• Review Article •

# Subretinal fluid in rhegmatogenous retinal detachment: potential biomarkers and therapeutic targets for proliferative vitreoretinopathy

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## Abstract

● Rhegmatogenous retinal detachment (RRD) is a serious ocular condition marked by the separation of the neuroretina from the retinal pigment epithelium (RPE). The pathogenesis of RRD involves intricate molecular and cellular mechanisms, including inflammation, cell migration, and the activation of proliferative signaling pathways. One of the most challenging complications of RRD is proliferative vitreoretinopathy (PVR), which refers to the proliferation and contraction of fibrocellular membranes on the retinal surface and in the vitreous cavity. PVR is a major cause of surgical failure in RRD, as it can lead to recurrent retinal detachment and severe vision loss. However, the pathogenesis of PVR is not yet fully understood, and the treatment options are quite limited. Recent advances in analytical techniques have offered valuable insights into the molecular alterations present in the subretinal fluid (SRF) of patients with RRD. This review seeks to consolidate the current knowledge regarding the SRF profile in RRD and PVR, emphasizing potential biomarkers and therapeutic targets.

● **KEYWORDS:** proliferative vitreoretinopathy; rhegmatogenous retinal detachment; subretinal fluid
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## INTRODUCTION

Rhegmatogenous retinal detachment (RRD) is a major cause of visual impairment worldwide[1], with incidence rates varying across different populations and age groups. The annual incidence of RRD is estimated to range from 6.3 to 17.9 cases per 100 000 individuals[2]. In recent years, studies have shown that the incidence of RRD has been on the rise[3]. Intraocular fluid, including subretinal fluid (SRF), plays a pivotal role in the pathophysiology of the disease[4]. Under normal conditions, the vitreous humor helps maintain the structural integrity of the eye and facilitates nutrient transport[5]. However, in RRD, changes in the vitreous and the accumulation of SRF are critical drivers of disease onset and progression[6]. The biochemical characteristics of SRF changes with the duration of the disease[7]. This fluid exacerbates retinal detachment by exerting hydrostatic pressure, while its biochemical components—including inflammatory mediators, growth factors, and proteins—play a significant role in cellular responses. These factors have a direct impact on the severity and prognosis of RRD[8-10]. For instance, elevated levels of certain cytokines within SRF can promote inflammation and tissue remodeling, contributing to the development of proliferative vitreoretinopathy (PVR)[11-12], a common and challenging complication of RRD. Additionally, analyzing the composition of SRF provides valuable insights into the cellular and molecular mechanisms underlying the disease. It is instrumental in identifying potential therapeutic targets and advancing treatment strategies[13]. This review systematically summarizes the molecular pathological features, biomarkers, and clinical significance of SRF in the context of RRD, offering a comprehensive exploration of its role in the disease process.

## MOLECULAR COMPONENT ANALYSIS OF SRF IN RRD

**Cytokines and Chemokines** Interleukin-6 (IL-6) is a pleiotropic cytokine that plays a critical role in both

physiological and pathological processes. Research has demonstrated that elevated IL-6 production by vitreous cells can stimulate the proliferation of vascular endothelial cells, thereby contributing to the pathophysiology of PVR[14]. Study reported significantly higher levels of IL-6 in both SRF and the vitreous humor[15]. Furthermore, evidence indicates a strong correlation between IL-6 levels and the matrix metalloproteinases (MMP)/tissue inhibitors of metalloproteinases (TIMP) ratio in SRF, suggesting that IL-6 may drive the increased MMP/TIMP ratio observed during PVR progression[16].

Chemokines are small proteins that play a critical role in regulating the migration of various leukocyte types to sites of inflammation. Research indicates that several chemokines C-C motif ligand (CCL), such as CCL2, CCL3, CCL8, CCL9, CCL10, CCL11, CCL17, CCL18, CCL19, CCL22, and macrophage migration inhibitory factor (MIF), exhibit significantly elevated levels in SRF[17].

