

The Application of Artificial Intelligence in the Analysis of Biomarkers for Diagnosis and Management of Uveitis and Uveal Melanoma: A Systematic Review

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Purpose: This study aims to identify the available literature describing the utilization of artificial intelligence (AI) as a clinical tool in uveal diseases.

Methods: A comprehensive literature search was conducted in 5 electronic databases, finding studies relating to AI and uveal diseases.

Results: After screening 10,258 studies, 18 studies met the inclusion criteria. Uveal melanoma (44%) and uveitis (56%) were the two uveal diseases examined. Ten studies (56%) used complex AI, while 13 studies (72%) used regression methods. Lactate dehydrogenase (LDH), found in 50% of studies concerning uveal melanoma, was the only biomarker that overlapped in multiple studies. However, 94% of studies highlighted that the biomarkers of interest were significant.

Conclusion: This study highlights the value of using complex and simple AI tools as a clinical tool in uveal diseases. Particularly, complex AI methods can be used to weigh the merit of significant biomarkers, such as LDH, in order to create staging tools and predict treatment outcomes.

Keywords: uveal melanoma, uveitis, artificial intelligence, biomarkers

Introduction

The uvea of the eye is a highly vascular structure including the anterior uvea and the posterior uvea or choroid,¹ which are susceptible to breakdown of the blood-aqueous barrier and inflammatory response in cases of various diseases. Uveitis is a common sight-threatening disease that leads to 5–10% of vision impairment worldwide.² It has been suggested that there are several markers that can predict the prognosis of the disease, pathogenesis and treatment outcome.^{3,4} Sauer et al found that elevated levels of interleukin (IL)-1 β , IL-2, IL-6, interferon (IFN)- γ and tissue necrosis factor (TNF)- α may be implicated in uveitis.⁵ Additionally, elevated intraocular levels of IL-6 has been associated with idiopathic uveitis and uveitis in Behçet's disease, sarcoidosis and ankylosing spondylitis.⁵ For uveal diseases such as uveal melanoma, the most common primary intraocular malignancy in adults,⁶ limited information is known on the characteristics that predict survivability for patients.⁸ Ericsson et al established that Human Leukocyte Antigen (HLA)-I expression is upregulated in metastatic disease resulting in a poor prognosis.⁹

As artificial intelligence (AI) methods are rapidly progressing, breakthrough technologies are changing the landscape of healthcare research with powerful diagnostic and prognostic value.¹⁰ Machine learning methods (also referred to as

complex AI), supervised and unsupervised, are employed by AI systems to account for complex interaction either by collecting input data including biofluid and tissue to predict output values based on new input samples or by finding underlying patterns in an unlabelled data set to identify sub-cluster and outliers in the data.¹⁰

Although AI methods are well described in other healthcare fields, there is limited information on the value of using AI methods in understanding the complex nature of uveal diseases. Machine learning has allowed for more robust discovery of biomarkers that have been approved by the Food and Drug Administration (FDA) to guide treatment which can be valuable in diseases such as uveitis and uveal melanoma.¹⁰ Additionally, the biomarkers act as powerful clinical predictors that can individualize treatment options for patients for more desired outcomes.¹⁰

Herein, we aim to systematically review the available literature describing the application of AI methods in uveal diseases, highlighting the important biomarkers identified by AI methods for treatment, prognosis, and disease profile. We also characterize the type of AI methods utilized in uveal disease including sample selection and preferred analysis method, goals of the AI, and guide future research in this ever-evolving field.

Methods

This systematic review adhered to the Preferred Reporting Items for a Systematic Review and Meta-analysis (PRISMA) guidelines and the protocol was registered in PROSPERO (reg. CRD42020196749).¹¹

Search Strategy

The search strategy was developed with the aid of an expert librarian and was conducted across five electronic databases (EMBASE, Medline, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Web of Science). The search was initially conducted from inception to August 11, 2020, and updated on August 1, 2021. Terms related to the concepts of “ophthalmology” and “AI/bioinformatics” and “proteomics, metabolomics, lipidomics” were used in the formal search to capture all relevant articles ([Supplemental File 1](#)). Additionally, backward and forward citation tracking was conducted for completeness. Gray literature indexes were included via EMBASE.

Study Selection Criteria

The inclusion and exclusion criteria were determined prior to screening. The inclusion criteria were as follows: (1) original peer-reviewed studies that analyzed biomarker concentrations to predict or modify patient therapy or outcome/diagnosis in intraocular ophthalmic conditions; (2) studies that analyzed biomarker using any type of AI and/or bioinformatics approaches; (3) articles that studied biomarker samples from vitreous fluid, aqueous fluid, tear fluid, plasma, serum, or ophthalmic biopsies and analyzed a protein, lipid, or metabolite; (4) studies that combined biofluid biomarkers with other types of biomarkers (eg imaging) in their statistical models; and (5) simple regression studies that were longitudinal. The exclusion criteria included (1) articles studying ophthalmic diseases that only affect pediatric patients (eg retinopathy of prematurity), (2) studies on non-human subjects (animal or cell studies), (3) studies utilizing post-mortem samples from eyes, (4) non-English studies, (5) abstracts, or reviews, systemic reviews and meta-analyses. This study is part of a series of review papers focused on use of AI and biofluids, and for this particular study a subset of all studies concerning uveal diseases (uveal melanoma and uveitis) were included.

Study Selection and Data Extraction

All studies identified by the databases were imported into Covidence (Covidence, Veritas Health Innovation, Melbourne, Australia) for screening. Upon automatic removal of duplicate articles, the remaining articles underwent two levels of screening: title and abstract and full text by two independent reviewers. Disagreements were resolved at a follow-up consensus meeting mediated by a third reviewer after each level of screening.

