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REVIEW ARTICLE

Emerging applications of bioinformatics and artificial intelligence in the analysis of biofluid markers involved in retinal occlusive diseases: a systematic review

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Abstract

Purpose To review the literature on the application of bioinformatics and artificial intelligence (AI) for analysis of biofluid biomarkers in retinal vein occlusion (RVO) and their potential utility in clinical decision-making.

Methods We systematically searched MEDLINE, Embase, Cochrane, and Web of Science databases for articles reporting on AI or bioinformatics in RVO involving biofluids from inception to August 2021. Simple AI was categorized as logistics regressions of any type. Risk of bias was assessed using the Joanna Briggs Institute Critical Appraisal Tools.

Results Among 10,264 studies screened, 14 eligible articles, encompassing 578 RVO patients, met the inclusion criteria. The use and reporting of AI and bioinformatics was heterogenous. Four articles performed proteomic analyses, two of which integrated AI tools such as discriminant analysis, probabilistic clustering, and string pathway analysis. A metabolomic study used AI tools for clustering, classification, and predictive modeling such as orthogonal partial least squares discriminant analysis. However, most studies used simple AI ($n=9$). Vitreous humor sample levels of interleukin-6 (IL-6), vascular endothelial growth factor (VEGF), and aqueous humor levels of intercellular adhesion molecule-1 and IL-8 were implicated in the pathogenesis of branch RVO with macular edema. IL-6 and VEGF may predict visual acuity after intravitreal injections or vitrectomy, respectively. Metabolomics and Kyoto Encyclopedia of Genes and Genomes enrichment analysis identified the metabolic signature of central RVO to be related to lower aqueous humor concentration of carbohydrates and amino acids. Risk of bias was low or moderate for included studies.

Conclusion Bioinformatics has applications for analysis of proteomics and metabolomics present in biofluids in RVO with AI for clinical decision-making and advancing the future of RVO precision medicine. However, multiple limitations such as simple AI use, small sample volume, inconsistent feasibility of office-based sampling, lack of longitudinal follow-up, lack of sampling before and after RVO, and lack of healthy controls must be addressed in future studies.

Keywords Artificial intelligence · Bioinformatics · Retinal vein occlusion · Biomarkers · Retinal disease · Central retinal vein occlusion

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Key messages

- Applications of bioinformatics and artificial intelligence (AI) to analyze biofluids in ophthalmological diseases are increasingly popular. However, their application in retinal vein occlusions (RVO) is not known.
- We highlighted that bioinformatic analyses using metabolomics and proteomics, and to a lesser extent AI-based analyses have the potential to drive RVO biomarker discovery, provide insight into the pathogenesis of RVO secondary complications, and may help guide treatment strategies by mapping treatment responses.
- Studies performing bioinformatics in conjunction with AI tools using biofluids as biomarkers are limited by the use of simple AI methodology, small sample volume, inconsistent feasibility of office-based sampling, lack of longitudinal follow-up, lack of sampling before and after RVO, and lack of healthy control.

Introduction

Traditionally, artificial intelligence (AI) refers to the ability of computing systems to recognize patterns and mimic human cognitive features (e.g., generalize and learn from experience) in high volumes of data [7]. Machine learning (ML) is a type of AI that informs extraction of generalized principles from data, by using algorithms comprised of explicit instructions about the data represented as mathematical models [8]. Although the line between ML models and traditional statistical models (e.g., logistic regression) is not well-defined, distinctions between simple AI or sophisticated ML models (i.e., complex AI) have been proposed. ML differs from traditional statistical approaches, hereafter referred to as "simple AI," in that ML is programmed to learn from examples rather than being programmed with rules [9]. Bioinformatics involves both storing and analysis of biological information using computer technology [10]. In proteomics, which involves the analysis of the expression levels of large numbers of proteins and identification of their biological function and pathways [10], ML techniques can be used to (1) identify the functional significance of resultant proteins using Gene Ontology [11] (a process referred to as enrichment analysis); (2) scrutinize putative biological pathways using comprehensive pathway databases including Kyoto Encyclopedia of Genes and Genomes (KEGG) [12]; and (3) interactively map protein–protein interaction networks by referring to large data mining repositories such as STRING [13]. In metabolomics, computational methods are used to obtain information about endogenous and exogenous metabolites in various tissues as to assess pathophysiological changes and disease-related metabolic pathways using sources such as MetaboAnalyst software [14, 15]. These techniques have provided the opportunity for exploration into the molecular events involved in the development of RVO and generate large datasets of data that can be further analyzed using AI tools, which are well-suited for the extraction of useful information from these biological data [16]. As such, an increasing number of ophthalmology studies have performed bioinformatics in conjunction with AI tools using biofluids as biomarkers.

Exploration of biofluids using AI and bioinformatics may provide insight for the development of more targeted future therapies for retinal diseases such as RVO. Therefore, we set out to systematically review the literature describing applications of AI and bioinformatics-based analyses using biofluids as biomarkers in RVO. Additionally, this comprehensive review provides a summary and appraisal of both the methodology and conclusions of eligible studies with a focus on evaluating the potential of clinical implementation of these technologies.

Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for a Systemic Review and Meta-analysis (PRISMA) guidelines [17]. The complete protocol for the study is available on PROSPERO (reg. CRD42020196749). This systematic review is focused on retinal occlusive diseases and is part of a series of systematic reviews on AI/bioinformatic applications in ophthalmology using biofluids.

Search strategy

A comprehensive search of five databases, including Embase, MEDLINE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Web of Science from inception through August 11, 2020, was conducted. An update of the search strategy was undertaken on August 1, 2021. The search strategy was developed to include the following medical subject

headings (MeSH) derived from three categories including ophthalmology terms, AI/bioinformatics terms, as well as proteomics, metabolomics, and lipidomics (Appendix 1). No language or study design restrictions were applied to the search strategy.

Inclusion and exclusion criteria

All studies pertaining to intra-ocular ophthalmic conditions (i.e., affecting the anatomy or function of the internal structures or surface of the eye) investigating the role of biofluid marker concentrations to predict outcomes, disease conversion/prognosis, disease etiology, and risk factors or to modify patient treatment plans using AI/bioinformatic analyses were included. Biofluid samples extracted from vitreous fluid, aqueous fluid, tear fluid, plasma serum, or ophthalmic biopsies from patients enrolled in the study were considered eligible. Studies that combined biofluid markers with other markers such as imaging, demographics, and genetics in their statistical analyses were acceptable provided that they included at least one biofluid that was a type of protein, cytokine, lipid, or metabolite.

Studies were excluded based on the following criteria: (1) articles that referred exclusively to eye diseases that only affect pediatric patients (e.g., retinopathy of prematurity), (2) studies on non-human subjects (animal or in vitro cell studies), (3) studies including post-mortem biofluid samples, (4) cross-sectional, simple regression analyses without an application of their findings in the study's populations, and (5) abstracts, reviews, systematic reviews, meta-analyses, single-case reports, editorials (without adequate study details and data presentation), and any type of non-peer-reviewed article.

Finally, the subset of studies that met the inclusion criteria and referred to retinal occlusive diseases was selected for the current review.

Study selection and quality assessment

All studies were screened by two independent reviewers (DRP, AP) first by title and abstract, followed by full-text screening. All disagreements were adjudicated by a third independent reviewer (SK and TF). Data extraction was performed by one reviewer using a standardized data abstraction form. To ensure completeness and consistency of our methodology, throughout the data extraction process, 10% of extractions were randomly checked by a second independent reviewer.

Risk of bias (ROB) and quality assessment of the identified studies were performed using the Joanna Briggs Institute Critical Appraisal Tools (JBI) [18, 19]. For each article, JBI criteria questions were noted as "yes," "no," "unclear," or "not applicable." The assessment was performed by one reviewer (DRP), and none of the studies were excluded from the review. Studies that reached up to 49% of questions as "yes" were classified as high ROB; from 50 to 69% as moderate ROB; and more than 70% as low ROB [20].

Data synthesis

Given the heterogeneity in biofluids, AI tools used, and study designs, a meta-analysis was not performed. Means and standard deviations (SD) were used to describe the age of the study populations. For each article, study design, location, type of RVO, biofluids examined, sample size, sex (proportion of males to females), and study aim were tabulated. Additionally, studies were categorized based on the type of statistical model, AI, or bioinformatic analyses used. The purpose of the methodology was also noted.

