations primarily related to the small sample size, which may restrict the findings in a broader population of PVR patients. A larger, randomized, controlled trial comparing vitreous inflammatory biomarkers in PVR patients and the control group is needed to determine the high inflammatory response in PVR, particularly the arachidonic acid pathway. Additionally, it could offer supporting evidence for using



PVR: proliferative vitreoretinopathy; PGE2: Prostaglandin E 2; COX-2: Cyclooxygenase enzyme 2; TGF- β : transforming growth factor beta.

Figure 1. Vitreous inflammatory biomarkers in proliferative vitreoretinopathy based on the severity of PVR.

Table 3. Association of onset of rhegmatogenous retinal detachment with vitreous inflammatory biomarker

Subjects	Vitreous Inflammatory Biomarkers				
	PGE2 (pg/mL)	COX-2 (ng/mL)	TGF- β (pg/mL)	Monocytes (%)	Total Protein
< 14 days	81.57 (\pm 27.88)	1.44 (1.26-1.53)	70.83 (15.61-140.57)	90.25 (40.82-93.57)	4.81 (0.29-20.4)
\geq 14 days	100.7 (\pm 31.40)	1.30 (1.25-1.55)	46.74 (17.85-319.58)	90.30 (24.85-95.24)	4.09 (0.19-15.37)
p	0.09 ^a	0.13 ^b	0.58 ^b	1.00 ^b	0.45 ^b

PVR: proliferative vitreoretinopathy; PGE2: Prostaglandin E 2; COX-2: Cyclooxygenase enzyme 2; TGF- β : transforming growth factor beta; ^aT-independent test; ^bMann-Whitney.

anti-inflammatory drugs as a potential treatment for preventing PVR. It may benefit RRD, especially when immediate surgery is impossible or if treatment delay is inevitable.

CONCLUSION

This study justified that the arachidonic pathway is already present at the early stage of RRD and may potentially have a role in the PVR progression. Inhibition of the arachidonic pathway by the anti-inflammatory agent at the early stage may provide a therapeutic approach for PVR prevention. Targeting the inflammatory response may offer benefits in controlling inflammation and improving surgical anatomic and functional outcomes.

CONFLICT OF INTEREST

The authors declare no conflict of interest regarding the publication of this article.

ETHICAL CONSIDERATIONS

This study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Indonesia, and Cipto Mangunkusumo Hospital (KET-87/UN2.F1/ETIK/PPM.00.02/2021) on February 8th, 2021.

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AUTHORS CONTRIBUTIONS

AD initiated the idea and concept of the research; responsible for literature search, managing the clinical and experimental study, and manuscript preparation, editing, and review. AAV, RLDN, HW, ARW, RS, and IS were involved in the conception and planning of the research and manuscript review. HW and ARW were involved in the experimental data acquisition and analysis. SHA was responsible for literature search, statistical analysis, and manuscript preparation and editing. AKA was responsible for literature search, data acquisition, and manuscript preparation and editing.