A standardized data collection form developed prior to the commencement of data extraction was used to ensure a comprehensive and consistent extraction. Data was extracted by one reviewer followed by a quality check where 10% of the extractions were verified by a second independent reviewer to ensure consistency of extracted data. Key parameters extracted from each article included study population demographics, biofluid biomarker characterization and significance, and the AI/bioinformatics tool used in the analysis.

Synthesis of Evidence

Data were synthesized for each study including details regarding the biofluid sample, type of analysis conducted, significant biomarkers, and demographic information of mean age and sex. Furthermore, data concerning the type of AI and/or bioinformatic analysis of the biomarkers used in uveal diseases was categorized based on the study objective and utility including disease progression, disease prognosis, disease profile, disease treatment and differentiating between differential diagnosis. Due to the heterogeneity of the study designs and AI methods employed by researchers, a meta-analysis was not undertaken.

Risk of Bias Assessment

The Joanna Briggs Institute Critical Appraisal Tool was used for critical appraisal of the included studies.¹² Risk of bias assessment was completed by one independent reviewer, and a quality check of 10% of the articles was completed by a second reviewer to ensure consistency between the data extractors. High ROB was applied to studies that reached up to 49% of questions as “yes”, moderate ROB was classified as 50–69%, and low ROB was classified as greater than 70%.²⁸

Results

The search strategy yielded 27,702 articles from all the databases. After the duplicates were removed, 10,258 studies were screened and a total of 18 studies met the criteria for inclusion in the systematic review. A PRISMA flow-chart summarizing the results of the literature can be found in [Figure 1](#).

Study and Patient Characteristics

The two diseases of interest were uveal melanoma (44%) and uveitis (56%) ([Table 1](#)). With regard to study design, 9 studies were cohort studies (50%), 8 are cross-sectional studies (44%) and 1 is a case report (6%). Fifteen studies were conducted retrospectively (83%) and 3 were completed prospectively (17%). The studies were conducted in 9 different countries, with the majority from China (7,39%). The total number of subjects in each study ranged from 18 to 10,453, while the median age of the patients ranged from 30 to 63 years ([Table 1](#)).

Samples and Biomarkers

The most common type of bio-sample taken from the uveal melanoma patients was tissue (63% studies) from of enucleated eyes and aqueous humor in the uveitis patients (50%, [Table 2](#)). Other types of biofluid samples were serum, plasma, undifferentiated blood and vitreous humor. The biomarker sample types collected varied across all studies, as 6 studies included cytokines, 6 metabolites, 5 proteins, 2 serum products, 2 at chemokines, 2 at cellular infiltrates, 2 at immune cells, 1 at lipids, 1 at electrolytes, and 1 at stromal cells. Furthermore, the number of individual biomarkers analyzed varied from 1 to 4386 per study with most studies researching less than 10 (50%). Although all except one study found significant biomarkers for their respective study objective, there is little to no overlap in the specific biomarkers found to be significant. The only overlap was that of lactate dehydrogenase (LDH) in 50% of the uveal melanoma studies.^{8,17–19}

Algorithm/Bioinformatic Applications

Ten (56%) studies used machine learning methods, and 13 (72%) studies used regression methods to interpret the data. Of the 10 studies that used machine learning methods, 2 used unsupervised methods, 3 used supervised methods and 5 used a combination of both methods. The studies that used regression analysis all employed supervised methods. The most common complex AI method used was principal component analysis (33%), whereas logistic regression (38%) analysis was the most common regression tool. Other types of complex AI methods used were artificial neuronal network (6%), hierarchal neural network (6%), decision tree analysis (6%), random forest (6%), partial least square-discriminant analysis (25%), and orthogonal projection to latent structure discriminant analysis (6%). In addition to AI methods, there were 8 studies that conducted analysis using bioinformatics. Bioinformatics was used for either pathway analysis (5 out of 8 bioinformatics studies) or cluster analysis (3 out of 8 bioinformatics studies). Most commonly, the studies that utilized bioinformatics in their methodology did so in order to differentiate between disease diagnosis (4 out of 8 bioinformatics studies) and understand disease profile (4 out of 8 bioinformatics