Results

Study characteristics

The search strategy identified 10,264 articles after removal of duplicates (Fig. 1). Of the 14 articles included in the current study, 7 were prospective (50%), 3 retrospective (21%), and 4 cross-sectional (24%) studies (Table 1). The country of origin of the studies spanned globally, with the majority from Japan (5, 54%) and China (4, 29%). The studies included 578 individuals with RVO (342 BRVO, 191 CRVO, 9 hemi-CRVO, 36 RVO type unspecified) and 201 controls. The mean age was 62.6 (SD = 5.1), and 46% of participants were female. Most studies aimed to identify an optimal treatment strategy (9; 54%) or the pathophysiology underlying the disease (4; 29%).

Appendix Fig. 2 provides details on risk of bias assessment. Overall, three articles were deemed to have a high [6, 21, 22], four moderate [3, 5, 23, 24], and seven low risk of bias [4, 18, 25–29]. Three of the four cross-sectional studies assessed did not identify confounding factors [3, 4, 6], and two did not use objective, standard criteria for measurement of RVO [5, 6]. Most of the cohort studies ($n = 5$, 66%) did not identify confounding factors nor statistical strategies for addressing them [21–23].

Characteristics of biofluid markers

The majority of biofluids were obtained from the aqueous humor (9, 64%), followed by vitreous humor (3, 21%), and only two used serum or whole blood (Table 2). The number of biofluids (514 in total across all studies) reported varied between 94 in RVO including CRVO and BRVO (Clusterin, Complement C3, Ig lambda-like polypeptide 5, Opticin,

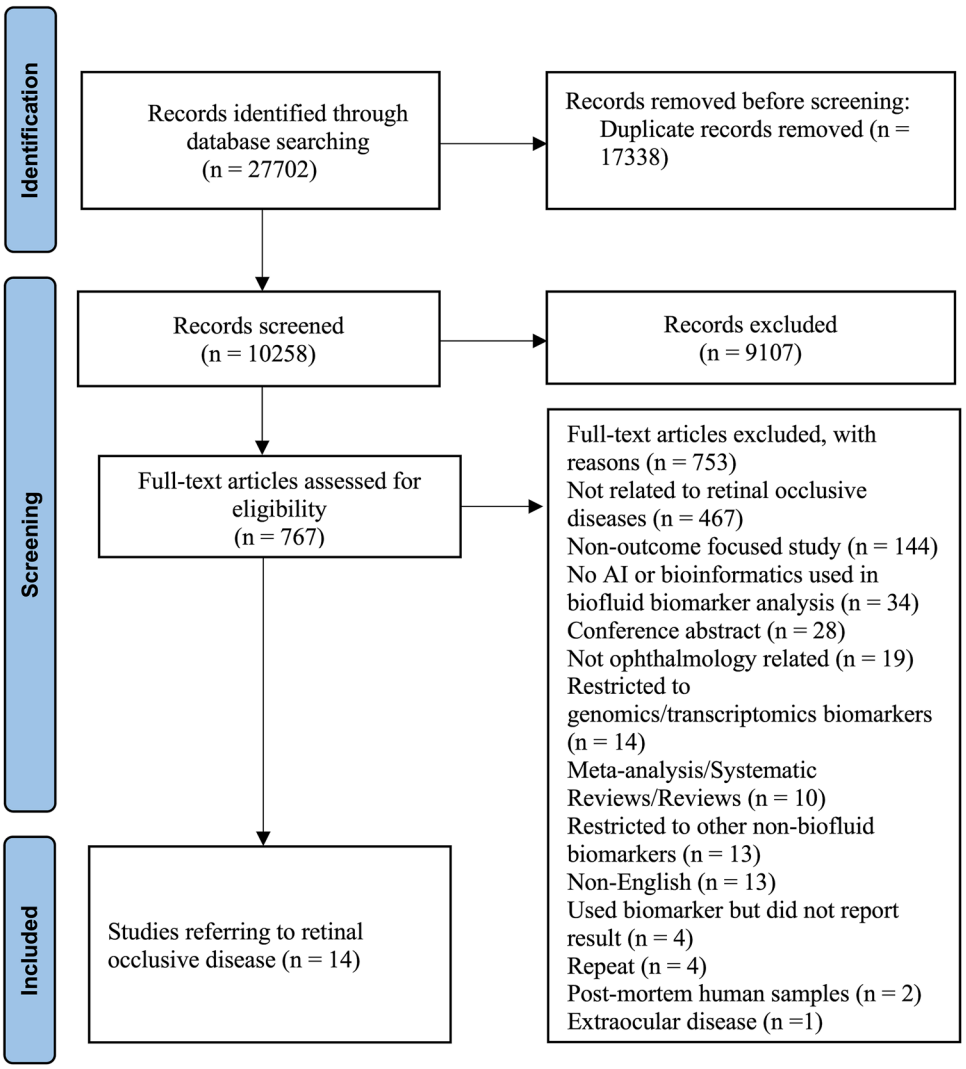

Fig. 1 PRISMA flowchart diagram for study identification and selection. The PRISMA flow diagram for the systematic review presenting the number of studies included and excluded at each screening step, and reasons for exclusion

Vitronectin, etc.) [3] and 49 proteins, mainly implicated in angiogenesis, oxidative stress, and collage synthesis (fibroblast growth factor-4, alpha crystallin A chain, etc.) [6], in BRVO.

Biofluid markers involved in pathogenesis

A metabolomic analysis [4] of contributing proteins to CRVO pathophysiology identified 37 out of 248 metabolites related to aberrations in amino acid metabolism, carbohydrate, and fatty acid metabolism in the aqueous humor of CRVO patients compared to controls (i.e., cataract patients). Total plasma homocysteine (HCY) during fasting and low vitamin B12 levels were associated with an increased risk of RVO, especially CRVO [25], while post-methionine load test HCY, serum folate, and methylenetetrahydrofolate reductase (MTHFR) mutation were not. Zeng et al. [5] reported 29 out of 39 vitreous chemokines (IFN-γ, IL-1β, IL-2, IL-4) to have a statistically higher concentration in CRVO or BRVO complicated with unresolved or condensed vitreous hemorrhage compared to patients with idiopathic preretinal membranes (PRMs) and idiopathic macular holes (IMHs) and 3 chemokines, IL-8, CXCL9, and TNF-α concentrations being more than six times higher in the RVO group compared to control (i.e., PRMs and IHMs patients). Another proteomic study found 5 out of 94 measured vitreous proteins to differ between RVO (CRVO, hemi-CRVO, BRVO) and control group [3] (idiopathic floaters). Clusterin, Complement C3, IGLL5, Opticin, and Vitronectin were suggested to be involved in the inflammatory response pathway, complement activation, and coagulation cascade.

Biofluid markers involved in secondary complications

A proteomic study on 6 patients [6] suggested the implication of 49 proteins related to angiogenesis, oxidative stress, and collagen synthesis in BRVO with macular edema. Other studies found reported various inflammatory factors such

