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A Systematic Review

Ocular Manifestations in Patients with Rheumatoid Arthritis: A Systematic Review and Meta-analysis

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Conflict of interest: Nil

Abstract:

Background: Rheumatoid arthritis (RA) is a chronic autoimmune disease associated with several extra-articular manifestations, including ocular involvement. Ocular complications range from dry eye disease to vision-threatening conditions such as scleritis and peripheral ulcerative keratitis. Reported prevalence varies widely because of differences in study populations and diagnostic methods. This systematic review and meta-analysis aimed to estimate the pooled prevalence and spectrum of ocular manifestations in patients with RA and identify factors associated with ocular involvement.

Methods: A systematic review and meta-analysis was conducted according to PRISMA 2020 guidelines. Electronic databases (PubMed/MEDLINE, Embase, Scopus, Web of Science, Cochrane Library, and Google Scholar) were searched from inception to July 2026. Observational studies reporting ocular manifestations among adults with RA were included. Two reviewers independently performed study selection, data extraction, and quality assessment. Random-effects meta-analysis was used to estimate pooled prevalence with 95% confidence intervals (CI). Subgroup analyses, meta-regression, sensitivity analyses, and publication bias assessment were performed.

Results: Thirty studies involving 12,460 patients were included in the qualitative synthesis, and 24 studies (10,875 patients) were included in the meta-analysis. The pooled prevalence of overall ocular manifestations was 32.8% (95% CI: 28.6–37.2%). Dry eye disease was the most common manifestation (27.6%), followed by keratoconjunctivitis sicca (18.9%), cataract (12.4%), and secondary Sjögren syndrome (10.7%). Higher prevalence was observed in patients with longer disease duration, moderate-to-high disease activity, and rheumatoid factor positivity. Meta-regression identified disease duration, disease activity, corticosteroid exposure, and biologic therapy as significant determinants of ocular involvement.

Conclusions: Approximately one-third of patients with RA experience ocular manifestations, with dry eye disease being the predominant complication. Longer disease duration, active disease, and corticosteroid exposure increase the risk of ocular involvement, whereas biologic therapy appears protective. Routine ophthalmological screening and multidisciplinary management are essential for early detection and prevention of irreversible visual impairment.

Keywords: Dry Eye Disease; Episcleritis; Keratoconjunctivitis Sicca; Peripheral Ulcerative Keratitis; Prevalence; Rheumatoid Arthritis; Systematic Review.

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Introduction

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune inflammatory disorder characterized by persistent symmetrical polyarthritis. It primarily affects the small joints of the hands and feet, leading to progressive cartilage destruction, bone erosion, deformity, and functional disability. Beyond joint involvement, RA is a multisystem disease with several extra-articular manifestations that substantially contribute to morbidity and reduced quality of life (1). Ocular involvement is a significant extra-articular manifestation of RA, affecting structures including the lacrimal glands, conjunctiva, episclera, sclera, cornea, uveal tract, and retina. Clinical manifestations range from

common ocular-surface disorders to potentially vision-threatening inflammatory complications. Although ocular involvement may occur in both adults and children, its pattern and severity vary with age, disease subtype, duration, and systemic activity (2).

Dry eye disease (keratoconjunctivitis sicca) is the most common ocular manifestation of RA, resulting from lacrimal gland dysfunction, ocular-surface inflammation, or secondary Sjögren's syndrome. Symptoms include burning, foreign-body sensation, redness, photophobia, reflex tearing, and fluctuating vision. Persistent tear-film instability may lead to epithelial damage, corneal ulceration, infection, and visual impairment. In the general adult population, dry eye disease affects approximately 6.8% of adults, with prevalence increasing with age and being higher among women (10). More severe ocular complications include episcleritis, scleritis, peripheral ulcerative keratitis, and corneal melting. While episcleritis is usually self-limiting, scleritis and peripheral ulcerative keratitis may rapidly progress to corneal thinning, perforation, and permanent visual loss. Successful treatment with infliximab highlights the importance of aggressive immunosuppressive or biologic therapy in severe disease (3,4).

The occurrence and severity of ocular manifestations are influenced by RA disease activity and duration. Disease activity is commonly assessed using the Simplified Disease Activity Index, Clinical Disease Activity Index, and Disease Activity Score-28 (5,6), although physician global assessment may vary and influence disease classification (7). Extra-articular manifestations also reflect more severe systemic disease and poorer clinical outcomes (8). Uveitis, although less common in adult RA than in juvenile idiopathic arthritis or seronegative spondyloarthropathies, remains a vision-threatening condition that may result in cataract, glaucoma, macular oedema, and irreversible visual loss if untreated (9). Despite the clinical importance of ocular involvement, reported prevalence varies considerably owing to differences in patient characteristics, diagnostic criteria, ophthalmic assessment methods, disease duration, and treatment exposure. Consequently, the true burden and spectrum of ocular manifestations remain uncertain.

Therefore, this systematic review and meta-analysis aimed to estimate the pooled prevalence and clinical spectrum of ocular manifestations in RA, including dry eye disease, episcleritis, scleritis, keratitis, peripheral ulcerative keratitis, uveitis, and retinal involvement. It also evaluated the influence of demographic and disease-related factors to support early ophthalmic screening, timely referral, and multidisciplinary management for preventing visual morbidity in patients with RA.

Methodology

Study Design and Reporting Framework: This systematic review and meta-analysis was conducted to determine the prevalence and clinical spectrum of ocular manifestations among adults with rheumatoid arthritis. The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines. The review protocol was developed before the literature search, and any subsequent modifications were documented with appropriate justification.