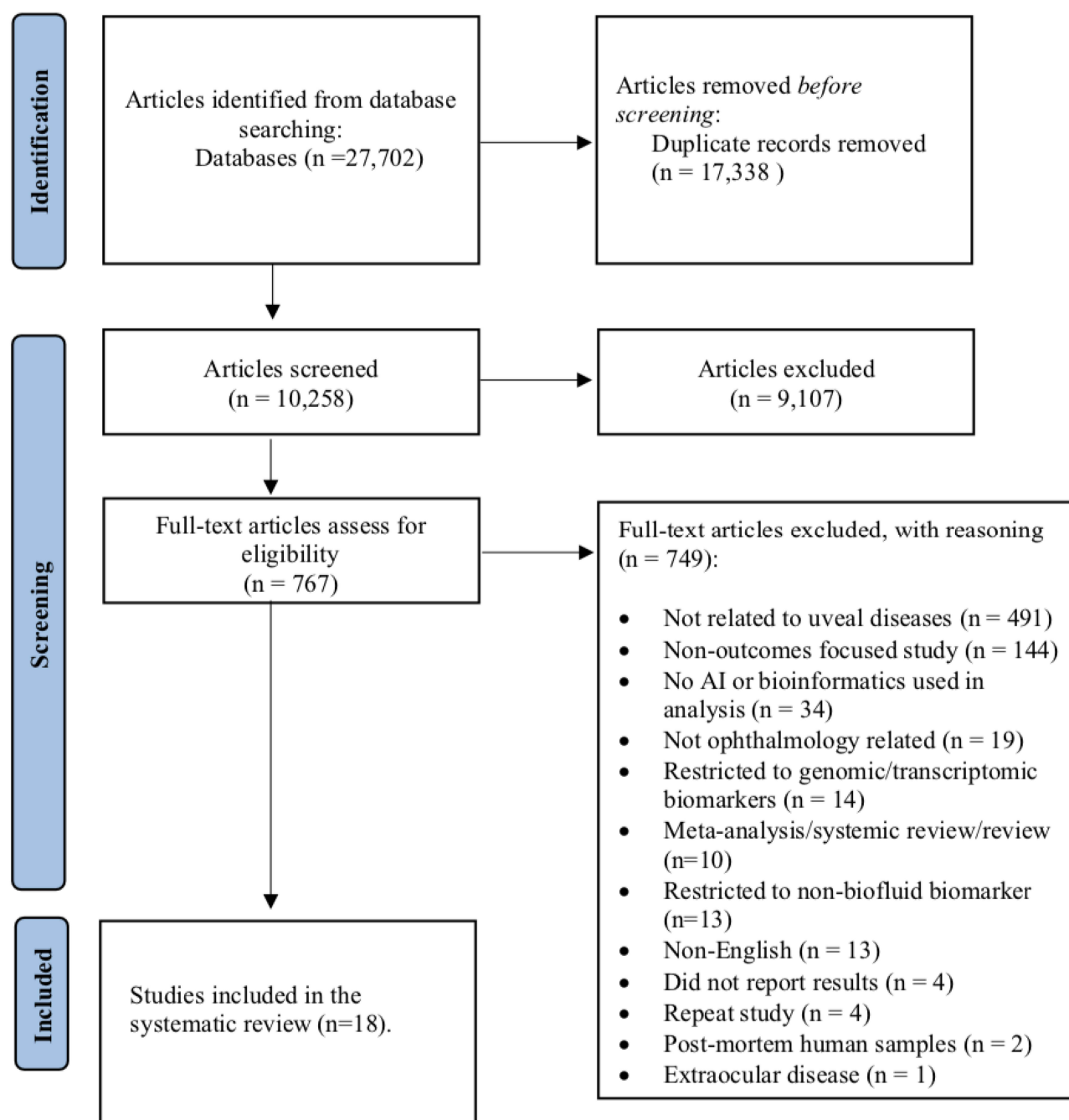


Figure 1 PRISMA flow diagram of search strategy.

Abbreviation: AI, artificial intelligence.

studies). Overall the study objectives included disease progression (6%), disease prognosis (50%), disease treatment (28%), disease profile (22%), and differentiating between differential diagnosis (22%).

Applications of AI in Uveitis

Of the 10 studies focused on uveitis, 4 focused on disease differentiation in which 3 of the 4 studies used machine learning methods. Curnow et al studied cytokine levels of uveitis-presenting diseases such as Behcet's disease, herpes-induced, Fuchs' heterochromic cyclitis and idiopathic uveitis and used cluster analysis and random forest analysis for disease differentiation and specifically found T_H 1 cytokines, IL-6, IL-8, CCL2 and IFN γ are elevated in idiopathic

Table I Summary of Study and Patient Characteristics

Author (Year)	Study Design	Country of Publication	Sample Size	Demographics: Age (Years, Mean and SD)	Demographics: Sex (Male/Female)
Johansson (2010) ²⁵	Retrospective Cohort	Sweden	100	62 ± 12	50/40
Indini (2019) ¹⁷	Retrospective Cohort	Italy	173	60.8 ± 14.1	107/66
Zhang (2020) ²²	Retrospective Cross-sectional	China	10,453 (710 controls)	Unknown	Unknown
Sun (2019) ⁷	Retrospective Cohort	China	47	63 ± 14	22/25
Lorenzo (2018) ⁸	Retrospective Case Series	Spain	99	57.33 ± 13.55	50/49
Ehlers (2005) ²⁰	Retrospective and Prospective Cohort	United States	25	Unknown	Unknown
Heppt (2017) ¹⁸	Prospective Cohort	Germany	96	Pembrolizumab = Age <60 years Nivolumab = Age <60 years Combined PD-I inhibitor and ipilimumab = Age <60 years	Pembrolizumab = 29/25 Nivolumab = 19/13 Combined PD-I inhibitor and ipilimumab = 10/5
Nicholas (2018) ¹⁹	Retrospective Cohort	Canada	132	58.2	55/77
Guo (2014) ¹⁴	Retrospective Cross-sectional	China	21 (9 controls)	35 ± 11	6/6
Curnow (2005) ³	Retrospective Cross-sectional	United Kingdom	49 (12 controls)	Median: 40.2 years	Unknown
Verhagen (2019) ⁴	Retrospective Cross-sectional	The Netherlands	66 (30 idiopathic HLA-B27 negative AUU, 16 idiopathic HLA-B27 negative AUU, 20 cataract)	B27-AAU age: 44.6 ± 15.5. Idiopathic AAU: 55.0 ± 11.6	DIMS1 Cohort: (B27-AAU 60%/40%, Idiopathic AAU 13%/87%, CAT 25%/75%). DIMS2 Cohort: (B27-AAU 67%/33%, Idiopathic AAU 50%/50%, CAT 50%/50%). LC-MS/MS (B27-AAU 67%/33%, Idiopathic AAU 0%/100%, CAT 0%/100%)
Wang (2019) ¹⁶	Retrospective Cross-sectional	China	24 (12 controls)	51.3 ± 9.9	5/7
Cai (2020) ²⁶	Retrospective Cross-sectional	China	164 (94 controls)	33.11 ± 5.97	63/27
Sun (2016) ²¹	Retrospective Cross-sectional	China	400 (352 controls)	33.8 ± 0.7	31/7
Xu (2021) ¹⁵	Retrospective Cross-sectional	China	45 (15 VKH, 15 BD, 15 cataract controls)	VKH: 45.8 ± 9.79 BD: 35.93 ± 10.72	VKH: 8/7 BD: 9/6

(Continued)

Table I (Continued).