Table 1 Summary characteristics of the included studies

Author(s), publication year	Study design*	Study location	Eye disease	Sample size	Mean age (SD)	Sex (proportion of males to females)	Study aim
Shimura et al. (2008)	Prospective, cohort	Japan	BRVO with ME	BRVO: 60 C: 5 IMH, 7 IEM	BRVO: 62.88 (5.59) C: 63.9 (5.82)	BRVO: 32/28 C: 6/6:	Identification of treatment strategy
Minniti et al. (2014)	Case–control	Italy	CRVO and BRVO	RVO: 91 BRVO: 44 CRVO: 47 C: 71	RVO: 57 (12) BRVO: 57 (10) CRVO: 56 (13) C: 55 (13)	RVO: 51/40; BRVO 20/24; CRVO 29/18; C: 30/41	Identification of risk factors
Yi et al. (2020)	Prospective, cohort	China	CRVO, BRVO, DME, nAMD, pmCNV	CRVO: 21 DME: 22 BRVO: 34 nAMD: 35 pmCNV: 32 Total: 144	CRVO: 56 (14) DME: 56 (9) BRVO: 59 (10) nAMD: 65 (11) pmCNV: 45 (15) Total: 56 (14)	CRVO: 13/8 DME: 15/7 BRVO: 11/23 nAMD: 25/10 pmCNV: 12/20 Total: 76/68	Identification of treatment strategy
Madanagopalanet al. (2018)	Retrospective, cohort	India	CRVO with ME	70	59.84 (10.95)	45/25	Identification of treatment strategy
Noma et al. (2016)	Retrospective, cohort	Japan	BRVO with ME	46	69 (11.9)	23/23	Identification of treatment strategy
An et al. (2021)	Prospective, cohort	South Korea	BRVO with ME	28	63.2 (9.1)	8/20	Identification of treatment strategy
Wei et al. (2020)	Cross-sectional	China	CRVO	CRVO: 15 C: 20 cataract	CRVO: 64.7 (3.1) C: 69.6 (6.8)	CRVO: 8/7 C: 13/7	Identification of novel disease biomarkers
Kaneda et al. (2011)	Prospective, cohort	Japan	BRVO with ME	BRVO: 38 C: 28 cataract	BRVO: 67.1 (1.8) C: 71.4 (1.8)	-	Identification of treatment strategy
Noma et al. (2017)	Prospective, cohort	Japan	BRVO with ME	45	67.8 (11.2)	23/22	Identification of treatment strategy
Noma et al. (2011)	Prospective, cohort	Japan	CRVO	31	69.5 (8.3)	17/14	Identification of treatment strategy
Shchuko et al. (2015)	Prospective, cohort	Russia	CRVO and BRVO	CRVO: 18 BRVO: 26 C: 20 cataract	BRVO and CRVO: 60.7 (7.5) C: 60 (6.1)	CRVO: 5/13 BRVO: 6/20 C: 11/9	Identification of treatment strategy
Reich et al. (2016)	Cross-sectional	Germany	CRVO, Hemi-CRVO, BRVO	CRVO: 20 H-CRVO: 9 BRVO: 15 C: 24 idiopathic floaters	CRVO: 67.6 (14.3) H-CRVO: 69.2 (14.2) BRVO: 68.4 (12.2) C: 62.7 (11.7)	CRVO: 12/8 H-CRVO: 5/4 BRVO: 5/10 C: 11/13	Biomarker discovery Identification of pathophysiology of subtypes of RVO
Yao et al. (2013)	Cross-sectional,	China	BRVO with ME	BRVO: 6 C: 6 cataract	BRVO: 53 (4.98) C: 53.5 (2.35)	BRVO: 3/3 C: 3/3	Biomarker discovery Identification of pathophysiology
Zeng et al. (2019)	Cross-sectional	China	RVO	RVO: 25 C: 20 IMH and PRM	RVO: 57.84 (12.3) C: 56.20 (20.18)	RVO: 15/10 C: N/A	Identification of pathophysiology

"-" indicates that information was not available

*Incl, type, retrospective or prospective, longitudinal, or cross-sectional

Abbreviations: *BRVO* branch retinal vein occlusion, *C* comparator, *CRVO* central retinal vein occlusion, *DME* diabetic macular edema, *H-CRVO* hemi central retinal vein occlusion, *IEM* idiopathic epiretinal membrane, *IMH* idiopathic macular hole, *ME* macular edema, *nAMD* neovascular age-related macular degeneration, *pmCNV* pathological myopic choroidal neovascularization, *PRM* preretinal membranes, *RVO* retinal vein occlusion, *SD* standard deviation

Comparator refers to healthy individuals unless otherwise specified

Table 2 Characteristics of biofluids, and artificial intelligence/bioinformatics analysis categorization and purpose

Author(s) year	Biofluid sample type	Biofluids (total/significant)	Volume of sample/sample analysis	Statistical/AI model type	AI application / Bioinformatic type: Bioinformatic Purpose
Shimura et al. (2008)	Vitreous humor	(2/2) IL-6*, VEGF*	50 µl/ELISA	Multiple regression	Prediction
Minniti et al. (2014)	Serum	(4/2) fasting HCY*, B12*, serum folate, HCY post-methionine loading test	Not applicable	Multiple regression	Prediction
Yi et al. (2020)	Aqueous humor	(3/3) ICAM-1*, VEGF-A*, IL-6*	50 µl/ELISA	Multivariate linear regression	Prediction
Madanagopalan et al. (2018)	Whole blood and serum	(6/2) Blood urea*, serum creatinine*, hemoglobin, fasting and postprandial blood sugar, lipid profile, glycosylated hemoglobin	Not applicable	Binary logistic regression	Prediction
Noma et al. (2016)	Aqueous humor	(5/1) PDGF-AA*, sVEGF-1, sICAM-1, IL-6, IL-8	25 µl/suspension array technology	Multivariate stepwise regression	Prediction
An et al. (2021)	aqueous	(5/4) VEGF-A*, sVEGF- 2*, IL-8*, MCP-1*, PDGF-AA	100 µl /multiplexed sandwich ELISA	Multiple linear regression	Prediction
Wei et al. (2020)	Aqueous humor	(248/37) †L-Serine, L-5-oxoproline, citraconic acid, Ketoleucine, L-glutamine, citramalate, L-methionine, sn-glycerol 3-phosphoate, 2-isopropylmalic acid, D-fructose, glucose, L-tyrosine, D-glucuronic acid, 2-ketogluconic acid, gluconate, L-tryptophan, inosine, stearic acid, uracil, creatinine, L-proline, glycine betaine, nicotinamide, taurine, creatine, L-leucine, L-lysine, carnitine, L-tyrosine, N6, N6, N6-trimethyl-L-lysine, N-acetylhistidine, phosphocreatine, pantothenic acid, butyryl carnitine, uridine, 6-methyladenosine, N-fructosyl isoleucine, etc	80–100 µl/UHPL-MS/MS with UPLC equipped with tandem mass spectrometry	OPLS-DA, PLS-DA, PCA	Classification, prediction, clustering/metabolomics KEGG enrichment analysis: identify potential metabolic pathways
Kaneda et al. (2011)	Aqueous humor	(18/15) IL-1α*, IL-1β*, IFN-γ*, IL-2*, IL-4*, IL-5*, IL-6*, IL-8*, IL-10*, IL-12*, IL-13*, IL-15*, IL-17*, IL-23*, MCP-1*, TNF-α, lymphotoxin-α, VEGF	- /ELISA	multivariate logistic regression	Prediction
Noma et al. (2017)[9]	Aqueous humor	(11/6) sVEGFR-1*, sVEGFR-2, VEGF, PlGF*, sICAM-1*, MCP-1*, PDGF-AA, IL-6*, IL-8*, IL-12 (p70), IL-13	100 µl/suspension array technology	Univariate and multivariate linear regression	Prediction
Noma et al. (2011)	Aqueous humor	(3/2) VEGF*, PEDF*, sICAM-1	300–500 µl/ELISA	Simple linear regression Multiple regression	Prediction

Table 2 (continued)