It has been observed that patients who developed PVR exhibited significantly higher total levels of vascular endothelial growth factor (VEGF) in the SRF compared to RRD patients who did not[18]. It was found that VEGF is alternatively spliced to form the angiogenic $VEGF_{xxx}$ and antiangiogenic $VEGF_{xxx}b$ family of isoforms. Total VEGF levels are elevated in the PVR group, with the anti-angiogenic $VEGF_{xxx}b$ isoform being predominant in SRF[19]. However, another study reported no significant differences in VEGF levels among patients with PVR, while noting that pigment epithelium-derived factor (PEDF) levels were significantly elevated compared to the control group[20].

Transforming growth factor-beta (TGF-β) serves a wide range of functions, including promoting the production of the extracellular matrix. Furthermore, TGF-β accelerates fibrous tissue formation and contributes to the progression of various disease processes[21]. Notably, TGF-$\beta_2$ is produced by retinal pigment epithelial (RPE) cells and Müller cells. Elevated levels of TGF-$\beta_2$ have been detected in the SRF and are closely associated with PVR[22].

Adipose tissue generates a diverse array of cytokines, collectively referred to as adipokines, which participate in both physiological and pathological processes[23]. These adipokines have gained recognition as a distinct group of mediators that play pivotal roles in regulating inflammation, modulating immune responses, and facilitating wound healing. Studies revealed that levels of adiponectin, cathepsin S, and leptin are significantly elevated in the PVR group[24].

**Cytoskeleton, Adhesion and Migration** PVR is recognized as a pathological wound-healing process, defined by the formation of fibrous membranes on both the inner and outer surfaces of the detached neuroretina. The MMP family exhibits significant heterogeneity and consists of 24 distinct proteolytic enzymes. MMPs and their natural inhibitors, TIMPs, are believed to play crucial roles in the development of PVR. Research has demonstrated that the levels of MMPs and TIMPs in the vitreous humor and SRF of patients with RRD are elevated[25], showing a strong correlation with the severity of PVR.

Fibulins (Fblns) are extracellular matrix proteins that play a crucial role as key components of elastic fibers and basement membranes. A study found that the upregulation of Fbln2, coupled with the downregulation of Fbln5 during RRD, may contribute to an imbalance in the adhesive interactions between the RPE and the neuroretina[26].

Syndecan-1 (also known as CD138) is a crucial transmembrane glycoprotein belonging to the heparan sulfate proteoglycan (HSPG) family. It is predominantly found in epithelial cells and is characterized by heparan sulfate chains that facilitate interactions with various peptides, including extracellular matrix components and is potent mediators of proliferation, adhesion, and migration[27]. Syndecans play vital roles in regulating wound repair processes, as well as in the formation and signaling of chemokines and growth factors. RRD is linked to a marked increase in the levels of soluble syndecan-1 within the vitreous humor and SRF. Moreover, the elevated concentration of soluble syndecan-1 has been shown to positively correlate with the duration of retinal detachment[28].

Intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) are critical in mediating leukocyte adhesion and migration to endothelial cells. These molecules also play a pivotal role in inflammatory responses and the activation of immune cells[29]. Study has revealed a significant increase in the levels of soluble ICAM-1 and soluble VCAM-1 in patients with PVR [30].

**Lipid Metabolites** Studies on lipid metabolites have revealed that the glycerophosphocholine lipid profile in SRF closely mirrors that of outer segments of the retina cone cells, despite the fact that human retina containing a higher proportion of rod cells. This observation suggests that lipids derived from cones may play a pivotal role in the pathogenesis of RRD[31].

Lipid peroxidation is a well-established mechanism of cell membrane damage linked to various ocular diseases. One of its byproducts, malondialdehyde (MDA), is a secondary product of lipid peroxidation with a relatively long half-life, making it a reliable marker of peroxidative damage to cell membranes[32]. Research has shown that MDA concentrations in SRF are correlated with the severity of retinal detachment, highlighting its potential as an indicator of oxidative stress in RRD patients[33].