Author (Year)	Study Design	Country of Publication	Sample Size	Demographics: Age (Years, Mean and SD)	Demographics: Sex (Male/Female)
Bonacini (2020) ²⁴	Retrospective Cohort	Italy	30 (10 VKH, 10 BD, 10 cataract controls)	BD: median 30 yrs VKH: median 47 yrs	BD: 8/2 VKH: 1/9
Young (2009) ¹³	Prospective Cohort	UK	42 (20 CU, 16 panuveitis, 2 sarcoidosis, 2 intermediate uveitis, 2 Fuchs' heterochromic cyclitis, 9 lens-induced uveitis, 2 proliferative diabetic retinopathy, 2 proliferative vitreoretinopathy, 7 rhegmatogenous retinal detachment, 1 Candida endophthalmitis, 1 Varicella Zoster virus acute retinal necrosis)	Unknown	Unknown
Fabiani (2018) ²⁷	Prospective Cohort	Italy	45 (32 anti-TNF- α treatment for more than 48 months, 13 patients discontinued treatment before 24 months)	44.16 $\pm$ 11.37	25/20

Abbreviations: HLA-B27, human leukocyte antigen B27; AUU, Acute anterior uveitis; DIMSI, direct infusion mass spectrometry cohort I; CAT, cataracts; VKH, Vogt-Koyanagi-Harada; BD, Behcet's Disease; CU, Chronic non-infectious uveitis.

Table 2 Summary of Biofluid Samples, Biomarkers and Artificial Intelligence Applications in the Included Studies

Author (Year)	Disease of Interest	Study Topic	Bio-Sample Type	Biomarker (s) Studied	Number of Biofluid Markers Studied	Software Tool Used for AI	Statistical/AI/Bioinformatics Methods Used	Significant Biomarkers Identified
Johansson (2010) ²⁵	Uveal Melanoma	Disease progression, Disease Prognosis	Tissue	Enzyme	1	Statistica version 7.0 and SPSS version 16.0	Supervised Regression: Cox's proportional hazards regression	iNOS
Indini (2019) ¹⁷	Uveal Melanoma	Disease prognosis, Disease treatment	Tissue, Blood	Cells, Protein	4	GraphPad Prism version 6.0 (GraphPad Software, San Diego, CA) and IBM-Microsoft SPSS (version 20.0, SPSS Statistics	Unsupervised Machine Learning: ANN	NLR, LDH
Zhang (2020) ²²	Uveal Melanoma	Disease prognosis	Tissue	Immune cells, and stromal cells, chemokines	14	R package called "survival."	Supervised Regression: Multivariable Cox regression and Kaplan–Meier survival curves Bioinformatics: GO and KEGG	T cells, CD8 T cells, cytotoxic lymphocytes, B cell lineage, monocytic lineage, CTLA-4, CCL5, CXCL10, and CXCL9
Sun (2019) ⁷	Uveal Melanoma	Disease prognosis	Tissue	Protein	1	PyTorch toolkit and Python 3.6	Unsupervised Machine Learning: Hierarchical neural network	BAP1
Lorenzo (2018) ⁸	Uveal Melanoma	Disease Prognosis	Blood	Protein	5	IBM SPSS software	1. Supervised Regression: Logistic Regression 2. Supervised Machine Learning: Decision tree analysis	LDH, GGT
Ehlers (2005) ²⁰	Uveal Melanoma	Disease prognosis	Tissue	Protein	1	Spotfire DecisionSite 7.0 software, GIST	1. Supervised Regression: Logistics Regression 2. Supervised: PCA and Support Vector Machine	Nbs1
Heppt (2017) ¹⁸	Uveal Melanoma	Disease prognosis, Disease treatment	Serum	Cytokine, serum products	5	SPSS statistics version 23.0 (IBM, Armonk, USA) or GraphPad Prism version 5.01 (GraphPad Software Inc., La Jolla, USA).	Supervised Regression: Multivariate Cox regression	LDH, CRP, REC

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Table 2 (Continued).