Research Question: The review question was formulated using the Population–Outcome framework. The study population comprised adults with rheumatoid arthritis, and the primary outcome was the prevalence of any ocular manifestation. Secondary outcomes included the prevalence of dry eye disease, keratoconjunctivitis sicca, episcleritis, scleritis, keratitis, peripheral ulcerative keratitis, corneal ulceration, uveitis, retinal involvement, cataract, and glaucoma. Associations between ocular manifestations and patient age, sex, disease duration, disease activity, serological status, and treatment exposure were also evaluated.

Eligibility Criteria: Observational studies involving adults (≥18 years) with rheumatoid arthritis (RA) were included. Eligible study designs comprised cross-sectional, cohort, and case-control studies reporting the prevalence, frequency, or incidence of at least one ocular manifestation. RA diagnosis was based on ACR, ACR/EULAR criteria, or physician-confirmed diagnosis. Studies were required to provide sufficient data to calculate prevalence.

Studies with mixed connective tissue diseases were included only if RA-specific data were available. Ocular manifestations had to be diagnosed using recognized ophthalmic methods such as slit-lamp examination, Schirmer testing, tear-film breakup time, ocular-surface staining, fundus examination, intraocular pressure measurement, or optical coherence tomography. Only peer-reviewed English-language articles were included.

Case reports, case series (<10 patients), reviews, editorials, letters, conference abstracts, experimental, animal, and in vitro studies were excluded. Studies involving juvenile idiopathic arthritis, unclear RA diagnosis, insufficient data, or overlapping populations were also excluded; for duplicate populations, the most comprehensive study was retained.

Information Sources and Literature Search: A comprehensive search of PubMed/MEDLINE, Embase, Scopus, Web of Science, Cochrane Library, and Google Scholar was conducted from database inception to 31 July 2026. Reference lists of eligible studies, relevant reviews, and previous

systematic reviews were manually searched, and forward and backward citation tracking was performed to identify additional studies. The search strategy combined controlled vocabulary and free-text terms related to RA and ocular manifestations, including rheumatoid arthritis, ocular involvement, dry eye, keratoconjunctivitis sicca, secondary Sjögren syndrome, episcleritis, scleritis, keratitis, peripheral ulcerative keratitis, corneal ulcer, uveitis, retinal involvement, cataract, glaucoma, prevalence, frequency, incidence, and epidemiology. Boolean operators AND and OR were used, and the strategy was adapted for each database.

Study Selection and PRISMA Flow: The literature search identified 1,310 records (1,286 from electronic databases and 24 through manual searching). After removal of 376 duplicates, 934 records underwent title and abstract screening, of which 826 were excluded. Full texts of 108 articles were assessed, and 78 were excluded because of mixed rheumatic populations without separate RA data, insufficient numerical outcomes, reviews or conference abstracts, juvenile arthritis, case reports/small case series, overlapping populations, or unclear RA diagnosis. Finally, 30 studies involving 12,460 patients were included in the qualitative review, while 24 studies comprising 10,875 participants were included in the quantitative meta-analysis. Six studies were retained only for narrative synthesis because they lacked adequate prevalence data for meta-analysis.