REFERENCES

- Mudhar HS. A brief review of the histopathology of proliferative vitreoretinopathy (PVR). *Eye (Basingstoke)*. 2020 Feb 1;34(2):246–50. <https://doi.org/10.1038/s41433-019-0724-4>.
- Chaudhary R, Scott RAH, Wallace G, Berry M, Logan A, Blanch RJ. Inflammatory and Fibrogenic Factors in Proliferative Vitreoretinopathy Development. *Transl Vis Sci Technol*. 2020 Feb 21;9(3):23. <https://doi.org/10.1167/tvst.9.3.23>.
- Charteris DG. Proliferative vitreoretinopathy: revised concepts of pathogenesis and adjunctive treatment. *Eye (Lond)*. 2020 Feb;34(2):241–245. <https://doi.org/10.1038/s41433-019-0699-1>.
- Lukmana IR, Widjaja SA, Sasono W, Firmansjah M, Yustiarini I, Prakosa AD, Moestijab, Suhendro G. Characteristics of Retinal Detachment Patients with Proliferative Vitreoretinopathy at Dr. Soetomo General Academic Hospital. *International Journal of Retina (IJRETINA)*. 2019;2(2):54–61. <https://doi.org/10.35479/ijretina.2019.vol002.iss002.75>.
- Schaub F, Schiller P, Hoerster R, Kraus D, Holz FG, et al. Intravitreal 5-Fluorouracil and Heparin to Prevent Proliferative Vitreoretinopathy: Results from a Randomized Clinical Trial. *Ophthalmology*. 2022 Oct;129(10):1129–1141. <https://doi.org/10.1016/j.ophtha.2022.05.024>.
- Wong CW, Cheung N, Ho C, Barathi V, Storm G, Wong TT. Characterization of the inflammatory cytokine and growth factor profile in a rabbit model of proliferative vitreoretinopathy. *Sci Rep*. 2019 Oct 28;9(1):15419. <https://doi.org/10.1038/s41598-019-51633-8>.
- Dai Y, Dai C, Sun T. Inflammatory mediators of proliferative vitreoretinopathy: hypothesis and review. *Int Ophthalmol*. 2020;40(6):1587–601. <https://doi.org/10.1007/s10792-020-01325-4>.
- Kähler CM, Herold M, Kaufmann G, Andreas-Bernd Pischel, Schratzberger P, Reinisch N, et al. Induction of arachidonic acid metabolite release by human fibroblasts in proliferative vitreoretinopathy. *Eur J Pharmacol*. 1998;341(1):111–7. [https://doi.org/10.1016/S0014-2999\(97\)01466-0](https://doi.org/10.1016/S0014-2999(97)01466-0).
- Parapuram SK, Chang B, Li L, Hartung RA, Chalam K V, Nair-Menon JU, et al. Differential Effects of TGFβ and Vitreous on the Transformation of Retinal Pigment Epithelial Cells. *Investigative Ophthalmology & Visual Science*. 2009;50(12):5965. <https://doi.org/10.1167/iovs.09-3621>.
- Wang X, Miller EB, Goswami M, Zhang P, Ronning KE, Karlen SJ, et al. Rapid monocyte infiltration following retinal detachment is dependent on non-canonical IL6 signaling through gp130. *J Neuroinflammation*. 2017;14(1):121. <https://doi.org/10.1186/s12974-017-0886-6>.
- Palomares-Ordóñez JL, Sánchez-Ramos JA, Ramírez-Estudillo JA, Robles-Contreras A. Correlation of transforming growth factor β-1 vitreous levels with clinical severity of proliferative vitreoretinopathy in patients with rhegmatogenous retinal detachment. *Arch Soc Esp Oftalmol*. 2019;94(1). p12–7. <https://doi.org/10.1016/j.oftale.2018.11.003>.
- Davies JA. Arachidonic Acid. In: *xPharm: The Comprehensive Pharmacology Reference*. Elsevier; 2008. p. 1–4.
- Tikhonovich M, Lyskin P, Ioyleva E, Gavrilova S. Expression of cyclooxygenases and trophic and growth factors in epiretinal membranes at late stages of proliferative vitreoretinopathy. *Graefes Arch Clin Exp Ophthalmol*. 2016 Nov 2;254(11):2277–9. <https://doi.org/10.1007/s00417-016-3445-4>.
- Xu M, Fan X, Huang X, Chen X, Shao Y, Li X. Steroid Drugs as an Adjunct for Reducing the Incidence of Proliferative Vitreoretinopathy after Rhegmatogenous Retinal Detachment Surgery: A Meta-Analysis of Randomized Controlled Studies [published online ahead of print, 2023 Feb 8]. *Ophthalmic Res*. 2023;66(1):599–610. <https://doi.org/10.1159/000529451>.
- Ben Ghezala I, Mariet AS, Benzenine E, et al. Incidence of Rhegmatogenous Retinal Detachment Following Macular Surgery in France Between 2006 and 2016. *Am J Ophthalmol*. 2022;243:91–97. <https://doi.org/10.1016/j.ajo.2022.07.017>.
- Schoenberger SD, Kim SJ, Sheng J, Rezaei KA, Lalezary M, Cherney E. Increased prostaglandin E2 (PGE2) levels in proliferative diabetic retinopathy and correlation with VEGF and inflammatory cytokines. *Invest Ophthalmol Vis Sci*. 2012;53(9):5906–5911. <https://doi.org/10.1167/iovs.12-10410>.
- Vichai V, Suyarnsesthakorn C, Pittayakhajonwut D, Sriklung K, Kirtikara K. Positive feedback regulation of COX-2 expression by prostaglandin metabolites. *Inflammation Research*. 2005 Apr;54(4):163–72. <https://doi.org/10.1007/s00011-004-1338-1>.
- Massagué J. TGF-β SIGNAL TRANSDUCTION. *Annu Rev Biochem*. 1998 Jun;67(1):753–91. <https://doi.org/10.1146/annurev.biochem.67.1.753>.
- Urbančič M, Petrovič D, Živin AM, Korošec P, Fležar M, Petrovič MG. Correlations between vitreous cytokine levels and inflammatory cells in fibrovascular membranes of patients with proliferative diabetic retinopathy. *Mol Vis*. 2020 Jun 26;26:472–482.
- Ulrich JN, Spannagl M, Kampik A, Gandorfer A. Components of the fibrinolytic system in the vitreous body in patients with vitreoretinal disorders. *Clinical and Experimental Ophthalmology*. 2008;36:431–6.
- Yu J, Liu F, Cui SJ, Liu Y, Song ZY, Cao H, et al. Vitreous proteomic analysis of proliferative vitreoretinopathy. *Proteomics*. 2008;8:3667–8. <https://doi.org/10.1002/pmic.200700824>.
- Chen C, Chen P, Liu X, Li H. Combined 5-Fluorouracil and Low Molecular Weight Heparin for the Prevention of Postoperative Proliferative Vitreoretinopathy in Patients with Retinal Detachment: A Meta-Analysis. *Frontiers in Medicine*. 2021;8:790460. <https://doi.org/10.3389/fmed.2021.790460>.
- Wiedemann P, Hilgers RD, Bauer P, Heimann K. Adjunctive daunorubicin in the treatment of proliferative vitreoretinopathy: results of a multicenter clinical trial. *Daunomycin Study Group. Am J Ophthalmol*. 1998;126(4):550–559. [https://doi.org/10.1016/S0002-9394\(98\)00115-9](https://doi.org/10.1016/S0002-9394(98)00115-9).



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