Author (Year)	Disease of Interest	Study Topic	Bio-Sample Type	Biomarker (s) Studied	Number of Biofluid Markers Studied	Software Tool Used for AI	Statistical/AI/Bioinformatics Methods Used	Significant Biomarkers Identified
Nicholas (2018) ¹⁹	Uveal Melanoma	Disease prognosis, Disease treatment	Serum	Serum products	6	SAS system for Windows	Supervised Regression: Multivariate logistic regression	Absolute neutrophil count, LDH, alkaline phosphatase; neutrophil lymphocyte ratio;
Guo (2014) ¹⁴	Uveitis	Disease profile, Differentiating between disease	Plasma	Metabolites	4386	SIMCA-P software (Version 11.5)	1. Unsupervised Machine Learning: PCA 2. Supervised Machine Learning: PLS-DA Bioinformatics: KEGG, METLIN, HMDB	Down Regulated: Tuftsin, Coniferin, Enkephalin L, 3-O-a-L-Fucopyranosyl-D-glucose, Alpha-Tocotrienol, Hydrocinnamic acid, 11-Oxo-androsterone glucuronide, Ceramide (d18:1/26:0), 2,8-Dihydroxyquinoline-beta-D-glucuronide, 5,6-Dihydrouridine, Chenodeoxycholic acid sulfate, D-Glutamine, O-Phospho-4-hydroxy-L-threonine, Niacinamide, L-Threoneopterin, 3-Hydroxydodecanedioic acid, 2-Methyl-3-hydroxy-5-formylpyridine-4-carboxylate, Cholestane-3,7,12,25-tetrol-3-glucuronide, 3-(3,4) Dihydroxyphenyl)lactic acid, Xanthylic acid Up Regulated: D-Pantethine, 2-Methylguanosine, 11-beta-hydroxyandrosterone-3-glucuronide, Dihydrocortisol, Homocitric acid, D-Erythrose 4-phosphate, 1-Methylnicotinamide, Succinic acid, deoxyinoside diphosphate (dIDP), Linoleic acid, S-Lactoylglutathione, Trimethylamine N-oxide, Dihydroneopterin phosphate
Curnow (2005) ³	Uveitis	Differentiating between different diseases	Aqueous humour	Cytokines and immune cells	18	Web-based toolset GEPAS	1. Supervised Regression: Dunn's multiple comparison tests 2. Supervised Machine Learning: Random forest Bioinformatics: Cluster Analysis	IL-6, IL-8, IFN, and CCL2, CCL2 and IL-8, TGF2 and CXCL12, IL-10

Verhagen (2019) ⁴	Uveitis	Differentiating between different diseases	Aqueous humour	Metabolites	2	Unknown	1. Unsupervised Machine Learning: PCA 2. Supervised Machine Learning: PLS-DA Bioinformatics: Cluster Analysis	Ketoleucine
Wang (2019) ¹⁶	Uveitis	Disease profile	Aqueous Humour and Serum	Cytokine, metabolites	Unknown	1. SPSS 18 2. SIMCA-P 3. SPSS	1. Supervised Regression: Logistic regression and receiver-operating characteristic 2. Unsupervised Machine Learning: PCA 3. Supervised Machine Learning: OPLS-DA Bioinformatics: Pathway Analysis and KEGG	3-Hydroxybutyric acid, antivirus IgG, allose, alpha-ketoisovaleric acid, etc. (14 metabolites)
Cai (2020) ²⁶	Uveitis	Disease prognosis	Serum	Cytokines, lipids, electrolytes	17	SPSS 21.0	Supervised Regression: Univariate logistic regression, forward stepwise (conditional), multivariate logistic regression	Triglycerides, total cholesterol, low-density lipoprotein, and serum amyloid A
Sun (2016) ²¹	Uveitis	Differentiating between different diseases,	Serum	Cytokines, chemokines, antibody	16	SPSS (Ver 22.0, Chicago, IL)	Supervised Regression: Logistic regression	CIC, ASO
Xu (2021) ¹⁵	Uveitis	Disease profile	Serum	Metabolites	84	SIMCA-P 14.1	1. Supervised Regression: Univariate logistic regression 2. Unsupervised Machine Learning: PCA 3. Supervised Machine Learning: PLS-DA Bioinformatics: Pathway Analysis (Metaboanalyst)	Amino acids, fatty acids (palmitic acid, oleic acid) differentially expressed VKH: 64 metabolites (VKH vs control: L-histidine, ornithine, and L-valine) BD: 65 metabolites (BD vs control: L-phenylalanine, D-arginine, N-acetyl-L-aspartic acid, L-alanine, arginyl-cysteine, and L-arginine)
Bonacini (2020) ²⁴	Uveitis	Disease profile, disease treatment	Aqueous humor	Metabolites	27	GraphPad Prism 6	Supervised Regression: Non-parametric Mann–Whitney <i>U</i> -test (quantitative variables), Fisher's exact test (qualitative variables), Kruskal–Wallis test with Dunn's correction, Spearman correlation, Bonferroni correction Bioinformatics: Cluster Analysis	11 cytokines: IL-6, IP-10, G-CSF, IFN γ , L-2, IL-8, IL-13, TNF α , eotaxin, IL-1ra, GM-CSF

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Table 2 (Continued).

Author (Year)	Disease of Interest	Study Topic	Bio-Sample Type	Biomarker (s) Studied	Number of Biofluid Markers Studied	Software Tool Used for AI	Statistical/AI/Bioinformatics Methods Used	Significant Biomarkers Identified
Young (2009) ¹³	Uveitis	Differentiating between different diseases	Vitreous Humour	Metabolites	7	PLS_Toolbox	1. Unsupervised Machine Learning: PCA 2. Supervised Machine Learning: PLS-DA Bioinformatics: GALGO	Oxaloacetate, glucose, urea, leukocyte-derived metabolites
Fabiani (2018) ²⁷	Uveitis	Disease treatment	Serum	Metabolites, cellular infiltrates	1	SPSS 24.0	Supervised Regression: Binary forward stepwise regression	HLA-B27 protein ligand

Notes: Disease prognosis: studying prognostic factors, disease progression: studying the progression of the disease of interest, disease treatment: studying factors that affect treatment outcome, disease profile: determining unique factors related to the disease of interest, differentiating between different diseases: studying factors that allow one to differentiate between diseases.