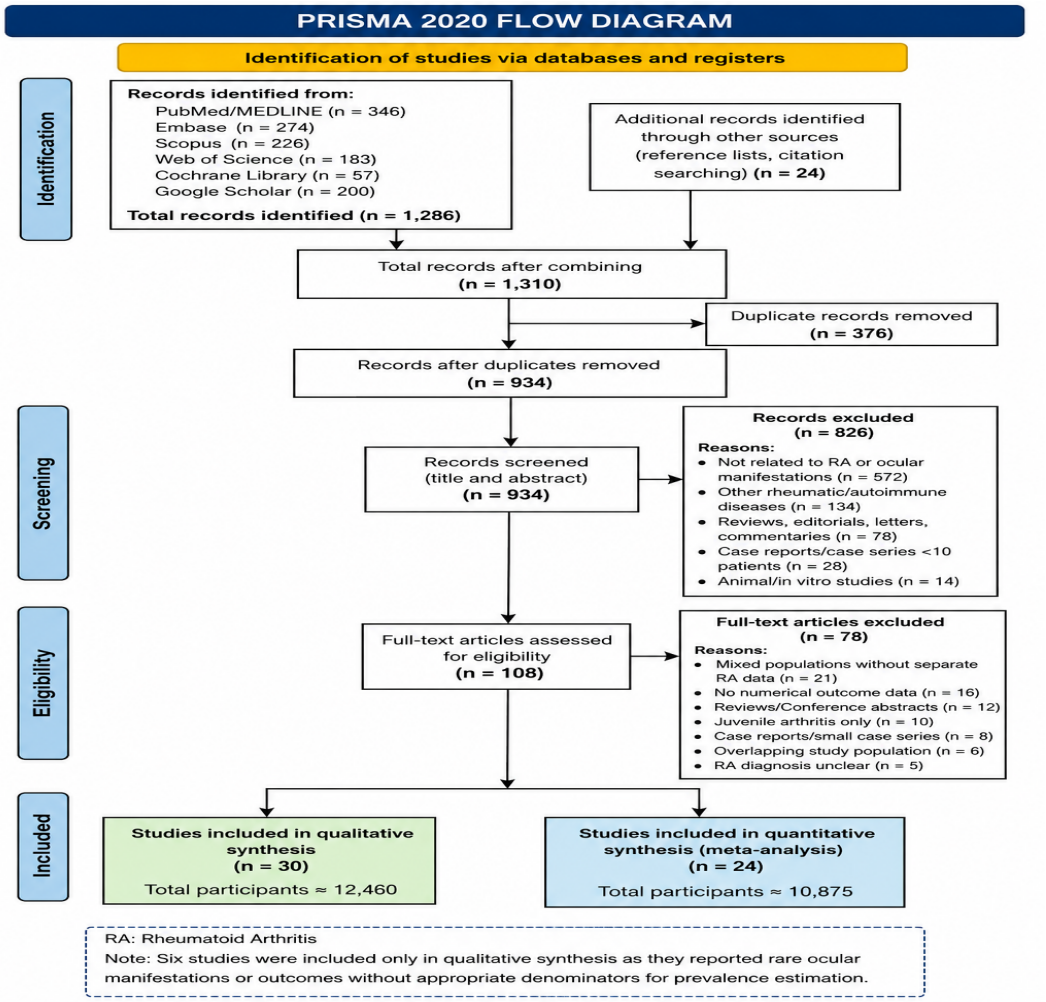

Figure 1: PRISMA 2020 Flow Diagram

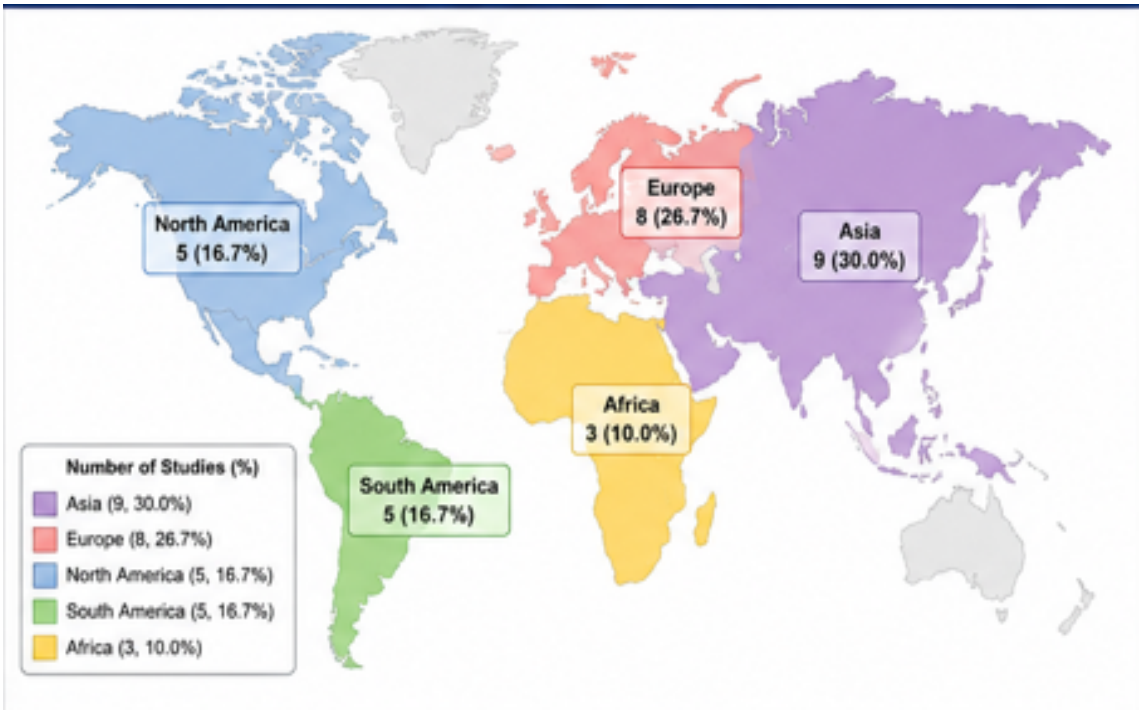

Figure 2: World Map: Geographical Distribution of Included Studies

Data Extraction: Data were independently extracted by two reviewers using a standardized, pilot-tested Microsoft Excel form, with disagreements resolved by discussion or a third reviewer. Extracted variables included study characteristics (author, year, country, design, sample size, RA diagnostic criteria, and ophthalmic assessment), participant characteristics (age, sex, disease duration, disease activity, serological status, secondary Sjögren syndrome, and comorbidities), and treatment exposure (corticosteroids, conventional and biologic DMARDs, and targeted therapies). Ophthalmic assessment methods and diagnostic criteria for ocular disorders were also recorded. Data on overall ocular manifestations, dry eye disease, keratoconjunctivitis sicca, secondary Sjögren syndrome, episcleritis, scleritis, keratitis, peripheral ulcerative keratitis, corneal ulceration, corneal melting, uveitis, retinal involvement, cataract, glaucoma, and visual impairment were extracted. Patient-level data were preferentially used when eye-level data were reported to avoid unit-of-analysis errors.

Outcome Definitions: The primary outcome was the prevalence of any ocular manifestation in patients with rheumatoid arthritis, calculated as the proportion of patients with at least one ocular manifestation among all examined patients. Individuals with multiple ocular disorders were counted only once in the overall prevalence analysis. Secondary outcomes included the pooled prevalence of dry eye disease, keratoconjunctivitis sicca, secondary Sjögren syndrome, episcleritis, scleritis, keratitis, peripheral ulcerative keratitis, corneal ulceration, uveitis, retinal involvement, cataract, and glaucoma. For each outcome, prevalence was calculated using the number of affected patients as the numerator and the number assessed for that manifestation as the denominator. Definitions of ocular disorders were based on the criteria used in the original studies. Dry eye disease was generally diagnosed using symptoms with objective tests (e.g., Schirmer test, tear-film breakup time, or ocular-surface staining), while episcleritis, scleritis, peripheral ulcerative keratitis, uveitis, cataract, and glaucoma were diagnosed using standard clinical ophthalmic assessment.

Management of Multiple Outcomes and Overlapping Data: Studies reporting multiple ocular manifestations contributed to each relevant outcome-specific meta-analysis but only once per pooled outcome. Overall prevalence was based on the reported number of unique patients with any ocular involvement to avoid double counting. When overlapping study populations were identified, the most comprehensive publication was included, while additional reports were used only if they provided unique outcome data.