Author(s) year	Biofluid sample type	Biofluids (total/significant)	Volume of sample/sample analysis	Statistical/AI model type	AI application / Bioinformatic type: Bioinformatic Purpose
Shchuko et al. (2015)	Aqueous humor	(27/11) VEGF*, RAIL-1*, IL-6*, IL-8*, IL-9*, IL-10*, IL-12r70*, IL-13*, IL-15*, MCP-1*, RANTES*, IL-1β, IL-2, IL-4, IL-5, IL-7, IL-17A, eotaxin, FGF-basic, G-CSF, GM-CSF, IFN-γ, MCP-1, MIP-1α, MIP-1β, PDGF-BB, TNF-α, VEGF	100–150 µl/Bio-Plex Protein Assay	Discriminant analysis using Mahalanobis distance	Prediction and classification/proteomic: measure level of cytokines in the aqueous humor samples
Reich et al. (2016)	Vitreous humor	(94/5)** Clusterin*, Complement C3*, Ig lambda-like polypeptide 5*, Opticin*, Vitronectin*, Alpha-1-acid glycoprotein 1, Alpha-1-acid glycoprotein 2, Alpha-1-antitrypsin, Alpha-1B-glycoprotein, Alpha-2-HS-glycoprotein, Alpha-2-macroglobulin, Alpha-crystallin B chain, Amyloid-like protein 2, Fibrinogen alpha chain, Fibrinogen beta chain, Fizzy-related protein homolog, Gelsolin, Glutathione peroxidase 3, etc	10 µl‡ /ELISA, CE-MS	Probabilistic clustering	Clustering/proteomics, Mosaiques-Visu, Proteome Discoverer with SEQUEST algorithm: identify isotopes from CE-MS, peptide sequencing and protein identification
Yao et al. (2013)	Aqueous humor	(49/6) FGF-4*, HDGF*, crystallins, Hpca*, GRTP1*, AP3M2*, CFI*, LIM2, NINJ2, DNAJC15, PMS2CL, MED27, ANAPC5, HAVCR2, PNAS-139, CCNL1, PDCD1L62, ACTB, ALB, P4HA3, OLIG3, AKNA, CRYAA, SPTAN1, ANXA2P2, TTC3, FAM76B, CRYAB, KIFC1, CRYAB, AP3M2, FGF4, CRYGS, CRYBB2, CRYBB2, HLA-A26, ALB, HHAT, ZFP62, CNTROB, Dynamin 3, isoform CRA_e, minichromosome maintenance deficient domain containing 1, isoform CRA_b. cDNA FLJ58860, LRRC10-like protein, cDNA FLJ55029, hCG2040067	100 µl/ ELISA	Proteomics	Proteomics/MASCOT search engine, Gene ontology: identify proteins, potential molecular function, biological process, cellular component analysis

Table 2 (continued)

Author(s) year	Biofluid sample type	Biofluids (total/significant)	Volume of sample/sample analysis	Statistical/AI model type	AI application / Bioinformatic type: Bioinformatic Purpose
Zeng et al. (2019)	Vitreous humor	(39/29) CCL21*, CXCL13*, CCL27*, CCL24*, CX3CL1*, CXCL6*, IFN-γ*, IL-1β*, IL-2*, IL-4*, IL-6*, IL-8*, IL-10*, IL-16*, CXCL10*, CXCL11*, CCL8*, CCL7*, CCL13*, CCL22*, MIF*, CXCL9*, CCL3*, CCL15*, CCL20*, CCL19*, CCL23*, CCL25*, TNF-α*, CCL2, TNF-α, CCL21, CXCL5, CCL26, CCL27, CX3CL1, CXCL6, GM-CSF, CXCL1, CXCL2, CCL1	200–400 µl/Bio-Plex Protein Assay	Proteomics	Proteomics, STRING database: identify functional interactions between proteins

*That had significant implications as determined by statistical analysis

†Complete metabolites are available in figure format but not listed. Significant metabolites available and listed

‡Specified as a sample of a larger unknown quantity

**Full list available in Supplementary Table 1

Abbreviations: *ACTB* actin cytoplasmic 1, *AKNA* AKNA transcript F2, *ALB* isoform 1 of serum albumin precursor, *ANAPC5* anaphase promoting complex subunit 5, *ANXA2P2* putative annexin A2-like protein, *CCL2* C–C motif ligand 2, *CE-MS* capillary electrophoresis coupled to mass spectrometer, *CNTROB* LYST-interacting protein LIP8 centrobin, *CRYAA* alpha crystallin A chain, *CRYAB* alpha crystallin B chain, *CRYBB2* beta-crystallin S, *CRYGS* beta crystallin S, *CXCL10* C-X-C motif ligand 10, *DNAJC15* DnaJ homolog subfamily C member 15, *ELISA* enzyme-linked immunosorbent assay, *FGF-basic* fibroblast growth factor basic, *FGF4* fibroblast growth factor 4 precursor, *G-CSF* granulocyte-colony stimulating factor, *GM-CSF* granulocyte macrophage-CSF, *GRTP1* growth hormone-regulated TBC protein 1, *HAVCR2* hepatitis A virus cellular receptor 2, *HDGF* hepatoma-derived factor isoform a, *HHAT* protein cysteine N-palmitoyltransferase, *Hpca* neuron-specific calcium-binding protein hippocalcin, *IFN-γ* interferon-γ, *IL* interleukin, *KIFC1* kinesin family member C1, *LIM2* lens intrinsic membrane protein 2, *MCP-1* induced protein-10, monocyte chemotactic protein-1, *MCP-1* monocyte chemo-attractant protein 1, *MED27* mediator of RNA polymerase II transcription subunit 27, *MIP-1α* macrophage inflammatory protein-1α, *NINJ2* Ninjurin-2, *OLIG3* oligodendrocyte transcription factor 3, *P4HA3* prolyl 4-hydroxylase alpha III subunit precursor, *PCA* principal component analysis, *PDCD1LG2* programmed death ligand 2 type III isoform, *PDGF-AA* platelet-derived growth factor-AA, *PDGF-BB* platelet derived growth factor-BB, *PEDF* pigment epithelium-derived factor, *PLS-DA* partial least square discriminant analysis, *PMS2CL* PMS2-C terminal like, *RAIL-1* receptor antagonist interleukin-1, *RANTES* normal T expressed and secreted, *sICAM-1* soluble intercellular adhesion molecule 1, *sICAM-1* soluble intercellular adhesion molecule-1, *SPTAN1* spectrin alpha, non-erythrocytic 1, *sVEGF-1* soluble vascular endothelial growth factor receptor-1, *TNF-α* tumor necrotizing factor alpha, *TTC3* tetratricopeptide repeat domain 3, *ZFP62* isoform, 2 of zinc finger protein 62 homolog, *OPLS-DA* orthogonal partial least squares discriminant analysis model

as vitreous IL-6 and VEGF [23], aqueous humor baseline platelet-derived growth factor-AA (PDGF-AA) [27], IL-8, and VEGF-A [24], to be related to pathogenesis of BRVO with macular edema. Patients with vitreous hemorrhage secondary to ischemic RVO were found to have 29 increased concentrations of chemokines in their vitreous, with IL-8, CXCL9, and TNF-a showing the greatest increase compared to controls (PRMs and IMHs).

Biofluid markers indicated in treatment response

In patients with BRVO, macular edema improvement in VA and decrease in foveal thickness after pars plana vitrectomy were predicted by vitreous IL-6 levels [23]. Four other studies showed that the level of certain aqueous humor biofluids were associated with treatment response in BRVO macular edema. Age, baseline central macular thickness (CMT), and baseline aqueous PDGF-AA predicted the number of intravitreal injections needed to control macular edema [27], and IL-8, chemo-attractant protein 1, and soluble VEGF receptors predicted visual gain and CMT reduction at 6 months of intravitreal anti-VEGF injections [24]. Higher pre-treatment aqueous IL-12 was found to be associated with inferior response to bevacizumab treatment (defined as CMT recovery < 90% at 1 month after treatment) [21]. Aqueous flare, another factor predictive of intravitreal anti-VEGF injections treatment of BRVO macular edema, was correlated with aqueous levels of soluble VEGFR-1, PlGF, MCP-1, sICAM-1, IL-6, and IL-8. Similarly, 11 out of 27 measured cytokines (VEGF, receptor antagonist interleukin-1, IL-6, IL-8, IL-9, IL-10, IL-12r70, IL-13, IL-15, etc.) were significantly different compared to cataract patients and significantly changed after intravitreal anti-VEGF injections both in CRVO and BRVO [22]. Finally, a prospective observational study on 31 patients reported that a smaller improvement in visual acuity (LogMAR units) after vitrectomy for macular edema in patients with CRVO was associated with higher VEGF and lower pigment epithelium-derived factor (PEDF) vitreous levels compared to those with a better outcome [29].

Applications of AI and bioinformatics

Studies varied in their reporting of AI algorithm development, ranging from simply describing the standard analysis protocol of established bioinformatics software, such as Gene Ontology analysis (6), STRING database (5), MASCOT search engine (6), Proteome Discoverer with SEQUEST algorithm (3), to dividing the protein data into a discovery and testing stage and performing additional validation analyses using receiver operating characteristic curves (ROC) [3]. Four articles performed proteomic analyses [3, 5, 6, 22], two of which integrated complex AI tools such as discriminant analysis [22] (prediction and classification), probabilistic clustering [3], and string pathway analysis [5] for identification of pathophysiology or biomarker discovery. One study performed metabolomics in conjunction with AI tools for clustering (principal component analysis), classification, and predictive modeling (orthogonal partial least squares discriminant analysis) of contributing proteins to CRVO pathophysiology [4]. There were nine studies that employed simple AI, logistic, and linear regression, to predict various outcomes in RVO using biofluid biomarkers. Compared to the complex AI papers, which were mainly aimed at investigating pathogenesis, most of the simple AI papers investigated cytokines, chemokines, or other biofluids sampled from aqueous, vitreous, serum, or blood, as predictors of treatment response.