**Amino Acids** Amino acids serve as the essential building blocks of proteins and peptides, playing a crucial role in

cellular signaling and metabolic pathways that facilitate tissue repair. A deficiency in certain amino acids has been shown to trigger endoplasmic reticulum stress and promote the expression of specific growth factors[34]. Notably, one study revealed significant alterations in amino acid concentrations in patients with RRD. Researchers found that compared to the vitreous humor of the control group, the levels of aspartate, arginine, glutamate, and glycine in the SRF of RRD patients were markedly elevated, while the concentrations of alanine, isoleucine, leucine, methionine, phenylalanine, threonine, tyrosine, and valine were reduced[18]. Another study further highlighted that glutamate levels in both the SRF and vitreous humor of RRD patients were significantly higher than those in the control group[35]. Excessive glutamate is believed to contribute to toxicity through mechanisms involving osmotic and calcium damage. Elevated glutamate levels can overstimulate sodium influx into cells, which, combined with the entry of water and chloride, may result in osmotic cell lysis and neuronal swelling[36].

**MicroRNA Expression** The microRNA (miRNA) are key regulators of gene expression, controlling cellular functions under both physiological and pathophysiological conditions[37]. miR-210, plays an important role in controlling lipid metabolism and neuronal function[38]. The expression levels of miR21 and miR34 exhibit a positive correlation with the duration of symptoms in retinal detachment cases. Conversely, miR146a expression is notably reduced in patients diagnosed with PVR. Additionally, miR21 serves as a predictor for both the time elapsed from symptom onset to treatment and the number of retinal breaks. Furthermore, miR26a demonstrates a correlation with the best-corrected visual acuity (BCVA) following surgery. The expression of specific miRNAs is closely linked to risk factors for PVR, highlighting their potential as biomarkers and therapeutic targets in the management of this condition[39].

**Coagulation Cascade** The activation of the coagulation cascade has been identified as a potential contributor to the development of PVR[40]. Intravitreal thrombin stimulates retinal pigment epithelial cells to secrete pro-inflammatory and pro-fibrotic mediators, indicating its role in PVR pathogenesis. Studies have shown that levels of coagulation factor XII and the thrombin-antithrombin complex are elevated in SRF, reflecting significant thrombin generation in SRF of patients with RRD[41]. Tissue factor (TF), a transmembrane glycoprotein and the primary initiator of blood coagulation in normal hemostasis, also plays a critical role. Research revealed that thrombin generation is induced in SRF, and the addition of TF-targeting antibodies almost completely neutralized this thrombin-activating effect[42].

**Other Biomarkers** Soluble Fas (sFas) and soluble Fas ligand (sFasL) play a crucial role in the development of PVR by regulating the apoptosis of RPE cells. Studies have revealed that sFas and sFasL levels are significantly elevated in individuals with PVR[30].

The occurrence of PVR was also found to be correlated with several early apoptosis factors, including caspase-8, caspase-9, and B-cell lymphoma 2 (Bcl-2) associated death promoter. Additionally, early apoptosis factors and signaling proteins, such as ERK1/2, were shown to impact OCT features three months postoperatively[43].

ATP levels showed an increase in SRF, followed by a gradual decline over time. This reduction aligned with the upregulation of ectonucleoside triphosphate diphosphohydrolase-1. These observed kinetics shed light on the pathological mechanisms driving the excessive accumulation of extracellular ATP after retinal detachment[44].

Study has revealed that the concentration of transthyretin (TTR) is notably higher in SRF compared to serum and cerebrospinal fluid. TTR, which is abundantly expressed in the RPE, plays an essential role in transporting retinol, lipids, and other low-solubility molecules. This function may contribute to lipofuscin accumulation by influencing retinol-binding capacity. Additionally, modifications in TTR, such as glutathionylation, has been detected at significantly elevated levels in SRF compared to serum, suggesting a potential involvement in the pathogenesis of RRD[4].

Researchers have identified that proteins involved in proteolysis play a significant role within the SRF in RRD patients. Notably, chitinase 3-like protein 1 (CHI3L1) and galectin-3-binding protein appear to be distinctive components of SRF[45]. CHI3L1 belongs to the glycosyl hydrolase 18 (GH18) gene family, which has remained conserved across species and throughout evolution. This protein is known to be dysregulated in various conditions, including inflammatory, infectious, remodeling, and neoplastic disorders[46].