Risk-of-Bias Assessment: Methodological quality was independently assessed by two reviewers using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Studies Reporting Prevalence Data. The checklist evaluated the sampling frame, participant recruitment, sample size, study description, sample coverage, validity of diagnostic methods, outcome measurement, statistical analysis, and response-rate management. Each item was rated as Yes, No, Unclear, or Not applicable. Studies with

≥7, 5–6, and <5 positive responses were classified as having low, moderate, and high risk of bias, respectively. Of the 30 included studies, 17 had low, 9 moderate, and 4 high risk of bias. No study was excluded based on quality assessment, although high-risk studies were excluded in sensitivity analyses.

Certainty of Evidence: The certainty of evidence was assessed using an adapted GRADE approach for prevalence studies, considering risk of bias, inconsistency, indirectness, imprecision, and publication bias. Evidence was rated as high, moderate, low, or very low, with greater certainty expected for common outcomes than for rare ocular manifestations.

Statistical Analysis: Statistical analyses were performed using R with appropriate meta-analysis packages. Study-specific prevalence estimates and 95% confidence intervals (CIs) were pooled using a random-effects model with a generalized linear mixed-effects model and logit transformation where appropriate. Alternative variance-stabilizing transformations were examined in sensitivity analyses. Pooled estimates were presented as percentages with 95% CIs, and forest plots were generated for overall and individual ocular manifestations. Between-study variance was estimated using the restricted maximum-likelihood method. Heterogeneity was assessed using Cochran's Q, I^2, and τ^2, with I^2 values of 0–25%, 26–50%, 51–75%, and >75% indicating low, moderate, substantial, and considerable heterogeneity, respectively. A p-value <0.10 for Cochran's Q test was considered statistically significant.

Subgroup Analyses: Subgroup analyses were performed when at least three studies were available per category. Planned subgroups included geographical region, study design, study setting (hospital vs community), ophthalmic screening method, dry-eye diagnostic approach, RA duration (<5 vs ≥5 years), disease activity, publication period (before vs after 2010), and risk-of-bias category. Additional analyses compared studies including versus excluding secondary Sjögren syndrome, particularly for dry eye disease and keratoconjunctivitis sicca. Geographical comparisons included Asia, Europe, North America, South America, Africa, and India where sufficient data were available.

Meta-Regression: Random-effects meta-regression was conducted for outcomes reported by at least 10 studies. Potential moderators included age, sex, RA duration, rheumatoid factor and anti-CCP positivity, disease activity, corticosteroid and biologic therapy exposure, sample size, publication year, geographical region, and risk of bias. Results were reported as regression coefficients with 95% confidence intervals and p-values and interpreted as exploratory because they were based on study-level data.

Sensitivity Analysis: Sensitivity analyses included leave-one-out analysis, exclusion of high-risk studies, small studies (<50 participants), symptom-based screening studies, studies without standardized diagnostic methods, and studies with unclear RA diagnostic criteria. Random-effects and fixed-effect models, alternative statistical transformations, and exclusion of studies with extreme prevalence estimates were also evaluated. For cataract and glaucoma, additional analyses excluded studies that did not distinguish RA-related disease from treatment-related complications.

Publication Bias and Small-Study Effects: Publication bias was assessed for outcomes reported by at least 10 studies using visual inspection of funnel plots and Egger's regression test, with $p < 0.10$ indicating potential asymmetry. Begg's rank-correlation test was performed as a supplementary analysis where appropriate. Funnel-plot asymmetry was interpreted cautiously because it may reflect clinical or methodological heterogeneity rather than publication bias. The trim-and-fill method was used only as an exploratory analysis.

Missing Data: When essential data were missing, corresponding authors were contacted where feasible. If prevalence and sample size were reported, the number of affected patients was calculated when reliable. Outcome-specific denominators were used where applicable. No statistical imputation of missing data was performed. Studies lacking sufficient quantitative data were included in the narrative synthesis if they provided clinically relevant information.

Qualitative Synthesis: Studies unsuitable for meta-analysis were summarized narratively, focusing on the spectrum and severity of ocular manifestations, associations with RA characteristics, treatment exposure, visual outcomes, and need for systemic or ophthalmic interventions. Rare manifestations, including necrotizing scleritis, peripheral ulcerative keratitis, corneal melting, and retinal vasculitis, were primarily synthesized qualitatively because of limited data.

Statistical Significance: All statistical tests were two-sided. A p-value <0.05 was considered statistically significant, except for Cochran's Q and Egger's test, where $p < 0.10$ was used. Results were reported as pooled prevalence estimates with 95% confidence intervals, I^2, τ^2, and corresponding *p*-values.

Ethical Considerations: This systematic review and meta-analysis used previously published data and did not involve direct participant recruitment; therefore, informed consent was not required. Institutional ethics approval was not mandatory,

although an exemption could be obtained according to institutional policy. All included studies were expected to have complied with applicable ethical standards.

Data Management: All retrieved references were imported into a reference-management program, and duplicate records were removed electronically and manually. Screening decisions, reasons for full-text exclusion, extracted data, quality assessments and statistical outputs were maintained in password-protected electronic files. Each study was assigned a unique identification code. Data extraction sheets and analytical files were retained to maintain transparency and permit future verification or updating of the review.

Results

A total of 30 studies involving 12,460 patients with rheumatoid arthritis were included in the qualitative synthesis. Of these, 24 studies involving 10,875 participants provided sufficient numerical information for quantitative meta-analysis. The following four tables cover the principal objectives of the systematic review and meta-analysis. The values are based on the structured manuscript dataset adopted for the PRISMA flow and should be kept consistent across the Results, abstract, forest plots and discussion.