Discussion

This is the first systematic review, to our knowledge, to describe the applications of AI and bioinformatics-based analyses using biofluids as markers in RVO. We evaluated the potential of these tools to aid clinical decision-making, specifically whether the levels of biofluid markers could predict visual prognosis [18, 23], treatment response [21, 28], and number of intravitreal injections needed to control RVO complications [22, 26, 27].

For example, the difference in aqueous humor cytokine concentration before and after intravitreal ranibizumab therapy for RVO may be used to predict which patients will have a more favorable response to the therapy and which will have an insufficient response [22]. Such cytokine profiling can be performed using proteomics and complex AI such as multifactorial discriminant analysis using Mahalanobis distance [22]. Bioinformatics approaches can make use the proteome of the aqueous humor to predict which patients may proceed to develop macular edema with BRVO [6].

Additionally, three of the four articles utilizing proteomic analyses proceeded to bring proteomic data into a functional context using bioinformatic tools such as SEQUEST as part of Proteome Discoverer (3), MASCOT search engine and GO analysis (6), and STRING database (5). Given the large output of data produced by proteomic analyses, bioinformatic tools are crucial in providing functional interpretation of protein–protein interactions in the case of STRING database, protein identification in the case of SEQUEST and MASCOT, and prediction of biological function using GO analysis. The results provided are probabilistic, and consequently the interpretation is constantly evolving as new experimental data is added to the bioinformatic databases. The risk of bias ranged from high in 21% to low in 50% of studies. The main methodological quality concerns were the lack of identification and strategies for confounding factors and not recruiting consecutive patients. We identified that

operation of AI/bioinformatics as black-box models, lack of validation and testing, small sample volumes, and lack of healthy controls may serve as some of the challenges for their use in analysis of biofluids.

The reviewed studies used established AI tools such as discriminant analysis [22], probabilistic clustering [19], and principal component analysis [4], in conjunction with proteomic and metabolomic tools that are freely available and well-documented. However, only one study implemented a biomarker validation stage using ROC [3]. Cross-validation involves partitioning data into training, testing, and validation and provides estimations of the predictive value of the AI algorithm, which can reduce the bias associated with small sample sizes and the bias related to choosing the type of AI tools to use [30]. OCTs provide non-invasive near-microscopic visualization of retinal structures, are obtained relatively fast [31, 32], and can be used to support biofluid predictions. The combination of biofluids and OCTs has the potential to increase the clinical decision-making value of both techniques. For example, in BRVO, foveal thickness change post-vitrectomy has been correlated with vitreous IL-6 levels and found to predict best-corrected VA at 6 months [23], and central macular thickness and PDGF-AA were predictors of the number of intravitreal injections required to control macular edema [27]. In CRVO, anatomical response to anti-VEGF therapy, measured as central retinal thickness (CRT), was best predicted by baseline CRT and ICAM-1 [26]. Thus, individual-level measurements of cytokine expression correlated with OCT measures may help guide personalized treatment regiments that account for the fact that the rate of progression of disease is variable among patients.

Biofluid sampling is challenging due to small sample volume, inconsistent feasibility of office-based sampling, and lack of healthy controls. It was demonstrated that multiplex cytometric bead assay can reliably use a volume as small as 25 µl for cytokine analysis [33]. Half of the studies used enzyme-linked immunosorbent assay for sample analysis [6, 19, 21, 23, 24, 26, 29], a standard assay kit. One study [3] included in our analysis used a volume of 10 µl, and another did not mention the sample volume [21]. However, bias related to sample handling and processing must also be considered and could be reduced by appropriate protocol documentation and replication studies. While aqueous humor is more accessible in an office setting, vitreous samples are mostly obtained during vitrectomies. An alternative to vitrectomy samples is the collection of vitreous reflux after intravitreal injection using Schirmer's tear strips, which can be done in the office [34]. Another challenge is that the interpretation of proteomic and metabolic studies may be confounded by the lack of healthy controls. Samples obtained from patients undergoing cataract surgery or intravitreal injections for other macular diseases may serve as good comparators with regards to biomarker levels [26, 35]. It is important to note, however, that the inflammatory markers identified in cases may be underestimated/overestimated when using comparators with and existing inflammatory state secondary to mild pathologies and/or exposure to procedures. Additionally, all of the samples from the assessed articles were taken after RVO had occurred, and therefore, it is not possible to definitely conclude if the biofluids identified are contributory to RVO and/or a reflection of the downstream consequences of RVO.

Changes in both serum and intraocular biofluid levels have been observed in RVO. None of the studies in the current review sampled the same biofluids in both serum and intraocular fluids. However, a consecutive case series, in which patients with proliferative vitreoretinopathy (PVR) and rhegmatogenous retinal detachment (RRD) were compared with macular hole (MH) or epiretinal membrane (ERM) patients, indicated that while the serum inflammatory profiles did not differ between groups, the concentrations of several cytokines were upregulated in PVR patients [36]. Additionally, concentrations of lipocalin-2 (LCN2) were found to be higher in the aqueous humor of CRVO patients compared to cataract patients, while no differences were noted in serum LCN2 levels [37]. These findings suggest that changes in serum biofluids, which largely indicate circulating systemic factors, have distinctive predictive significance compared to changes in the concentration of biofluids pertaining to the intraocular milieu. Nevertheless, as demonstrated in the current review, both serum and intraocular fluids may play a role in the identification of treatment strategy. Further studies are required to understand how to make use of the predictive value of the distinct profiles of serum and intraocular fluid inflammation-related factors of RVO patients in a clinical setting.

Conclusion

In this systematic review of 578 individuals and 514 biofluids, we documented the applications of AI and bioinformatics-based analyses using biofluids as markers in RVO etiology, prognosis, treatment response, and management. Overall, several studies have combined proteomics and metabolomics with AI analyses for clinical decision-making. Considering the limitations of these studies (e.g., lack of healthy controls, small sample sizes, small volumes), further validation of the studies outlined and comparison and integration of data obtained from various RVO severity, types, and treatment regiments are required before these techniques can be adopted for individual-level clinical treatment. In addition to these limitations, this review also highlights that although the application of AI and bioinformatics in RVO is poised to grow in the future, currently its use is only at its infancy.

Appendix 1. Search terms used to query databases (August 1, 2021)

OVID MEDLINE

1 (ophth* or ocular or intraocular or eye* or retina* or macula* or fovea* or uvea* or sclera* or cornea* or conjunctiva* or iris or "vitreous body" or "vitreous humo?r" or "vitreous fluid" or vitreo* or "aqueous humo?r" or "aqueous fluid" or tears or ((tear or lacrimal) adj fluid) or glaucoma or retinop* or retinoblastoma or uveitis or iritis or choroiditis or retinitis or chorioretinitis or conjunctivitis or endophthalmitis or cataract* or ?????????opia or "optic atrophy" or "optic neuropathy" or vitrectomy or phacoemulsification or trabeculotomy or (paracentesis adj3 "anterior chamber")).tw.

2 ("precision medicine" or "precision health" or "personalized medicine" or "personalized proteomics" or thera?nostic? or "tailored medicine" or "artificial intelligence" or "machine learning" or "deep learning" or algorithm? or ((supervised or unsupervised or biased or unbiased or bayesian or hierarchical or neur??al) adj (cluster* or learning or learner? or classifi* or network?)) or "k-nearest neighbo?r?" or "naive bayes" or (decision adj (tree? or forest? or jungle?)) or "random forest?" or "gradient-boost*" or "support vector machine" or "k-means" or "association rules" or "recursive partitioning" or "discriminant analysis" or "feature selection" or ((linear or nonlinear or "non-linear" or logistic or ordinal or poisson or quantile or analysis) adj1 (regression? or model?)) or bioinformatic? or "gene ontology" or "Kyoto Encyclopedia of Genes and Genomes" or "KEGG" or ((progress* or regress* or recover* or respond* or response*) and (predict* or stratif*))).tw.