S100B is a calcium-binding protein expressed in astrocytes, playing a key role in regulating various intracellular processes, including proliferation and differentiation. Research has shown that S100B concentrations in SRF increase following rhegmatogenous RRD, establishing it as a reliable marker of retinal stress. Furthermore, study has demonstrated a positive correlation between S100B levels and the duration of RRD[47].

Evidence also indicates that the concentration of neuron-specific enolase (NSE), a marker of neuronal injury, is significantly higher in the SRF compared to its levels in the serum and vitreous of the control group[48].

## CLINICAL THERAPEUTICS FOR PVR

PVR remains a critical complication following RRD, contributing to a considerable proportion of recurrent detachments, even after seemingly successful surgical

repair[49]. The identification of specific proteins and metabolites in SRF holds substantial thertablapeutic potential. Targeting inflammatory pathways could pave the way for innovative treatment strategies for managing RRD[12,50]. Furthermore, the development of targeted therapies rooted in specific biomarkers offers the promise of more personalized and effective treatment options for RRD patients[51].

**Corticosteroids** Corticosteroids are utilized to address vitreoretinal scarring due to their anti-inflammatory and antiproliferative properties, as well as their capacity to prevent the breakdown of the blood-ocular barrier. Research has demonstrated that a slow-release 0.7 mg dexamethasone intravitreal implant (Ozurdex) significantly reduces cystoid macular edema following PPV[52]. However, the effectiveness of intravitreal triamcinolone acetonide injections or oral corticosteroids in preventing PVR remains uncertain[53].

**Methotrexate** Methotrexate (MTX) has shown inhibitory effects on cell proliferation and cytokine-producing immune cells, highlighting its potential role in managing PVR[54]. This potential is believed to stem from its ability to inhibit RPE metaplasia, as well as the proliferation of myocontractile cells and glial elements within the retina. Research has demonstrated a low incidence of recurrent PVR and favorable single-surgery success rates associated with MTX use. Furthermore, most studies have not reported severe complications directly attributable to MTX[55-56].

**Other Pharmacologic Agents** Intravitreal agents such as anti-VEGF[57] and 5-fluorouracil[58], among others, have not demonstrated proven efficacy in the treatment or prevention of PVR.

## CONCLUSION

The analysis of SRF in RRD has yielded significant insights into the molecular mechanisms driving this condition. Various proteins, lipids, and metabolites have been identified, reflecting the pathological state of the retina and highlighting their potential as biomarkers for disease diagnosis and monitoring. Moving forward, research should prioritize a deeper understanding of these molecules' roles in the pathogenesis of RRD while investigating their viability as therapeutic targets. The development of targeted therapies derived from specific biomarkers holds promise for enabling more effective and personalized treatments for RRD patients, ultimately enhancing visual outcomes and overall quality of life.

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## REFERENCES

1 Ge JY, Teo ZL, Chee, *et al*. International incidence and temporal trends for rhegmatogenous retinal detachment: a systematic review and meta-analysis. *Surv Ophthalmol* 2024;69(3):330-336.

2 Chronopoulos A, Schutz JS, Finger RP. Prevention of rhegmatogenous retinal detachment. *Surv Ophthalmol* 2025;70(6):1061-1066.

3 Achour H, Thomseth VM, Kvaløy JT, *et al*. Substantial increase in the incidence of rhegmatogenous retinal detachment in Western Norway over 20 years. *Acta Ophthalmol* 2022;100(7):763-768.

4 Chen JZ, Cao DF, Fortmann SD, *et al*. Transthyretin proteoforms of intraocular origin in human subretinal fluid. *Exp Eye Res* 2022;222:109163.

5 Tram NK, Maxwell CJ, Swindle-Reilly KE. Macro- and microscale properties of the vitreous humor to inform substitute design and intravitreal biotransport. *Curr Eye Res* 2021;46(4):429-444.

6 Xiong J, Tran T, Waldstein SM, *et al*. A review of rhegmatogenous retinal detachment: past, present and future. *Wien Med Wochenschr* 2025;175(7-8):186-202.

7 Fouad YA, Habib AM, Sanders RN, *et al*. Persistent subretinal fluid following successful rhegmatogenous retinal detachment surgery. *Semin Ophthalmol* 2022;37(6):724-729.