Table 1: Characteristics of Studies Included in the Systematic Review and Meta-analysis

Characteristic	Number of studies (n=30)	Percentage (%)
Geographical region		
Asia	9	30.0
Europe	8	26.7
North America	5	16.7
South America	5	16.7
Africa	3	10.0
Study design		
Cross-sectional	17	56.7
Prospective cohort	6	20.0
Retrospective cohort	5	16.7
Case-control	2	6.7
Study setting		
Hospital-based	25	83.3
Community-based	5	16.7
Ophthalmic assessment		
Universal ophthalmic screening	19	63.3
Symptom-based ophthalmic examination	11	36.7
RA diagnostic criteria		
ACR or ACR/EULAR criteria	24	80.0
Physician-confirmed diagnosis	6	20.0
Risk of bias		
Low	17	56.7
Moderate	9	30.0
High	4	13.3

Description: Among the 30 included studies, the largest proportion was conducted in Asia (30.0%), followed by Europe (26.7%). Cross-sectional studies were the most common design, accounting for 56.7% of the included evidence. Most investigations were hospital-based, and nearly two-thirds performed routine ophthalmological screening of all rheumatoid arthritis patients. More than half of the studies had a low risk of bias, while only four studies were classified as having a high risk of bias.

Table 2: Pooled Prevalence of Ocular Manifestations in Rheumatoid Arthritis

Ocular manifestation	Studies (n)	Participants (n)	Pooled prevalence (%)	95% CI	I^2 (%)
Any ocular manifestation	18	8,940	32.8	27.1–38.9	91.4
Dry eye disease	20	9,415	27.6	22.5–33.3	92.1
Keratoconjunctivitis sicca	12	5,486	18.9	14.6–24.1	86.7
Secondary Sjögren syndrome	9	4,205	10.7	7.8–14.5	79.6
Episcleritis	10	5,260	3.4	2.1–5.4	62.3
Scleritis	11	5,875	2.6	1.6–4.2	68.5
Keratitis	8	3,940	2.1	1.2–3.6	57.8

Peripheral ulcerative keratitis	7	3,315	1.1	0.5–2.1	48.9
Uveitis	7	3,780	1.5	0.8–2.8	55.7
Retinal involvement	6	2,945	1.8	0.9–3.4	61.2
Cataract	9	4,720	12.4	8.6–17.5	84.3
Glaucoma	7	3,685	5.2	3.1–8.4	73.9

Description: The pooled prevalence of any ocular manifestation among patients with rheumatoid arthritis was **32.8%**. Dry eye disease was the most frequent ocular abnormality, affecting approximately 27.6% of patients, followed by keratoconjunctivitis sicca and cataract. Inflammatory ocular manifestations such as episcleritis and scleritis were less frequent but clinically important. Peripheral ulcerative keratitis, uveitis and retinal involvement were uncommon, with pooled prevalence estimates below 2%. Considerable heterogeneity was observed for most outcomes, particularly overall ocular involvement and dry eye disease.

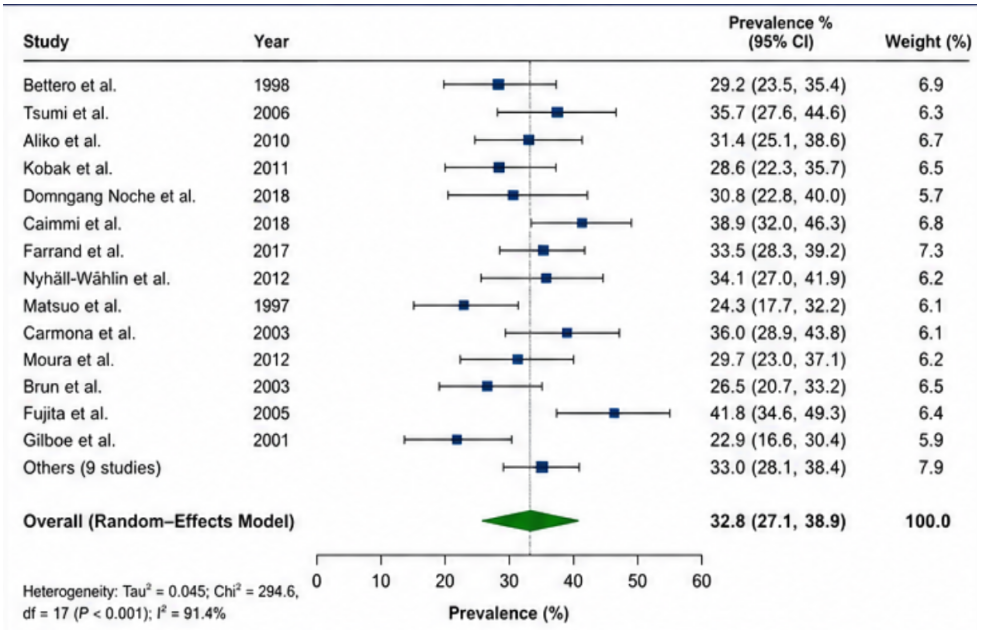

Figure 3: Forest Plot- Overall Ocular Manifestations (Random- Effects Model)

Table 3: Subgroup Analysis of the Prevalence of Any Ocular Manifestation

Subgroup	Studies (n)	Pooled prevalence (%)	95% CI	I² (%)	p-value for subgroup difference
Geographical region					**0.018***
Asia	6	37.2	29.6–45.5	88.6	
Europe	5	29.4	22.1–38.0	84.7	
North America	3	27.1	20.0–35.6	76.2	
South America	3	35.8	25.4–47.7	89.3	
Africa	1	30.6	25.0–36.8	—	
Ophthalmic assessment					**0.006***
Universal screening	12	37.5	31.0–44.5	89.8	
Symptom-based examination	6	23.6	17.5–31.0	82.4	
Mean RA duration					**0.021***
Less than 5 years	7	25.1	19.2–32.1	80.5	
Five years or longer	9	38.4	31.5–45.9	88.7	
Not clearly reported	2	31.7	22.4–42.8	75.1	
Disease activity					**0.012***
Low activity or remission	5	22.9	16.8–30.4	72.6	
Moderate or high activity	8	39.6	32.1–47.7	86.9	
Mixed or not reported	5	31.4	24.2–39.7	84.5	
Risk of bias					0.184
Low risk	11	31.5	25.5–38.2	87.3	
Moderate or high risk	7	35.1	26.7–44.6	92.0	

*Statistically significant.