3 (Proteomic? or proteome? or metabolomic? or metabolome? or lipidomic? or lipidome? or "?????inflammatory protein?" or "?????inflammatory marker" or cytokine? or interleukin? or lymphokine? or monokine? or interferon? or "colony stimulating factor?" or chemokine? or "growth factor?" or "necrosis factor?" or "chemotactic protein?" or "adhesion molecule?" or "adhesion protein?" or "matrix metalloproteinase-2" or myeloperoxidase? or "tissue inhibitor of metalloproteinase-2" or "macrophage inflammatory protein-1" or "brain-derived neurotrophic factor" or angiopoietin? or ((hemoglobin or haemoglobin) adj1 (a1c or glycated)) or hba1c or "c reactive protein" or "c-reactive protein" or crp or hscrp or "hs-crp" or ((protein or biomarker) and (concentration? or level? or quantif* or quantit* or mass spectrometry or iTRAQ or MALDI or SELDI or assay))).tw.

4 exp Ophthalmology/cl, di, dg, ec, pd, px, sn, sd, su, th, td, ed, es, hi, is, mt, og, rt, st [Classification, Diagnosis, Diagnostic Imaging, Economics, Pharmacology, Psychology, Statistics & Numerical Data, Supply & Distribution, Surgery, Therapy, Trends, Education, Ethics, History, Instrumentation, Methods, Organization & Administration, Radiotherapy, Standards]

5 eye/ or exp anterior eye segment/ or "anterior capsule of the lens"/ or conjunctiva/ or meibomian glands/ or exp "pigment epithelium of eye"/ or exp posterior eye segment/ or exp retina/ or sclera/ or tenon capsule/ or exp uvea/

Appendix 2

Fig. 2 Assessment of risk of bias and quality of included studies based on criteria from Joanna Briggs Institute Critical Appraisal Tools

6 Tears/
7 eye diseases/ or cogan syndrome/ or exp conjunctival diseases/ or exp corneal diseases/ or exp eye abnormalities/ or exp eye diseases, hereditary/ or exp eye hemorrhage/ or exp eye infections/ or exp eye injuries/ or exp eye manifestations/ or exp eye neoplasms/ or exp lens diseases/ or exp ocular hypertension/ or ocular hypotension/ or exp optic nerve diseases/ or exp pupil disorders/ or exp refractive errors/ or exp retinal diseases/ or exp scleral diseases/ or exp uveal diseases/ or exp vision disorders/ or vitreous detachment/

8 Vitrectomy/ae, ec, ed, es, hi, is, mt, mo, nu, px, rh, st, sn, td [Adverse Effects, Economics, Education, Ethics, History, Instrumentation, Methods, Mortality, Nursing, Psychology, Rehabilitation, Standards, Statistics & Numerical Data, Trends]

9 Phacoemulsification/ae, cl, ec, ed, hi, is, mt, mo, nu, px, rh, st, sn, td [Adverse Effects, Classification, Economics, Education, History, Instrumentation, Methods, Mortality, Nursing, Psychology, Rehabilitation, Standards, Statistics & Numerical Data, Trends]

10 Trabeculectomy/nu, px, rh, st, sn, td, ae, cl, ec, ed, hi, is, mt, mo [Nursing, Psychology, Rehabilitation, Standards, Statistics & Numerical Data, Trends, Adverse Effects, Classification, Economics, Education, History, Instrumentation, Methods, Mortality]

11 Precision Medicine/ae, cl, ec, es, hi, is, mt, mo, nu, px, st, sn, td [Adverse Effects, Classification, Economics, Ethics, History, Instrumentation, Methods, Mortality, Nursing, Psychology, Standards, Statistics & Numerical Data, Trends]

12 Theranostic Nanomedicine/
13 exp algorithms/
14 Neural Networks, Computer/
15 Decision Trees/
16 exp Regression Analysis/
17 Discriminant Analysis/
18 exp Proteomics/cl, ec, ed, es, hi, is, mt, og, st, sn, td [Classification, Economics, Education, Ethics, History, Instrumentation, Methods, Organization & Administration, Standards, Statistics & Numerical Data, Trends]

19 Proteome/

20 exp Metabolomics/cl, ec, ed, es, hi, is, mt, og, st, sn, td [Classification, Economics, Education, Ethics, History, Instrumentation, Methods, Organization & Administration, Standards, Statistics & Numerical Data, Trends]

21 Metabolome/
22 exp Cytokines/
23 exp Cell Adhesion Molecules/
24 Matrix Metalloproteinase 2/
25 Peroxidase/
26 "Tissue Inhibitor of Metalloproteinase-1"/

27 "Tissue Inhibitor of Metalloproteinase-2"/
28 Brain-Derived Neurotrophic Factor/
29 exp Angiopoietins/
30 Gene Ontology/
31 exp Proteins/
32 exp Peptides/
33 Biomarkers/
34 (concentration? or level? or quantif* or quantit* or mass spectrometry or iTRAQ or MALDI or SELDI or assay).tw.
35 (31 or 32 or 33) and 3
36 1 or 4 or 5 or 6 or 7 or 8 or 9 or 10
37 2 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 30
38 3 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 35
39 36 and 37 and 38
40 limit 39 to animals
41 limit 40 to humans
42 40 not 41
43 limit 39 to "review articles"
44 39 not (42 or 43)

Web of Science

(TI=(ophth* or ocular or intraocular or eye* or retina* or macula* or fovea* or uvea* or sclera* or cornea* or conjunctiva* or iris or "vitreous body" or "vitreous humo$r" or "vitreous fluid" or vitreo* or "aqueous humo$r" or "aqueous fluid" or tears or ((tear or lacrimal) NEAR/1 fluid) or glaucoma or retinop* or retinoblastoma or uveitis or iritis or choroiditis or retinitis or chorioretinitis or conjunctivitis or endophthalmitis or cataract* or *opia or "optic atrophy" or "optic neuropathy" or vitrectomy or phacoemulsification or trabeculotomy.tw. or (paracentesis NEAR/3 "anterior chamber")) or AB=(ophth* or ocular or intraocular or eye* or retina* or macula* or fovea* or uvea* or sclera* or cornea* or conjunctiva* or iris.tw. or "vitreous body" or "vitreous humo$r" or "vitreous fluid" or vitreo* or "aqueous humo$r" or "aqueous fluid" or tears or ((tear or lacrimal) NEAR/1 fluid) or glaucoma or retinop* or retinoblastoma or uveitis or iritis or choroiditis or retinitis or chorioretinitis or conjunctivitis or endophthalmitis or cataract* or "optic atrophy" or "optic neuropathy" or vitrectomy or phacoemulsification or trabeculotomy or (paracentesis NEAR/3 "anterior chamber"))) AND
(TI=("precision medicine" or "precision health" or "personalized medicine" or "personalized proteomics" or thera$nostic* or "tailored medicine" or "artificial intelligence" or "machine learning" or "deep learning" or algorithm$ or ((supervised or unsupervised or biased or unbiased or bayesian or hierarchical or neural or neuronal) NEAR/1 (cluster* or learning or learner$ or classifi* or network$)) or "k-nearest neighbo$r*" or "naive bayes" or (decision NEAR/1 (tree$ or forest$ or jungle$)) or "random forest$" or "gradient-boost*" or "support vector machine" or "k-means" or "association rules" or "recursive partitioning" or "discriminant analysis" or "feature selection" or ((linear or nonlinear or "non-linear" or logistic or ordinal or poisson or quantile or analysis) NEAR/1 (regression$ or model$)) or bioinformatic$ or ((progress* or regress* or recover* or respond* or response*) and (predict* or stratif*))) OR AB=("precision medicine" or "precision health" or "personalized medicine" or "personalized proteomics" or thera$nostic* or