Abbreviations: ANN, artificial neural network; NLR, neutrophil to lymphocyte ratio; LDH, lactate dehydrogenase; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; PCA, principal component analysis; PLS-DA, partial least square discriminant analysis; GGT, gamma-glutamyl transferase; CRP, C-reactive protein; HMDB, Human Metabolome Database; OPLS-DA, orthogonal projection to latent structure-discriminant analysis.

uveitis.³ Verhagen et al used PCA and PLS-DA to determine that ketoleucine is upregulated in Human-Leukocyte antigen-B27 (HLA-B27) positive acute anterior uveitis, which can be used to differentiate it from HLA-B27 negative acute anterior uveitis.⁴ Partial least square discriminant analysis (PLS-DA) was also used by Young et al to differentiate between lens-induced uveitis and chronic uveitis, with a sensitivity of 78% and specificity of 85%.¹³ Additionally, 3 studies used machine learning methods to examine disease profile.^{14–16} Guo et al used PLS-DA to identify 33 potential biomarkers and 10 metabolic pathways related to acute anterior uveitis after conducting metabolic analysis.¹⁴ Similarly, Xu et al also used PLS-DA to determine specific amino acids and fatty acids to differentiate between controls and uveitis induced by Vogt-Koyanagi-Harada and Behcet's disease.¹⁵ Wang et al used PCA to determine the profile of disease for Posner-Schlossman syndrome-induced uveitis and found 14 significant pathways.¹⁶ The remaining studies used regression methods to determine treatment outcomes and prognosis.^{21,24,26,27}

Applications of AI in Uveal Melanoma

Three studies determined factors predictive of treatment outcome; Indini et al used machine learning, whereas Heppt et al, and Nicholas et al used regression methods.^{17–19} Indini et al used unsupervised artificial neural network analysis (ANN) to determine the importance of baseline factors in predicting response to anti-PD1 treatment in a retrospective cohort patient.¹⁷ The specific biomarkers found in blood that showed significance in increasing overall survival and response to treatment value were neutrophil-to-lymphocyte ratio (NLR) and baseline lactate dehydrogenase (LDH).¹⁷ Similarly, Heppt et al and Nicholas et al found LDH levels as a significant prognostic factor.^{18,19} Lastly, all studies for UM found biomarkers significant in determining disease prognosis. While most studies employed regression modeling, 3 studies employed complex AI technology. However, each study used a different algorithm modality; Indini et al, as previously stated, used unsupervised ANN analysis, Sun et al used unsupervised hierarchical neural network and Ehlers et al used supervised principal component analysis.^{7,17,20} Specifically, Sun et al used hierarchical neural network for recognition of BAP1 expression in tissue samples for prognostic utility.²¹ Additionally, principal component analysis was conducted by Ehlers et al to analyze microarray expression results to determine that Nbs1 is a highly significant prognostic factor that can stand alone.²⁰ There was one study that used bioinformatics to conduct pathway analysis for disease prognosis.²¹ CTLA-4 was assessed in 33 types of cancers to determine its expression and pathway via KEGG and GO databases by Zhang et al.²²

Quality of Evidence

Most of the studies included in this review were of high quality (94%) and 1 was of moderate quality (6%), as highlighted in Figure 2. Of the cohort studies, 56% were unclear in identifying confounding factors and 78% of the

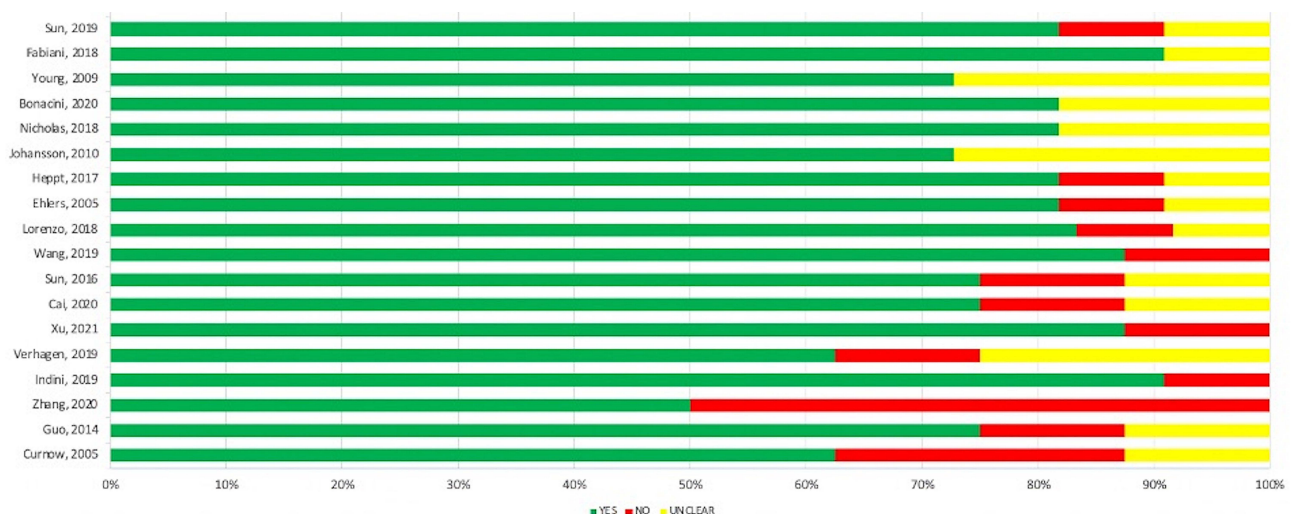


Figure 2 Risk of bias assessment using the Joanna Briggs Institute Critical Appraisal Tool.

Notes: Yes = clearly defined in the study; Unclear = not clearly defined in the study; No = not considered in the study.

studies were unclear or failed to identify strategies to account for the confounding variables. Similarly, 75% of the cohort studies did not describe their strategies for addressing confounding variables. Additionally, all 8 cohort studies (100%) did not clearly define the inclusion criteria for sample selection.