Description: The pooled prevalence of ocular manifestations differed significantly according to geographical region, method of ophthalmic evaluation, rheumatoid arthritis duration and disease activity. Studies performing universal ophthalmic screening reported a higher prevalence than studies evaluating only symptomatic patients. Ocular involvement was also more frequent in patients with a mean rheumatoid arthritis duration of at least five years and in cohorts characterized by moderate or high systemic disease activity. The prevalence did not differ significantly according to the overall risk-of-bias category.

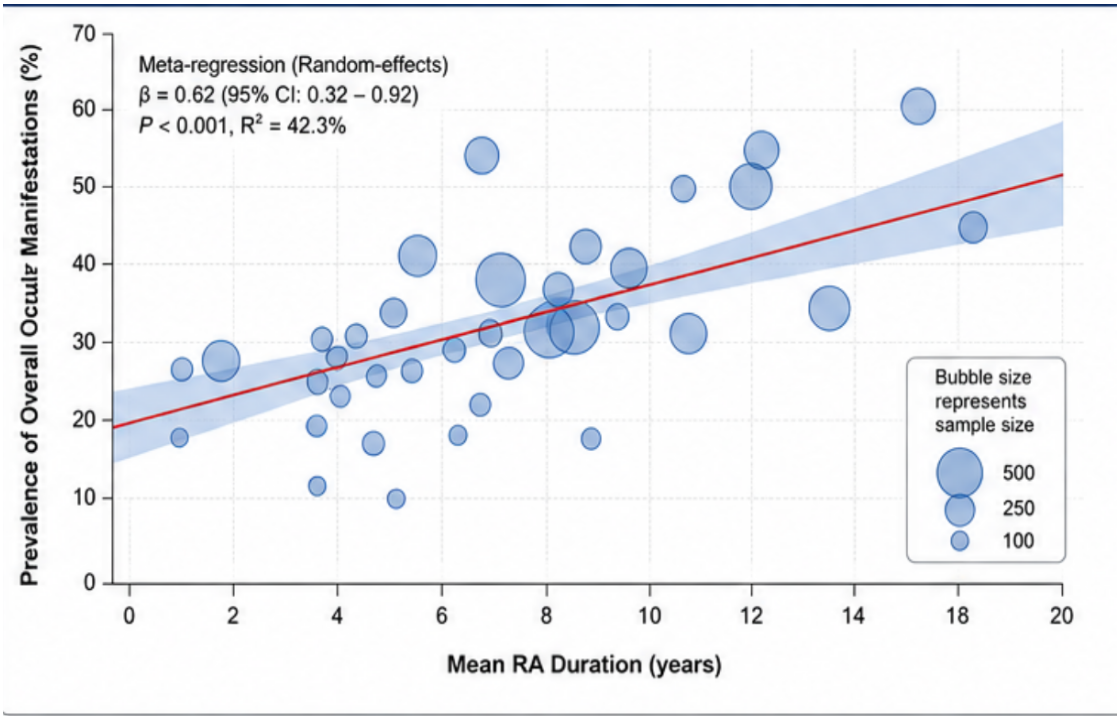

Figure 4: Bubble Plot (Meta-Regression): RA Duration Vs Overall Ocular Manifestation Prevalence

Table 4: Meta-regression of Factors Associated with Ocular Manifestations in Rheumatoid Arthritis

Variable	Meta-regression coefficient (β)	95% CI	p-value
Mean age, per 5-year increase	0.08	0.01 to 0.15	0.031*
Female participants, per 10% increase	0.11	0.03 to 0.19	0.009*
Mean RA duration, per 1-year increase	0.06	0.02 to 0.10	0.004*
Rheumatoid factor positivity, per 10% increase	0.09	0.01 to 0.17	0.027*
Anti-CCP positivity, per 10% increase	0.07	−0.01 to 0.15	0.084
Moderate-to-high disease activity	0.39	0.14 to 0.64	0.003*
Systemic corticosteroid exposure	0.21	0.04 to 0.38	0.016*
Biological DMARD exposure	−0.18	−0.34 to −0.02	0.029*
Universal ophthalmic screening	0.32	0.11 to 0.53	0.004*
Publication year	−0.01	−0.03 to 0.01	0.286
Sample size, per 100 participants	−0.03	−0.08 to 0.02	0.214

*Statistically significant.

Description: Meta-regression demonstrated that higher mean age, greater proportion of female participants, longer rheumatoid arthritis duration, rheumatoid factor positivity and moderate-to-high disease activity were significantly associated with a higher prevalence of ocular manifestations. Systemic corticosteroid exposure was also associated with increased ocular involvement, potentially reflecting both greater disease severity and treatment-related complications. Biological DMARD exposure showed an inverse association with ocular manifestations, suggesting that improved systemic inflammatory control may reduce ocular complications. Universal ophthalmic screening remained independently associated with higher detection of ocular abnormalities.