"tailored medicine" or "artificial intelligence" or "machine learning" or "deep learning" or algorithm$ or ((supervised or unsupervised or biased or unbiased or bayesian or hierarchical or neural or neuronal) NEAR/1 (cluster* or learning or learner$ or classifi* or network$)) or "k-nearest neighbo$r*" or "naive bayes" or (decision NEAR/1 (tree$ or forest$ or jungle$)) or "random forest$" or "gradient-boost*" or "support vector machine" or "k-means" or "association rules" or "recursive partitioning" or "discriminant analysis" or "feature selection" or ((linear or nonlinear or "non-linear" or logistic or ordinal or poisson or quantile or analysis) NEAR/1 (regression$ or model$)) or bioinformatic$ or ((progress* or regress* or recover* or respond* or response*) and (predict* or stratif*)))) AND
(TI=(Proteomic$ or proteome$ or metabolomic$ or metabolome$ or lipidomic$ or lipidome$ or "*inflammatory protein$" or "*inflammatory marker" or cytokine$ or interleukin$ or lymphokine$ or monokine$ or interferon$ or "colony stimulating factor$" or chemokine$ or "growth factor$" or "necrosis factor$" or "chemotactic protein$" or "adhesion molecule$" or "adhesion protein$" or "matrix metalloproteinase-2" or myeloperoxidase$ or "tissue inhibitor of metalloproteinase-2" or "macrophage inflammatory protein-1" or "brain-derived neurotrophic factor" or angiopoietin$ or ((hemoglobin or haemoglobin) NEAR/1 (a1c or glycated or glycosylated)) or hba1c or "c reactive protein" or "c-reactive protein" or crp or hscrp or "hs-crp" or ((protein or biomarker) and (concentration$ or level$ or quantif* or quantit* or mass spectrometry or iTRAQ or MALDI or SELDI or assay))) OR AB=(Proteomic$ or proteome$ or metabolomic$ or metabolome$ or lipidomic$ or lipidome$ or "inflammatory protein$" or "inflammatory marker" or cytokine$ or interleukin$ or lymphokine$ or monokine$ or interferon$ or "colony stimulating factor$" or chemokine$ or "growth factor$" or "necrosis factor$" or "chemotactic protein$" or "adhesion molecule$" or "adhesion protein$" or "matrix metalloproteinase-2" or myeloperoxidase$ or "tissue inhibitor of metalloproteinase-2" or "macrophage inflammatory protein-1" or "brain-derived neurotrophic factor" or angiopoietin$ or ((hemoglobin or haemoglobin) NEAR/1 (a1c or glycated or glycosylated)) or hba1c or "c reactive protein" or "c-reactive protein" or crp or hscrp or "hs-crp" or ((protein or biomarker) and (concentration$ or level$ or quantif* or quantit* or mass spectrometry or iTRAQ or MALDI or SELDI or assay))))

Cochrane

#1 ophth* or ocular or intraocular or eye* or retina* or macula* or fovea* or uvea* or sclera* or cornea* or conjunctiva* or iris or "vitreous body" or "vitreous humo*r" or "vitreous fluid" or vitreo* or "aqueous humo*r" or "aqueous fluid" or tears or ((tear or lacrimal) NEXT fluid) or glaucoma or retinop* or retinoblastoma or uveitis or iritis or choroiditis or retinitis or chorioretinitis or conjunctivitis or endophthalmitis or cataract* or *opia or "optic atrophy" or "optic neuropathy" or vitrectomy or phacoemulsification or trabeculotomy or (paracentesis NEAR/3 "anterior chamber") in Cochrane Reviews, Trials

#2 "precision medicine" or "precision health" or "personalized medicine" or "personalized proteomics" or thera*nostic* or "tailored medicine" or "artificial intelligence" or "machine learning" or "deep learning" or algorithm* or ((supervised or unsupervised or biased or unbiased or bayesian or hierarchical or neural or neuronal) NEXT (cluster* or learning or learner* or classifi* or network*)) or "k-nearest neighbo*r*" or "naive bayes" or (decision NEXT (tree* or

forest* or jungle*)) or "random forest*" or "gradient-boost*" or "support vector machine" or "k-means" or "association rules" or "recursive partitioning" or "discriminant analysis" or "feature selection" or ((linear or nonlinear or "non-linear" or logistic or ordinal or poisson or quantile or analysis) NEXT (regression* or model*)) or bioinformatic* or ((progress* or regress* or recover* or respond* or response*) and (predict* or stratif*)) in Cochrane Reviews, Trials

#3 Proteomic* or proteome* or metabolomic* or metabolome* or lipidomic* or lipidome* or "*inflammatory protein*" or "*inflammatory marker*" or cytokine* or interleukin* or lymphokine* or monokine$ or interferon* or "colony stimulating factor*" or chemokine* or "growth factor*" or "necrosis factor*" or "chemotactic protein*" or "adhesion molecule*" or "adhesion protein*" or "matrix metalloproteinase-2" or myeloperoxidase* or "tissue inhibitor of metalloproteinase-2" or "macrophage inflammatory protein-1" or "brain-derived neurotrophic factor" or angiopoietin* or ((hemoglobin or haemoglobin) NEXT (a1c or glycated or glycosylated)) or hba1c or "c reactive protein" or "c-reactive protein" or crp or hscrp or "hs-crp" or ((protein or biomarker) and (concentration* or level* or quantif* or quantit* or mass spectrometry or iTRAQ or MALDI or SELDI or assay)) in Cochrane Reviews, Trials

#4 MeSH descriptor: [Ophthalmology] this term only
#5 MeSH descriptor: [Eye] this term only
#6 MeSH descriptor: [Tears] this term only
#7 MeSH descriptor: [Eye Diseases] this term only
#8 MeSH descriptor: [Vitrectomy] this term only
#9 MeSH descriptor: [Phacoemulsification] this term only
#10 MeSH descriptor: [Trabeculectomy] this term only
#11 MeSH descriptor: [Precision Medicine] this term only
#12 MeSH descriptor: [Theranostic Nanomedicine] this term only
#13 MeSH descriptor: [Artificial Intelligence] 1 tree(s) exploded
#14 MeSH descriptor: [Algorithms] this term only
#15 MeSH descriptor: [Neural Networks, Computer] this term only
#16 MeSH descriptor: [Decision Trees] this term only
#17 MeSH descriptor: [Regression Analysis] 1 tree(s) exploded
#18 MeSH descriptor: [Discriminant Analysis] this term only
#19 MeSH descriptor: [Proteomics] 1 tree(s) exploded
#20 MeSH descriptor: [Metabolomics] 1 tree(s) exploded
#21 MeSH descriptor: [Proteins] explode all trees
#22 MeSH descriptor: [Peptides] explode all trees
#23 MeSH descriptor: [Biomarkers] explode all trees
#24 concentration* or level* or quantif* or quantit* or mass spectrometry or iTRAQ or MALDI or SELDI or assay
#25 (#21 or #22 or #23) and #24
#26 MeSH descriptor: [Cytokines] 1 tree(s) exploded
#27 MeSH descriptor: [Cell Adhesion Molecules] 1 tree(s) exploded
#28 MeSH descriptor: [Matrix Metalloproteinase 2] this term only
#29 MeSH descriptor: [Peroxidase] this term only
#30 MeSH descriptor: [Tissue Inhibitor of Metalloproteinase-1] this term only
#31 MeSH descriptor: [Tissue Inhibitor of Metalloproteinase-2] this term only