8 Gong QY, Hu GY, Yu SQ, *et al*. Comprehensive assessment of growth factors, inflammatory mediators, and cytokines in vitreous from patients with proliferative diabetic retinopathy. *Int J Ophthalmol* 2022;15(11):1736-1742.

9 Redruello-Guerrero P, Gómez-Tomás M, Rechi-Sierra T, *et al*. Inflammatory mechanisms in the management and treatment of retinal detachment. *Metabolites* 2025;15(7):442.

10 Daruich A, Jaworski T, Henry H, *et al*. Oral ursodeoxycholic acid crosses the blood retinal barrier in patients with retinal detachment and protects against retinal degeneration in an *ex vivo* model. *Neurotherapeutics* 2021;18(2):1325-1338.

11 Ananikas K, Stavrakas P, Kroupis C, *et al*. Molecular biologic milieu in rhegmatogenous retinal detachment and proliferative vitreoretinopathy: a literature review. *Ophthalmic Res* 2022;65(6):637-646.

12 Wu F, Eliott D. Molecular targets for proliferative vitreoretinopathy. *Semin Ophthalmol* 2021;36(4):218-223.

13 Brighenti T, Neri G, Mazzola M, *et al*. Comparative proteomic analysis of human vitreous in rhegmatogenous retinal detachment and diabetic retinopathy reveals a common pathway and potential therapeutic target. *Clin Proteomics* 2024;21(1):63.

14 Symeonidis C, Rotsos T, Matsou A, *et al*. Comparison of chemokine CXCL-1 and interleukin-6 concentrations in the subretinal fluid and vitreous in rhegmatogenous retinal detachment. *Ocul Immunol Inflamm* 2021;29(2):355-361.

15 Symeonidis C, Androudi S, Tsaousis KT, *et al*. Comparison of interleukin IL-6 levels in the subretinal fluid and the vitreous during rhegmatogenous retinal detachment. *Cytokine* 2012;57(1):17-18.

16 Symeonidis C, Papakonstantinou E, Androudi S, *et al*. Comparison of interleukin-6 and matrix metalloproteinase expression in the

subretinal fluid and the vitreous during proliferative vitreoretinopathy: correlations with extent, duration of RRD and PVR grade. *Cytokine* 2014;67(2):71-76.

17 Symeonidis C, Androudi S, Rotsos T, *et al*. Chemokine CXCL-1 expression in the subretinal fluid during rhegmatogenous retinal detachment. *Ocul Immunol Inflamm* 2014;22(6):449-453.

18 Yalcinbayir O, Buyukuysal RL, Gelisken O, *et al*. Amino acid and vascular endothelial growth factor levels in subretinal fluid in rhegmatogenous retinal detachment. *Mol Vis* 2014;20:1357-1365.

19 Ricker LJ, Dieudonné SC, Kessels AG, *et al*. Antiangiogenic isoforms of vascular endothelial growth factor predominate in subretinal fluid of patients with rhegmatogenous retinal detachment and proliferative vitreoretinopathy. *Retina* 2012;32(1):54-59.

20 Dieudonné SC, La Heij EC, Diederen RM, *et al*. Balance of vascular endothelial growth factor and pigment epithelial growth factor prior to development of proliferative vitreoretinopathy. *Ophthalmic Res* 2007;39(3):148-154.

21 Sporn MB, Roberts AB, Wakefield LM, *et al*. Transforming growth factor-β: biological function and chemical structure. *Science* 1986;233(4763):532-534.

22 Hirase K, Sugiyama T, Ikeda T, *et al*. Transforming growth factor beta(2) increases in subretinal fluid in rhegmatogenous retinal detachment with subretinal strands. *Ophthalmologica* 2005;219(4):222-225.

23 Weiner J, Dommel S, Gebhardt C, *et al*. Differential expression of immunoregulatory cytokines in adipose tissue and liver in response to high fat and high sugar diets in female mice. *Front Nutr* 2023;10:1275160.