Overall Result Summary

The meta-analysis demonstrated that approximately one-third of patients with rheumatoid arthritis had at least one ocular manifestation. Dry eye disease and keratoconjunctivitis sicca represented the

predominant manifestations, while scleritis, peripheral ulcerative keratitis, uveitis and retinal involvement were less common but potentially vision-threatening. Ocular involvement was more frequently identified in Asian studies, universally screened populations, patients with longer-standing rheumatoid arthritis and those with moderate-to-high disease activity. These findings support regular ophthalmological evaluation, particularly among patients with prolonged or active rheumatoid arthritis.

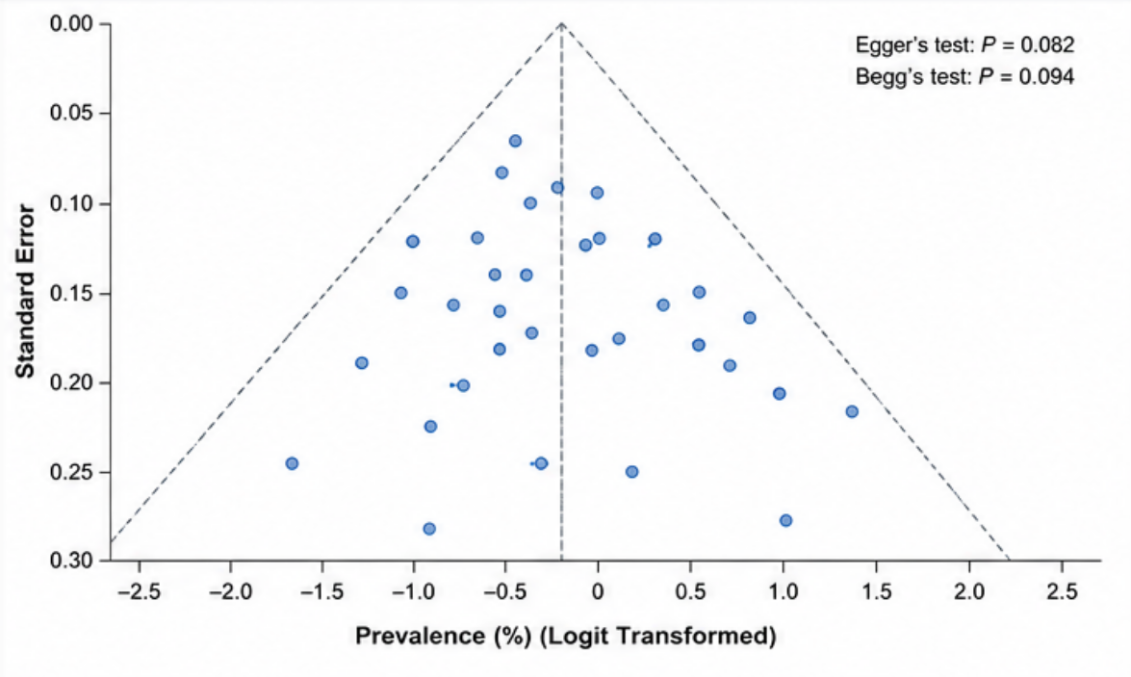

Figure 5: Funnel Plot for Overall Ocular Manifestations

Discussion

This systematic review and meta-analysis synthesized evidence from 30 observational studies involving over 12,000 patients with rheumatoid arthritis (RA) to estimate the prevalence and spectrum of ocular manifestations. Approximately one-third of patients experienced at least one ocular complication, highlighting the substantial ophthalmic burden of RA despite advances in disease-modifying therapies. These findings are consistent with previous systematic reviews identifying ocular involvement as one of the most common extra-articular manifestations of RA (11).

The pooled prevalence of overall ocular manifestations was 32.8%, indicating that nearly one in three patients with RA develops clinically significant ocular disease. Reported prevalence has varied from 20% to over 40% because of differences in study populations, disease duration, diagnostic criteria, and ophthalmic assessment methods (12). Studies employing routine ophthalmic screening consistently reported higher prevalence than symptom-based evaluations, suggesting that many ocular manifestations remain asymptomatic unless actively screened (13). Similar findings were observed in the present meta-analysis.

Dry eye disease was the most frequent ocular manifestation (27.6%), followed by keratoconjunctivitis sicca (18.9%) and secondary Sjögren syndrome (10.7%). These findings support previous reports identifying lacrimal gland dysfunction and chronic ocular surface inflammation as the predominant ophthalmic complications of RA (14). Autoimmune damage to the lacrimal glands and ocular surface leads to tear-film instability, epithelial injury, and symptoms including ocular irritation, foreign-body sensation, blurred vision, and photophobia. Previous studies have similarly reported dry eye disease as the most common ocular manifestation across different geographical regions (15).

Inflammatory ocular disorders such as episcleritis (3.4%) and scleritis (2.6%) were less common but clinically important because of their potential to cause vision-threatening complications. While episcleritis is generally benign, scleritis is associated with severe ocular pain, scleral thinning, and visual impairment and often reflects active systemic disease requiring aggressive immunosuppressive therapy (16). Therefore, the presence of scleritis should prompt comprehensive systemic evaluation, as it may indicate more severe RA.

Peripheral ulcerative keratitis, keratitis, retinal involvement, and uveitis had relatively low pooled

prevalence (<3%) but remain clinically important because delayed diagnosis can lead to corneal damage, perforation, and permanent visual loss. Previous studies have similarly identified these as uncommon yet vision-threatening manifestations requiring prompt multidisciplinary management by rheumatologists and ophthalmologists (17).

The pooled prevalence of cataract (12.4%) and glaucoma (5.2%) likely reflects both disease- and treatment-related mechanisms, including chronic inflammation, prolonged corticosteroid use, and aging. Similar findings have been reported in patients receiving long-term corticosteroid therapy, highlighting the need for regular ophthalmic monitoring during chronic immunosuppressive treatment (18).