Discussion

To our knowledge, this is the first systematic review that summarises the current advancements of AI for analysis of biomarkers involved in uveal diseases, specifically uveitis and uveal melanoma. Almost all studies found significant biomarkers related to their disease of interest through either regression or machine learning methods, emphasizing the value of AI. However, due to the heterogeneous nature of the biomarkers chosen in each study, no significant biomarkers have been identified consistently across all studies for uveal conditions.

We provided a wide overview of both complex AI methods and regressions models, highlighting their utility. Principal component analysis was used most commonly, in 33% of studies and was found to be a powerful tool to determine significant biomarkers in uveal diseases. Although there is a large variation in types of complex AI used, many showed strong predictive ability. For instance, the value of a random forest analysis was demonstrated by Curnow et al, where with 100% accuracy elevated cytokines were identified in idiopathic uveitis, specifically T_H 1 cytokines, IL-6, IL-8, CCL2 and IFN γ .³ The results from this study indicate the value of a random forest analysis and its future application in differentiating disease profile of uveitis in Behcet's disease, herpes-induced, and Fuchs' heterochromic cyclitis with larger sample sizes.³

Considering that uveal melanoma is one of the most common ocular malignancies with a high risk of developing metastatic cancer, it would be beneficial to determine biomarkers that may predict disease progression, prognosis and treatment outcomes.¹⁸ Although the number and type of significant biomarker varied from study to study, there was one biomarker that was found significant across multiple studies. Lactate dehydrogenase (LDH) was found to be an important biomarker for disease prognosis and disease treatment outcome by Indini et al, Lorenzo et al, Heppt et al and Nicholas et al.^{8,17–19} Indini et al determined that elevated baseline serum LDH was negatively correlated with anti-PD1 treatment outcome, whereas Lorenzo et al, Heppt et al and Nicholas et al observed high LDH levels with decreased prognosis.^{8,17–19} LDH has been previously established as an important prognostic biomarker and is incorporated in staging procedures, such as the Padova-Mayo model and AJCC model.¹⁹ The ability to use LDH as a validated prognostic marker supports the idea of biomarkers as valuable prognostic tools.²⁹ However, as highlighted by Indini et al, ANN is able to characterize the importance of such biomarkers in reference to treatment outcomes.¹⁷ Identification of important biomarkers involved in uveal diseases may enable better diagnostics and guide treatment decisions.¹⁹ In the current review, AI methods are used to confirm previous findings and weigh the significance of LDH against other prognostic variables with respect to treatment outcomes.¹⁹ Although the number of studies in this review offers a large amount of information regarding significant biomarkers, with a limited number of studies focusing on each biomarker, it is difficult to recognize definitive biomarkers for diagnostic and prognostic application.

Despite the large amount of data provided by the studies in this review, there are limitations that affect the ability to apply this information in a clinical setting. As assessed by the risk of bias, there were no studies that clearly defined the inclusion criteria for the sample, affecting the generalizability of findings and replicability for future studies. Additionally, there was no mention of the reliability of the biomarker sample collection process, which further affects the bias presented in the studies. This could potentially create confounding variables that were failed to be identified. Additionally, limited information is provided on the specificity and sensitivity of the analytic methods used, making it difficult to assess the precise utility of AI methods.

Conclusion

In the current study, we reviewed the literature on the use of AI or bioinformatics to determine significant biomarkers in disease progression, prognosis, differentiation, profile and treatment outcome of uveitis and uveal melanoma. Particularly, using complex AI methods can be used to weigh the merit of significant biomarkers, such as LDH, in order to create staging tools and predict treatment outcome. Identification of these important biomarkers may guide clinicians in clinical decision-making and optimizing management strategies. Although the information presently

available has a large degree of heterogeneity, future studies have the potential of creating impactful AI models that can result in clinical tool development and implementation.

Presentations

The contents of this manuscript may be presented at the International Conference of Ophthalmology (September 9 to September 12, 2022) pending acceptance.