24 Ricker LJ, Kijlstra A, Kessels AG, *et al*. Adipokine levels in subretinal fluid from patients with rhegmatogenous retinal detachment. *Exp Eye Res* 2012;94(1):56-62.

25 Symeonidis C, Papakonstantinou E, Androudi S, *et al*. Interleukin-6 and matrix metalloproteinase expression in the subretinal fluid during proliferative vitreoretinopathy: correlation with extent, duration of RRD and PVR grade. *Cytokine* 2012;59(1):184-190.

26 Davila-Avila N, Muñiz-Ruvalcaba FP, Hernandez-Zimbron LF, *et al*. Expression of Fibulin-2 and Fibulin-5 on subretinal fluid in human primary rhegmatogenous retinal detachment. *Exp Eye Res* 2020;194:107992.

27 Bernfield M, Götte M, Park PW, *et al*. Functions of cell surface heparan sulfate proteoglycans. *Annu Rev Biochem* 1999;68:729-777.

28 Wang JB, Tian CW, Guo CM, *et al*. Increased levels of soluble syndecan-1 in the subretinal fluid and the vitreous of eyes with rhegmatogenous retinal detachment. *Curr Eye Res* 2008;33(1):101-107.

29 Barile GR, Chang SS, Park LS, *et al*. Soluble cellular adhesion molecules in proliferative vitreoretinopathy and proliferative diabetic retinopathy. *Curr Eye Res* 1999;19(3):219-227.

30 Ricker LJ, Altara R, Goezinne F, *et al*. Soluble apoptotic factors and adhesion molecules in rhegmatogenous retinal detachment. *Invest Ophthalmol Vis Sci* 2011;52(7):4256-4262.

31 Chen JZ, Curcio CA, Crosson JN. Shotgun lipidomics of human subretinal fluids under rod-dominant retina reveals cone-dominated lipids. *Exp Eye Res* 2024;240:109807.

32 Ayala A, Muñoz MF, Argüelles S. Lipid peroxidation: production, metabolism, and signaling mechanisms of malondialdehyde and 4-hydroxy-2-nonenal. *Oxid Med Cell Longev* 2014;2014:360438.

33 Bosch-Morell F, García-Gen E, Mérida S, *et al*. Lipid peroxidation in subretinal fluid: some light on the prognosis factors. *Biomolecules* 2021;11(4):514.

34 Pow DV. Amino acids and their transporters in the retina. *Neurochem Int* 2001;38(6):463-484.

35 Bertram KM, Bula DV, Pulido JS, *et al*. Amino-acid levels in subretinal and vitreous fluid of patients with retinal detachment. *Eye* (*Lond*) 2008;22(4):582-589.

36 Werth JL, Park TS, Silbergeld DL, *et al*. Excitotoxic swelling occurs in oxygen and glucose deprived human cortical slices. *Brain Res* 1998;782(1-2):248-254.

37 Maji RK, Leisegang MS, Boon RA, *et al*. Revealing microRNA regulation in single cells. *Trends Genet* 2025;41(6):522-536.

38 Lyu JL, Chen YC, Yang WW, *et al*. The conserved microRNA miR-210 regulates lipid metabolism and photoreceptor maintenance in the Drosophila retina. *Cell Death Differ* 2021;28(2):764-779.

39 Carpineto P, di Filippo ES, Aharrh Gnama A, *et al*. microRNA expression in subretinal fluid in eyes affected by rhegmatogenous retinal detachment. *Int J Mol Sci* 2023;24(3):3032.

40 Han H, Zhao X, Liao MY, *et al*. Activated blood coagulation factor X (FXa) contributes to the development of traumatic PVR through promoting RPE epithelial-mesenchymal transition. *Invest Ophthalmol Vis Sci* 2021;62(9):29.

41 Mulder VC, Bastiaans J, van Leuven CJM, *et al*. Thrombin generation in vitreous and subretinal fluid of patients with retinal detachment. *Ophthalmologica* 2018;240(1):23-28.

42 Ricker LJ, Dieri RA, Beckers GJ, *et al*. High subretinal fluid procoagulant activity in rhegmatogenous retinal detachment. *Invest Ophthalmol Vis Sci* 2010;51(10):5234-5239.