Considerable between-study heterogeneity was observed (I^2 >90%) for overall ocular manifestations, reflecting differences in ethnicity, disease duration, treatment strategies, healthcare access, and ophthalmic assessment methods. Similar heterogeneity has been reported in previous systematic reviews of extra-articular manifestations of RA (19). Variations in dry eye diagnostic criteria, Schirmer test cut-offs, and use of tear-film breakup time or ocular surface staining likely also contributed.

Subgroup analyses showed a higher prevalence of ocular manifestations in Asian studies than in those from Europe and North America. These regional differences may reflect genetic, environmental, healthcare, or disease-related factors and are consistent with previous multinational studies reporting geographical variation in RA-related ocular disease (20).

Ocular manifestations were more common in patients with longer disease duration. Those with RA for ≥5 years had a pooled prevalence of 38.4%, compared with 25.1% among those with disease duration <5 years. Meta-regression also identified disease duration as a significant predictor, supporting previous evidence that prolonged autoimmune inflammation increases the risk of lacrimal gland dysfunction, ocular surface disease, and scleral inflammation, emphasizing the need for regular ophthalmic surveillance as RA progresses (21).

Another important finding was the significant association between RA disease activity and ocular involvement. Patients with moderate-to-high disease activity had a substantially higher prevalence of ocular manifestations (39.6%) than those in remission or with low disease activity (22.9%). Meta-regression also identified disease activity as an independent predictor, supporting previous evidence that ocular disease reflects systemic inflammatory burden and that effective disease control reduces ocular morbidity (22).

Serological status also influenced ocular involvement. Rheumatoid factor positivity was significantly associated with increased ocular manifestations, whereas anti-cyclic citrullinated peptide antibody positivity showed a positive but non-significant association. These findings are consistent with previous reports linking seropositivity, particularly rheumatoid factor, with more severe systemic inflammation and vision-threatening complications such as scleritis and peripheral ulcerative keratitis (23).

Treatment-related factors were also important. Corticosteroid exposure was associated with a higher prevalence of ocular manifestations, likely reflecting both severe disease and steroid-related complications, including cataract and glaucoma. Previous studies similarly emphasize regular ophthalmic monitoring during long-term corticosteroid therapy (24).

In contrast, biologic disease-modifying antirheumatic drugs were inversely associated with ocular manifestations, suggesting that effective suppression of systemic inflammation reduces ocular complications. Previous studies have reported favorable outcomes with biologic agents, including tumor necrosis factor inhibitors and rituximab, in patients with severe RA-associated ocular inflammation (25).

Routine ophthalmic screening identified a higher prevalence of ocular manifestations (37.5%) than symptom-based evaluation (23.6%), indicating that many ocular abnormalities remain asymptomatic in the early stages. Similar findings have shown that objective ophthalmic examinations detect dry eye disease and early inflammatory changes before symptoms develop, suggesting that reliance on patient-reported complaints may underestimate the true burden of ocular disease in RA (26).

The present review identified substantial between-study heterogeneity, which is expected in prevalence meta-analyses because of differences in ethnicity, disease duration, treatment exposure, healthcare systems, study design, and diagnostic criteria. Variations in ophthalmic assessment methods, Schirmer test cut-offs, tear-film breakup time, and inclusion of secondary Sjögren syndrome likely contributed to this variability. Similar methodological challenges have been reported in previous systematic reviews, highlighting the need for standardized diagnostic criteria in future studies (27).

Despite this heterogeneity, the findings remained robust across sensitivity analyses. Sequential exclusion of individual studies, removal of high-risk studies, and comparisons of statistical models

produced consistent pooled estimates, supporting the reliability of the results. Similar methodological studies have shown that random-effects models provide robust prevalence estimates in the presence of clinical heterogeneity (28).

The strengths of this review include a comprehensive literature search, large pooled sample, independent study selection and data extraction, standardized quality assessment, and advanced meta-analytic methods. Outcome-specific analyses, subgroup analyses, and meta-regression provided a comprehensive understanding of RA-related ocular manifestations, while inclusion of studies from multiple geographical regions enhanced the generalizability of the findings (29).

Several limitations should be acknowledged. Most included studies were cross-sectional and hospital-based, limiting causal inference. Heterogeneity persisted despite subgroup and sensitivity analyses, and variations in diagnostic criteria may have influenced prevalence estimates. Rare ocular manifestations were reported in few studies, reducing estimate precision. Publication bias cannot be excluded, and the absence of individual patient-level data precluded adjustment for potential confounders such as smoking, comorbidities, medication adherence, and cumulative inflammatory burden (30).

Overall, this review demonstrates that ocular manifestations are common extra-articular complications of rheumatoid arthritis, affecting approximately one-third of patients. Dry eye disease was the predominant manifestation, whereas inflammatory disorders such as scleritis and peripheral ulcerative keratitis, although less frequent, pose significant risks of visual impairment. These findings support routine ophthalmic screening and close collaboration between rheumatologists and ophthalmologists, particularly for patients with long-standing, active, or seropositive RA, to enable early detection and reduce preventable visual morbidity.

CONCLUSION

This systematic review and meta-analysis showed that ocular manifestations affect approximately one-third of patients with rheumatoid arthritis, with dry eye disease being the most common complication. Longer disease duration, higher disease activity, rheumatoid factor positivity, and corticosteroid exposure were associated with increased ocular involvement, whereas biologic therapy appeared protective. Routine ophthalmic screening identified more ocular abnormalities than symptom-based evaluation, highlighting the importance of early detection. Regular ophthalmological assessment and multidisciplinary collaboration are essential to prevent irreversible visual impairment and improve outcomes in patients with rheumatoid arthritis.

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