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Disclosure

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References

1. Van der Woerd A. Management of intraocular inflammatory disease. *Clin Tech Small Anim Pract*. 2001;16(1):58–61. doi:10.1053/svms.2001.22807
2. Tsirouki T, Dastiridou A, Symeonidis C, et al. A focus on the epidemiology of uveitis. *Ocul Immunol Inflamm*. 2018;26(1):2–16. doi:10.1080/09273948.2016.1196713
3. Curnow SJ, Falciani F, Durrani OM, et al. Multiplex bead immunoassay analysis of aqueous humor reveals distinct cytokine profiles in uveitis. *Invest Ophthalmol Vis Sci*. 2005;46(11):4251. doi:10.1167/iov.05-0444
4. Verhagen FH, Stigter ECA, Pras-Raves ML, Radstake TRDJ, de Boer JH, Kuiper JJW. Aqueous humor analysis identifies higher branched chain amino acid metabolism as a marker for human leukocyte Antigen-B27 acute anterior uveitis and disease activity. *Am J Ophthalmol*. 2019;198:97–110. doi:10.1016/j.ajo.2018.10.004
5. Sauer A, Villard O, Creuzot-Garcher C, et al. Intraocular levels of interleukin 17A (IL-17A) and IL-10 as respective determinant markers of toxoplasmosis and viral uveitis. *Clin Vaccine Immunol*. 2014;22(1):72–78. doi:10.1128/cvi.00423-14
6. Krantz BA, Dave N, Komatsubara KM, Marr BP, Carvajal RD. Uveal melanoma: epidemiology, etiology, and treatment of primary disease. *Clin Ophthalmol*. 2017;11:279–289. doi:10.2147/ophth.s89591
7. Sun M, Zhou W, Qi X, et al. Prediction of BAP1 expression in uveal melanoma using densely-connected deep classification networks. *Cancers*. 2019;11(10):1579. doi:10.3390/cancers11101579
8. Lorenzo D, Ochoa M, Piulats JM, et al. Prognostic factors and decision tree for long-term survival in metastatic uveal melanoma. *Cancer Res Treatment*. 2018;50(4):1130–1139. doi:10.4143/crt.2017.171
9. Ericsson C, Seregard S, Bartolazzi A, et al. Association of HLA Class I and Class II Antigen expression and mortality in uveal melanoma. *Invest Ophthalmol Vis Sci*. 2001;42(10):2153–2156.
10. Yu K-H, Beam AL, Kohane IS. Artificial intelligence in healthcare. *Nat Biomed Eng*. 2018;2(10):719–731. doi:10.1038/s41551-018-0305-z
11. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097. doi:10.1371/journal.pmed.1000097
12. JBI. Critical appraisal-tools - Critical Appraisal Tools. Joanna Briggs Institute. Jbi.global; 2021. Available from: <https://jbi.global/critical-appraisal-tools>. Accessed August 18, 2022.
13. Young SP, Nessim M, Falciani F, et al. Metabolomic analysis of human vitreous humor differentiates ocular inflammatory disease; 2009. Available from: www.molvis.org/molvis/v15/a129/#sec-discussion. Accessed August 18, 2022.
14. Guo J, Yan T, Bi H, et al. Plasma metabolomics study of the patients with acute anterior uveitis based on ultra-performance liquid chromatography-mass spectrometry. *Graefes Arch Clin Exp Ophthalmol*. 2014;252(6):925–934. doi:10.1007/s00417-014-2619-1
15. Xu J, Su G, Huang X, et al. Metabolomic analysis of aqueous humor identifies aberrant amino acid and fatty acid metabolism in Vogt-Koyanagi-Harada and Behcet's disease. *Front Immunol*. 2021;12. doi:10.3389/fimmu.2021.587393
16. Wang H, Zhai R, Sun Q, et al. Metabolomic profile of Posner-Schlossman syndrome: a gas chromatography time-of-flight mass spectrometry-based approach using aqueous humor. *Front Pharmacol*. 2019;10. doi:10.3389/fphar.2019.01322
17. Indini A, Di Guardo L, Cimminiello C, De Braud F, Del Vecchio M. Artificial intelligence estimates the importance of baseline factors in predicting response to Anti-PD1 in metastatic melanoma. *Am J Clin Oncol*. 2019;42(8):643–648. doi:10.1097/coc.0000000000000566
18. Heppt MV, Heinzerling L, Kähler KC, et al. Prognostic factors and outcomes in metastatic uveal melanoma treated with programmed cell death-1 or combined PD-1/cytotoxic T-lymphocyte antigen-4 inhibition. *Eur J Cancer*. 2017;82:56–65. doi:10.1016/j.ejca.2017.05.038
19. Nicholas MN, Khoja L, Atenafu EG, et al. Prognostic factors for first-line therapy and overall survival of metastatic uveal melanoma: the Princess Margaret Cancer Centre experience. *Melanoma Res*. 2018;28(6):571–577. doi:10.1097/cmr.0000000000000468
20. Ehlers JP, Harbour JW. NBS1 expression as a prognostic marker in uveal melanoma. *Clin Cancer Res*. 2005;11(5):1849–1853. doi:10.1158/1078-0432.ccr-04-2054
21. Sun L, Wu R, Xue Q, Wang F, Lu P. Risk factors of uveitis in ankylosing spondylitis. *Medicine*. 2016;95(28):e4233. doi:10.1097/MD.00000000000004233
22. Zhang C, Chen J, Song Q, et al. Comprehensive analysis of CTLA-4 in the tumor immune microenvironment of 33 cancer types. *Int Immunopharmacol*. 2020;85:106633. doi:10.1016/j.intimp.2020.106633
23. Armstrong GW, Lorch AC. A(eye): a Review of Current Applications of Artificial Intelligence and Machine Learning in Ophthalmology. *Int Ophthalmol Clin*. 2020;60(1):57–71. doi:10.1097/iao.0000000000000298
24. Bonacini M, Soriano A, Cimino L, et al. Cytokine profiling in aqueous humor samples from patients with non-infectious uveitis associated with systemic inflammatory diseases. *Front Immunol*. 2020;11. doi:10.3389/fimmu.2020.00358

25. Johansson CC, Mougiakakos D, Trocme E, et al. Expression and prognostic significance of iNOS in uveal melanoma. *Int J Cancer*. 2010;NA–NA. doi:10.1002/ijc.24984
26. Cai J, Qi L, Chen Y, et al. Evaluation of factors for predicting risk of uveitis recurrence in Behcet's disease patients. *Braz J Med Biol Res*. 2020;53(6). doi:10.1590/1414-431x20209118
27. Fabiani C, Vitale A, Rigante D, et al. Predictors of sustained clinical response in patients with Behçet's disease-related uveitis treated with infliximab and Adalimumab. *Clin Rheumatol*. 2018;37(6):1715–1720. doi:10.1007/s10067-018-4092-4
28. Valesan LF, Da-Cas CD, Réus JC, et al. Prevalence of temporomandibular joint disorders: a systematic review and meta-analysis. *Clin Oral Investig*. 2021;25(2):441–453. doi:10.1007/s00784-020-03710-w
29. Palmer SR, Erickson LA, Ichetovkin I, Knauer DJ, Markovic SN. Circulating serologic and molecular biomarkers in malignant melanoma. *Mayo Clin Proc*. 2011;86(10):981–990. doi:10.4065/mcp.2011.0287

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