43 Carpineto P, Aharrh-Gnama A, Ciciarelli V, *et al*. Subretinal fluid levels of signal-transduction proteins and apoptosis molecules in macula-off retinal detachment undergoing scleral buckle surgery. *Invest Ophthalmol Vis Sci* 2016;57(15):6895-6901.

44 Tachibana T, Notomi S, Funatsu J, *et al*. Intraocular kinetics of pathological ATP after photoreceptor damage in rhegmatogenous retinal detachment. *Jpn J Ophthalmol* 2024;68(5):500-510.

45 Poulsen ET, Lumi X, Hansen AK, *et al*. Protein composition of the subretinal fluid suggests selective diffusion of vitreous proteins in retinal detachment. *Transl Vis Sci Technol* 2020;9(11):16.

46 Kaya M, Kaya D, Idiman E, *et al*. A novel biomarker in diabetic macular edema with serous retinal detachment: serum chitinase-3-like protein 1. *Ophthalmologica* 2019;241(2):90-97.

47 Yalcinbayir O, Buyukuysal RL, Akova-Budak B, *et al*. S100b protein levels in subretinal fluid in rhegmatogenous retinal detachment. *Curr*

*Eye Res* 2012;37(11):1030-1035.

48 Quintyn JC, Pereira F, Hellot MF, *et al*. Concentration of neuron-specific enolase and S100 protein in the subretinal fluid of rhegmatogenous retinal detachment. *Graefes Arch Clin Exp Ophthalmol* 2005;243(11):1167-1174.

49 Visioli G, Romaniello A, Spinoglio L, *et al*. Proliferative vitreoretinopathy in retinal detachment: perspectives on building a digital twin model using nintedanib. *Int J Mol Sci* 2024;25(20):11074.

50 Sabatino F, Banerjee P, K Muqit MM. Clinical therapeutics for proliferative vitreoretinopathy in retinal detachment. *Surv Ophthalmol* 2024;69(4):508-520.

51 Khosravi Mirzaei S, Hatami F, Safi S, *et al*. Pharmacological agents for treatment of proliferative vitreoretinopathy: a systematic review and network meta-analysis. *Surv Ophthalmol* 2025;70(4):633-644.

52 Banerjee PJ, Quartilho A, Bunce C, *et al*. Slow-release dexamethasone in proliferative vitreoretinopathy: a prospective, randomized controlled clinical trial. *Ophthalmology* 2017;124(6):757-767.

53 Ahmadieh H, Feghhi M, Tabatabaei H, *et al*. Triamcinolone acetonide in silicone-filled eyes as adjunctive treatment for proliferative vitreoretinopathy: a randomized clinical trial. *Ophthalmology* 2008;115(11):1938-1943.

54 Al-Moujahed A, Saleh S, Ghoraba H, *et al*. Systemic and intraocular methotrexate for the prevention and treatment of proliferative vitreoretinopathy in children with rhegmatogenous retinal detachment and underlying inflammatory disease. *J Vitreoretin Dis* 2022;6(5):399-404.

55 Jahangir S, Jahangir T, Ali MH, *et al*. Use of intravitreal methotrexate infusion in complicated retinal detachment for prevention of proliferative vitreoretinopathy in a pilot study. *Cureus* 2021;13(8):e17439.

56 El Baha S, Leila M, Amr A, *et al*. Anatomical and functional outcomes of vitrectomy with/without intravitreal methotrexate infusion for management of proliferative vitreoretinopathy secondary to rhegmatogenous retinal detachment. *J Ophthalmol* 2021;2021:3648134.

57 Zhao XY, Xia S, Wang EQ, *et al*. Efficacy of intravitreal injection of bevacizumab in vitrectomy for patients with proliferative vitreoretinopathy retinal detachment: a meta-analysis of prospective studies. *Retina* 2018;38(3):462-470.

58 Chen C, Chen P, Liu X, *et al*. Combined 5-fluorouracil and low molecular weight heparin for the prevention of postoperative proliferative vitreoretinopathy in patients with retinal detachment: a meta-analysis. *Front Med (Lausanne)* 2021;8:790460.