#32 MeSH descriptor: [Brain-Derived Neurotrophic Factor] this term only
#33 MeSH descriptor: [Angiopoietins] 1 tree(s) exploded
#34 MeSH descriptor: [Anterior Eye Segment] explode all trees
#35 MeSH descriptor: [Anterior Capsule of the Lens] this term only
#36 MeSH descriptor: [Axial Length, Eye] this term only
#37 MeSH descriptor: [Pigment Epithelium of Eye] 1 tree(s) exploded
#38 MeSH descriptor: [Posterior Eye Segment] explode all trees
#39 MeSH descriptor: [Retina] explode all trees
#40 MeSH descriptor: [Sclera] this term only
#41 MeSH descriptor: [Tenon Capsule] this term only
#42 MeSH descriptor: [Uvea] explode all trees
#43 MeSH descriptor: [Asthenopia] this term only
#44 MeSH descriptor: [Cogan Syndrome] this term only
#45 MeSH descriptor: [Conjunctival Diseases] explode all trees
#46 MeSH descriptor: [Corneal Diseases] explode all trees
#47 MeSH descriptor: [Eye Abnormalities] explode all trees
#48 MeSH descriptor: [Eye Diseases, Hereditary] explode all trees
#49 MeSH descriptor: [Eye Hemorrhage] explode all trees
#50 MeSH descriptor: [Eye Infections] 1 tree(s) exploded
#51 MeSH descriptor: [Eye Injuries] 1 tree(s) exploded
#52 MeSH descriptor: [Eye Manifestations] 1 tree(s) exploded
#53 MeSH descriptor: [Eye Neoplasms] 1 tree(s) exploded
#54 MeSH descriptor: [Lens Diseases] explode all trees
#55 MeSH descriptor: [Ocular Hypertension] explode all trees
#56 MeSH descriptor: [Ocular Hypotension] this term only
#57 MeSH descriptor: [Optic Nerve Diseases] 1 tree(s) exploded
#58 MeSH descriptor: [Pupil Disorders] 1 tree(s) exploded
#59 MeSH descriptor: [Refractive Errors] explode all trees
#60 MeSH descriptor: [Retinal Diseases] explode all trees
#61 MeSH descriptor: [Scleral Diseases] explode all trees
#62 MeSH descriptor: [Uveal Diseases] explode all trees
#63 MeSH descriptor: [Vision Disorders] 1 tree(s) exploded
#64 MeSH descriptor: [Vitreous Detachment] this term only
#65 #1 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64
#66 #2 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18
#67 #3 or #19 or #20 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33
#68 #65 and #66 and #67

Ovid EMBASE: Embase Classic + Embase

1 (ophth* or ocular or intraocular or eye* or retina* or macula* or fovea* or uvea* or sclera* or cornea* or conjunctiva* or iris or "vitreous body" or "vitreous humo?r" or "vitreous fluid" or vitreo* or "aqueous humo?r" or "aqueous fluid" or tears or ((tear or lacrimal) adj fluid) or glaucoma or retinop* or retinoblastoma or uveitis or iritis or choroiditis or retinitis or

chorioretinitis or conjunctivitis or endophthalmitis or cataract* or ?????????opia or "optic atrophy" or "optic neuropathy" or vitrectomy or phacoemulsification or trabeculotomy or (paracentesis adj3 "anterior chamber")).tw.

2 ("precision medicine" or "precision health" or "personalized medicine" or "personalized proteomics" or thera?nostic? or "tailored medicine" or "artificial intelligence" or "machine learning" or "deep learning" or algorithm? or ((supervised or unsupervised or biased or unbiased or bayesian or hierarchical or neur??al) adj (cluster* or learning or learner? or classifi* or network?)) or "k-nearest neighbo?r?" or "naive bayes" or (decision adj (tree? or forest? or jungle?)) or "random forest?" or "gradient-boost*" or "support vector machine" or "k-means" or "association rules" or "recursive partitioning" or "discriminant analysis" or "feature selection" or ((linear or nonlinear or "non-linear" or logistic or ordinal or poisson or quantile or analysis) adj1 (regression? or model?)) or bioinformatic? or "gene ontology" or "Kyoto Encyclopedia of Genes and Genomes" or "KEGG" or ((progress* or regress* or recover* or respond* or response*) and (predict* or stratif*))).tw.

3 (Proteomic? or proteome? or metabolomic? or metabolome? or lipidomic? or lipidome? or "?????inflammatory protein?" or "?????inflammatory marker" or cytokine? or interleukin? or lymphokine? or monokine? or interferon? or "colony stimulating factor?" or chemokine? or "growth factor?" or "necrosis factor?" or "chemotactic protein?" or "adhesion molecule?" or "adhesion protein?" or "matrix metalloproteinase-2" or myeloperoxidase? or "tissue inhibitor of metalloproteinase-2" or "macrophage inflammatory protein-1" or "brain-derived neurotrophic factor" or angiopoietin? or ((hemoglobin or haemoglobin) adj1 (a1c or glycated)) or hba1c or "c reactive protein" or "c-reactive protein" or crp or hscrp or "hs-crp" or ((protein or biomarker) and (concentration? or level? or quantif* or quantit* or mass spectrometry or iTRAQ or MALDI or SELDI or assay))).tw.

4 exp Ophthalmology/cl, di, dg, ec, pd, px, sn, sd, su, th, td, ed, es, hi, is, mt, og, rt, st [Classification, Diagnosis, Diagnostic Imaging, Economics, Pharmacology, Psychology, Statistics & Numerical Data, Supply & Distribution, Surgery, Therapy, Trends, Education, Ethics, History, Instrumentation, Methods, Organization & Administration, Radiotherapy, Standards]

5 eye/ or exp anterior eye segment/ or "anterior capsule of the lens"/ or conjunctiva/ or meibomian glands/ or exp "pigment epithelium of eye"/ or exp posterior eye segment/ or exp retina/ or sclera/ or tenon capsule/ or exp uvea/

6 Tears/

7 eye diseases/ or cogan syndrome/ or exp conjunctival diseases/ or exp corneal diseases/ or exp eye abnormalities/ or exp eye diseases, hereditary/ or exp eye hemorrhage/ or exp eye infections/ or exp eye injuries/ or exp eye manifestations/ or exp eye neoplasms/ or exp lens diseases/ or exp ocular hypertension/ or ocular hypotension/ or exp optic nerve diseases/ or exp pupil disorders/ or exp refractive errors/ or exp retinal diseases/ or exp scleral diseases/ or exp uveal diseases/ or exp vision disorders/ or vitreous detachment/

8 Vitrectomy/ae, ec, ed, es, hi, is, mt, mo, nu, px, rh, st, sn, td [Adverse Effects, Economics, Education, Ethics, History, Instrumentation, Methods, Mortality, Nursing, Psychology, Rehabilitation, Standards, Statistics & Numerical Data, Trends]

9 Phacoemulsification/ae, cl, ec, ed, hi, is, mt, mo, nu, px, rh, st, sn, td [Adverse Effects, Classification, Economics, Education, History, Instrumentation, Methods, Mortality, Nursing, Psychology, Rehabilitation, Standards, Statistics & Numerical Data, Trends]

10 Trabeculectomy/nu, px, rh, st, sn, td, ae, cl, ec, ed, hi, is, mt, mo [Nursing, Psychology, Rehabilitation, Standards, Statistics & Numerical Data, Trends, Adverse Effects, Classification, Economics, Education, History, Instrumentation, Methods, Mortality]

11 Precision Medicine/ae, cl, ec, es, hi, is, mt, mo, nu, px, st, sn, td [Adverse Effects, Classification, Economics, Ethics, History, Instrumentation, Methods, Mortality, Nursing, Psychology, Standards, Statistics & Numerical Data, Trends]

12 Theranostic Nanomedicine/
13 exp algorithms/
14 Neural Networks, Computer/
15 Decision Trees/
16 exp Regression Analysis/
17 Discriminant Analysis/
18 exp Proteomics/cl, ec, ed, es, hi, is, mt, og, st, sn, td [Classification, Economics, Education, Ethics, History, Instrumentation, Methods, Organization & Administration, Standards, Statistics & Numerical Data, Trends]
19 Proteome/
20 exp Metabolomics/cl, ec, ed, es, hi, is, mt, og, st, sn, td [Classification, Economics, Education, Ethics, History, Instrumentation, Methods, Organization & Administration, Standards, Statistics & Numerical Data, Trends]
21 Metabolome/
22 exp Cytokines/
23 exp Cell Adhesion Molecules/
24 Matrix Metalloproteinase 2/
25 Peroxidase/
26 "Tissue Inhibitor of Metalloproteinase-1"/
27 "Tissue Inhibitor of Metalloproteinase-2"/
28 Brain-Derived Neurotrophic Factor/
29 exp Angiopoietins/
30 Gene Ontology/
31 exp Proteins/
32 exp Peptides/
33 Biomarkers/
34 (concentration? or level? or quantif* or quantit* or mass spectrometry or iTRAQ or MALDI or SELDI or assay).tw.
35 (31 or 32 or 33) and 3
36 1 or 4 or 5 or 6 or 7 or 8 or 9 or 10
37 2 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 30
38 3 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 35
39 36 and 37 and 38
40 limit 39 to animals
41 limit 40 to humans
42 40 not 41
43 limit 39 to "review articles"
44 39 not (42 or 43)

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Declarations

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

Conflict of interest The authors declare no competing interests.

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